Chapter 42
Exercise in the Therapy of Diabetes Mellitus

Sefton Vergano, Rajiv Bhambri, and Stephen H. Schneider

Introduction

Exercise has been advocated for patients with diabetes for centuries, but it was only in 1990 that the American Diabetes Association (ADA) felt there was enough evidence of benefit to recommend exercise as a routine part of the treatment of type 2 diabetes mellitus. Since that time, the use of exercise in the treatment of type 2 diabetes has become well accepted, although its place in the treatment of type 1 diabetes remains less clear. In recent years, the role of exercise in the prevention of type 2 diabetes and in the treatment of the metabolic syndrome has proven to be of particular interest. Indeed, current research seems to confirm a role for both aerobic exercise as well as resistance training in both the treatment and the prevention of the disease. Nevertheless, our understanding of the complex interactions of exercise with diabetes is still incomplete, and the most effective ways to use exercise in the treatment of the disease are still under investigation.

During exercise major cardiorespiratory and circulatory responses help to efficiently supply the increased oxygen and energy needs of the working muscles. Whole body oxygen consumption and glucose turnover may increase more than tenfold and even greater increases may occur in the skeletal muscles.[1] In healthy individuals, a complex hierarchy of hormonal responses regulates the alterations in fuel metabolism necessary to maintain normal plasma glucose levels during prolonged activity.[2] This metabolic response to exercise may be severely disordered in patients with diabetes mellitus. In order to understand the effects of diabetes on fuel metabolism during exercise, it is important to first review the normal physiology.

Metabolic Changes During Exercise in Normal Individuals

As exercise intensity increases there is a linear relationship between heart rate, oxygen consumption, and workload. Eventually, however, oxygen consumption plateaus in the face of increasing exercise intensity. The point at which oxygen uptake plateaus is known as the maximal aerobic exercise capacity, or VO_2max. Exercise above this point can only be sustained for a short time because it represents non-aerobic metabolism and is limited by lactic acid accumulation. The VO_2max is important for a number of reasons. It is a useful tool to express the degree of aerobic fitness of an individual. In general, a higher VO_2max predicts better performance in endurance-type activity. It also allows comparison of individuals of widely varying fitness levels. For example, at the same percentage of any individuals VO_2max, a roughly similar metabolic response will occur. In addition, the VO_2max has been useful in communicating recommendations for exercise in various groups of individuals. Because the VO_2max is rarely directly measured in individual patients, indirect techniques for estimating workloads as a percent of the VO_2max have been developed and are discussed later in the chapter.

S.H. Schneider (✉)
Division of Endocrinology, Metabolism and Nutrition, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA
e-mail: schneide@umdnj.edu

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Moderate Intensity Exercise (50–75% VO_2max)

In the initial stages of exercise muscle glycogen is the chief source of energy.[3] As continued exercise depletes muscle glycogen, the working muscles must take up glucose and nonesterified fatty acids (NEFA) from the circulation.[4] Recent evidence suggests that utilization of local triglyceride stores, both intra-myocellular and extra-myocellular, in skeletal muscle may also be an important source of free fatty acid for oxidation during physical activity. In the postprandial state glucose is derived from an increased hepatic production that closely matches peripheral glucose utilization and can maintain euglycemia during moderate intensity exercise for long periods of time. However, during prolonged exercise glucose utilization may exceed splanchnic glucose output and hypoglycemia may develop.

The role of neurohormonal adaptation during exercise is twofold:

(a) to supply the exercising muscles with their increased fuel and oxygen requirements and
(b) to maintain whole body glucose homeostasis to supply the brain with adequate substrate.

It is not clear what triggers the endocrine response to exercise; it may result from the stimulation of afferent nerves from the working muscles or from subtle deviations in the blood glucose and/or from feed forward mechanisms originating within the hypothalamus.[5] At the start of exercise, a fall in the circulating insulin levels occurs due to an increased alpha adrenergic input to the beta cells.[6] This physiologic decrease in insulin levels promotes peripheral lipolysis and removes the inhibiting effects of insulin on hepatic glycogenolysis and gluconeogenesis. As exercise continues, an increase in the level of the counterregulatory hormone glucagon facilitates liver glycogenolysis and later gluconeogenesis, further enhancing hepatic glucose output.[4] Figure 42.1 illustrates the hormonal response to exercise.

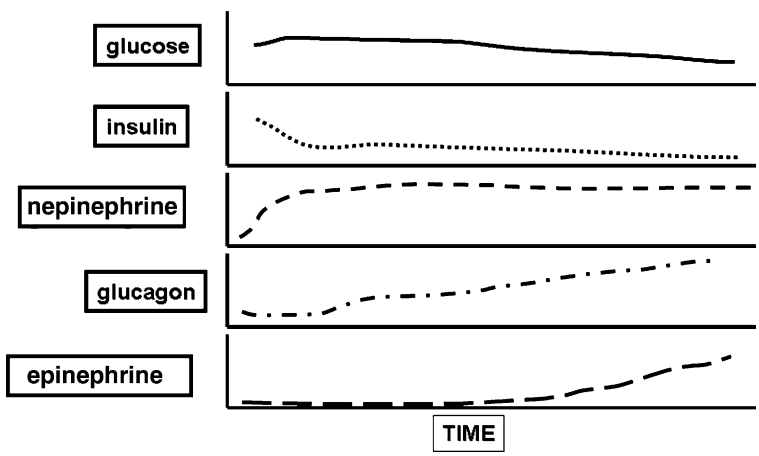

Fig. 42.1 The hormonal response to exercise

With more prolonged exercise insulin secretion continues to fall and there is a further release of counterregulatory hormones. A rise in circulating epinephrine levels and falling insulin levels lead to an increase in blood NEFA levels[7] due to both increased lipolysis and decreased NEFA re-esterification in the liver. The liver utilizes the glycerol released during triglyceride breakdown as a substrate for gluconeogenesis and the NEFA are delivered to the working muscles as an energy source. The increased availability of NEFA for muscle metabolism helps restrain the rate of muscle glucose utilization and therefore helps to limit the fall in glucose during prolonged exercise. In fact, the major role of catecholamines during prolonged exercise is to stimulate lipolysis. Their main impact on hepatic gluconeogenesis is probably via the mobilization of gluconeogenic precursors from peripheral sites and the provision of free fatty acids as an energy source for gluconeogenesis.[8] Catecholamines

also stimulate glycogenolysis in inactive muscles during the later stages of prolonged exercise.[9] In this situation the glycogen is metabolized to lactate in non-exercising muscle. Lactate can then be delivered to exercising muscle where it can be oxidized as fuel, as well as to the liver for gluconeogenesis. This complex and redundant series of hormonal responses regulate blood glucose during exercise with remarkable efficiency and the redundancy of the system insures that glucose homeostasis is robust.

High Intensity Exercise (>75% VO_2max)

During very high intensity exercise the relationship between peripheral glucose utilization and hepatic glucose production may be reversed. Because virtually all of the fuel for high intensity activity is provided by local energy stores of muscle glycogen, hepatic glucose production often significantly exceeds peripheral glucose utilization leading to hyperglycemia that persists into the postexercise state. The added glucose production most likely originates from hepatic glycogenolysis[5] and epinephrine may be involved in its regulation.[10] There may also be a brief period of relative insulin resistance following very intense exercise causing elevated blood glucose. When postexercise hyperglycemia occurs in normal individuals, it is transient and self-correcting.

Muscle Glucose Uptake During Exercise

The increased muscle glucose uptake during exercise is related to the intensity of the exercise once a steady state has been achieved.[5] In general, the greater the exercise intensity, the greater the relative utilization of carbohydrate as an energy source. For example, at exercise of roughly 50% of an individual's VO_2max, half of the energy requirement is supplied by carbohydrate while 80% of energy requirements may be supplied by carbohydrate at exercise approaching 80% of the VO_2max. Since plasma insulin levels fall during exercise, the increased muscle glucose uptake must be mediated by insulin-independent mechanisms or via an increased insulin action on muscle. Exercise probably acts in both ways[5] but the insulin-independent mechanism predominates. During exercise there is an insulin-independent increase in the concentration of the main glucose transporter protein GLUT 4 on the muscle membrane.[11] This is thought to be due to the translocation of the GLUT 4 from the cytoplasm to the sarcolemma.[12] This increase in the number of GLUT 4 on the surface of the cell leads to an increase in the glucose uptake from the circulation into the muscle cell. In addition to changes within the muscle itself, enhanced muscle perfusion during exercise improves glucose uptake through increased delivery of insulin and glucose to working muscle.

Postexercise State

In the postexercise period the hormones return to basal levels and glycogen and triglyceride stores are repleted. If exercise is of sufficient intensity and duration to deplete muscle glycogen and adequate carbohydrate is made available, the amount of glycogen will rebound to well above pre-exercise levels, a phenomenon called supercompensation. Of great therapeutic importance is the observation that muscle insulin sensitivity is enhanced for prolonged periods of time following a single bout of moderately intense activity. Insulin sensitivity is typically enhanced for 12–24 h, but after sufficient exercise, alterations lasting up to 72 h have been noted. This results in a sustained improvement of insulin sensitivity in individuals who exercise every other day or more. The mechanisms by which exercise results in these sustained benefits are unclear. A relationship to muscle glycogen levels is suggested by the observation that exercise of intensity and duration sufficient for glycogen depletion is generally required for this effect to occur. In addition, athletes who take in large amounts of glucose following exercise and achieve glycogen levels above basal have been reported to have impaired insulin sensitivity. On the other hand, the increase in insulin sensitivity that follows exercise clearly persists at a time when glycogen stores have returned to normal. Another mechanism for improved carbohydrate utilization following exercise may relate to

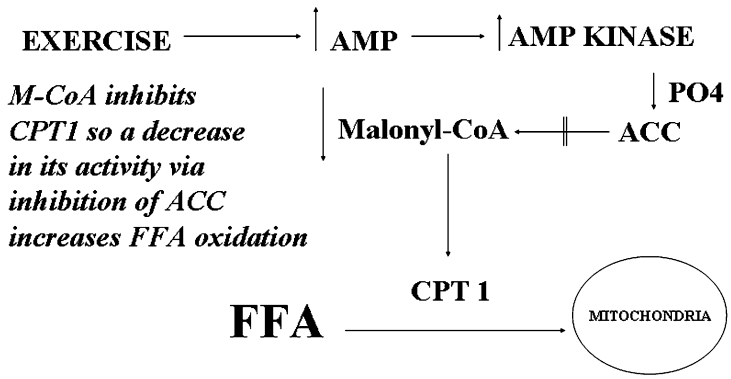

Fig. 42.2 The role of AMP kinase in enhancing free fatty acid utilization during exercise. During exercise, ATP is broken down to AMP which activates the enzyme AMP kinase. AMP kinase causes a downstream decrease in the inhibition of CPT1 allowing increased free fatty acid oxidation in the mitochondria. AMP = adenosine monophosphate, PO4 = phosphate group, ACC = acetyl-CoA carboxylase, M-CoA = malonyl-CoA, CPT1 = carnitine palmitoyltransferase, FFA = free fatty acids

the activation of the enzyme AMPK (AMP-activated protein kinase) (see Fig. 42.2). During exercise, ATP is broken down to AMP to release energy. As AMP builds up, it increases the activity of the enzyme AMPK. This enzyme is activated during exercise of the intensity required to lead to improved postexercise glucose uptake. In addition to shifting fuel utilization acutely toward the oxidation of FFA it may also stimulate subsequent glucose utilization by mechanisms independent of insulin action, possibly involving the nitrous oxide system.

Recently, attention has turned to the role of intra-myocellular triglyceride metabolism as a regulator of insulin sensitivity. In general, states of increased triglyceride accumulation in skeletal muscle and liver are associated with insulin resistance. Breakdown products of the metabolism of free fatty acids (FFA), the building blocks of triglycerides, can activate serine kinases and suppress the activity of the insulin receptor and insulin receptor substrates. Reduction of fat stores in skeletal muscle during exercise could be a mechanism enhancing subsequent insulin sensitivity. Nevertheless, when highly trained endurance athletes are studied, levels of triglyceride in skeletal muscle are actually increased in between exercise bouts. Despite this increase in myocellular fat stores, such athletes are characterized by a high degree of insulin sensitivity. This has been called the "athlete's paradox." New information suggesting that the breakdown products of FFA metabolism and not the storage triglyceride themselves may induce insulin insensitivity helps to clarify this apparent problem. In the postexercise period rapid restoration of triglyceride stores may actually result in a decrease in these metabolically active intermediates, thus improving insulin sensitivity.[13]

Adaptations to Physical Training

Exercise performed on a regular basis with an intensity, duration, and frequency sufficient to improve cardiorespiratory fitness, strength, and flexibility is called physical training. Alterations in cardiac and respiratory efficiency and in the neurologic coordination of motor activity are an important factor in improved performance. In addition, there are important cellular adaptations of skeletal muscles with physical training (see Table 42.1). This response differs during aerobic training (i.e., low to moderate intensity) as compared to resistance training. The changes associated with aerobic training include the following:

(a) An increase of the oxidative capacity of the type I slow twitch fibers as well as a change in the type II fast twitch fibers toward the so-called type IIa fiber type with a greater oxidative capacity.[14]
(b) An increase in the number of capillaries around muscle fibers[15] which allows for more efficient exchange of nutrients and waste products.

Table 42.1 Adaptations to aerobic training

– Transformation of the glycolytic type IIb muscle fibers to type IIa muscle fibers with a greater oxidative capacity
– Increased number of muscle capillaries and muscle perfusion
– Increased size, number, and metabolic capacity of mitochondria
– Increased availability of muscle glucose transporter GLUT 4
– Increased activity of the enzymes hexokinase and glycogen synthase
– Increased adiponectin receptors (adiponectin is a hormone produced by adipose tissue that is a major mediator of insulin sensitivity)
– Decreased inflammatory cytokines

(c) An increase in the size, number, and metabolic activity of mitochondria[16] with a greater capacity for ATP production and oxidative phosphorylation. (This may be mediated in part through the activation of AMPK.)
(d) An increase in the number of GLUT 4 transporters available for translocation to the cell surface.[17]
(e) An increase in the activity of the enzymes hexokinase and glycogen synthase with an improved capacity for increased glucose uptake, glucose phosphorylation, and storage, respectively.
(f) An increase in the expression of adiponectin receptors,[18] as well as a decrease in inflammatory cytokines known to be associated with insulin resistance.[19]

These changes occur in the face of little or no muscle hypertrophy and are most obvious in the type 1 and type 2a oxidative fibers.

The adaptive response to resistance training results predominantly in the hypertrophy of type 2b fast twitch fibers with minimal changes in oxidative capacity or vascularization. In addition to hypertrophy, much of the early improvement in strength during resistance training is related to more efficient neurologic regulation of fiber recruitment within the muscle.

These changes in muscle function along with the cardiorespiratory and circulatory adaptations to physical training lead to a more efficient use of energy and improvements in aerobic endurance. There is no evidence that the adaptations to exercise in patients with diabetes differ substantially from those of normal individuals.

Exercise Capacity of Patients with Diabetes

Patients with type 1 diabetes appear to have a normal exercise capacity when metabolic derangements are well controlled. In chronically under-insulinized patients, an inability to store glycogen and a tendency to dehydration can result in poor endurance capacity. In patients with autonomic dysfunction the cardiovascular response to exercise can be further impaired. The situation in patients with type 2 diabetes is more complex. A number of studies suggest that these patients may have a mild impairment of aerobic exercise capacity. Many studies show a VO_2max roughly 15% lower than controls with apparently similar levels of physical activity. Interestingly, preliminary studies suggest that this difference may be present prior to the onset of overt disease and can even be found in first-degree relatives (see Fig. 42.3). This is associated with a relatively high percentage of fast twitch fibers, which are less insulin sensitive as well as a decrease in mitochondrial and capillary density. It appears that the decrease in VO_2max in patients with diabetes could be related, at least in part, to acquired or genetic alterations in mitochondrial function.[20] Skeletal muscle mitochondria in individuals with type 2 diabetes have been shown to be reduced in size and may have a reduced oxidative phosphorylation capacity via decreased enzyme activity. These defects have also been demonstrated in preliminary studies in nondiabetic but insulin-resistant relatives of those with diabetes. In addition, impaired activation of AMPK has been found in insulin-resistant, obese, and diabetic individuals.[21] Nevertheless, patients with type 2 diabetes do respond to physical training with an increase in oxidative capacity, and it is important to note that the *relative* ability of these patients

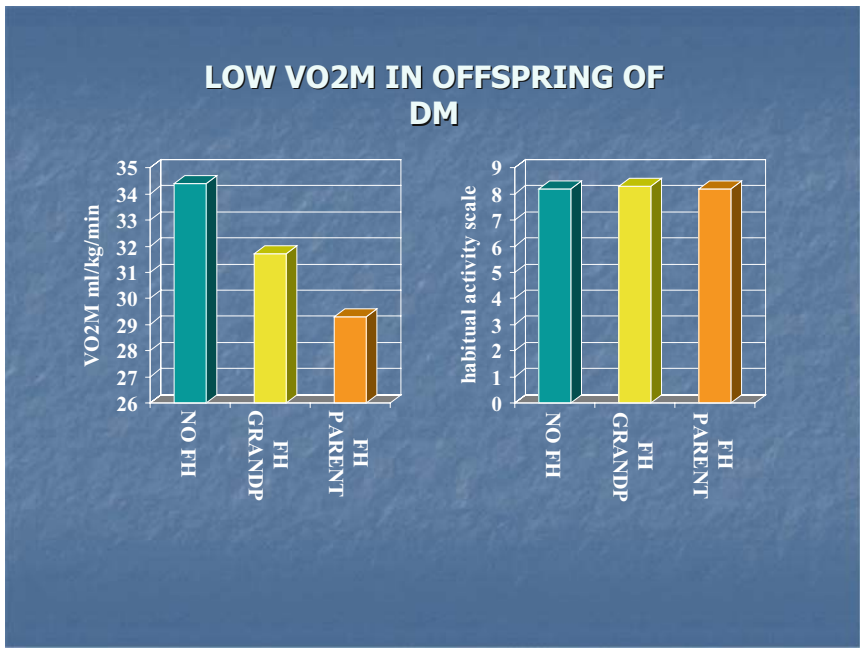

Fig. 42.3 Impaired aerobic exercise capacity in close relatives of individuals with type 2 diabetes mellitus. In subjects with equivalent baseline activity levels, there is a significant decrease in VO2max in those with a first- or second-degree relative with type 2 diabetes as compared to those with no family history. NO FH, no family history of diabetes; FH GRANDP, second-degree relative with diabetes; FH PARENT, first-degree relative with diabetes (from Thamer et al.[20])

to improve aerobic exercise capacity during training appears to be normal. There is no evidence that resistance training elicits a unique response in patients with diabetes.

Fuel Metabolism During Exercise in Patients with Diabetes

Type 1 Diabetes

A number of factors influence the metabolic response to exercise in patients with type 1 diabetes mellitus. These include the adequacy of insulinization, metabolic control, the presence or absence of complications, exercise intensity, duration, type, and recent food intake.[1] The ability of the body to maintain glucose levels in the face of intense exercise is remarkable. In trained athletes moderate activity of many hours duration may be associated with minimal changes in plasma glucose. Nevertheless, inadequate regulation of plasma glucose levels is common in patients with type 1 diabetes. Similar problems often occur in patients with long-standing type 2 diabetes mellitus who have reached a point of absolute insulin deficiency and are dependent upon exogenous insulin.

One of the major reasons for the sometimes disappointing results of exercise as a means of improving glucose control in type 1 diabetes is hypoglycemia. Hypoglycemia is common in patients with type 1 diabetes during exercise and may require increased carbohydrate intake and a decreased insulin dose which limits potential improvements in glucose control. While the various causes of hypoglycemia during exercise in patients with type 1 diabetes are not always clear there are a number of factors which contribute (see Table 42.2) to it:

(a) Relative hyperinsulinemia: Exercise is normally associated with a fall in circulating insulin. Subcutaneously injected insulin prior to exercise cannot be shut off and this can lead to a state of relative hyperinsulinemia.

Table 42.2 Contributing factors toward exercise-related hypoglycemia in insulin treated patients

1. Lack of physiologic suppression of plasma insulin levels
2. Enhanced absorption of insulin injected over exercising muscle
3. Impaired counterregulatory responses of glucagon and epinephrine
4. Increased insulin sensitivity
5. Medications (i.e., beta-adrenergic blockers) in those with impaired glucagon response

A dose of insulin appropriate at rest may be excessive during exercise. Also, if insulin is injected directly over the exercising muscle its absorption can be accelerated.[22,23] This effect is particularly important for regular insulin and when exercise occurs within 1–2 h after injection. The absorption of insulin is increased even further if the insulin is injected accidentally directly into the exercising muscle. In addition to the early hypoglycemia, rapid depletion of the insulin depot can actually result in insulin deficiency later in the day and contribute to hyperglycemia and erratic glucose control.

(b) Impaired counterregulatory response: Patients with type 1 diabetes and relatively long-standing disease (>5 years) may have a blunted glucagon and epinephrine response to hypoglycemia.[24] This may occur in the absence of overt autonomic neuropathy. When combined with the lack of physiological insulin suppression this may be an important contributor to hypoglycemia during exercise.

(c) Increased insulin sensitivity: Hypoglycemia can occur not only during exercise but also as long as 6–10 h after a brisk exercise bout. This is because of an exercise-induced increase in insulin action that may take some time to manifest and that can persist for hours.[25,26] Such clinically important episodes can be severe, and if exercise is performed in the evening, hypoglycemia may occur in the early morning hours while the patient is asleep.

(d) Drugs: Beta-adrenergic blockers may aggravate insulin-induced hypoglycemia. However, because of the redundancy of the hormonal system regulating plasma glucose, this problem is generally confined to patients who already have an impaired glucagon response. This is especially true for patients with long-standing type 1 diabetes where glucagon secretion is often impaired but is less common in the larger group of patients with type 2 diabetes.[27] Ethanol may also predispose the patient with type 1 diabetes to exercise-induced hypoglycemia by inhibiting gluconeogenesis and decreasing hepatic glycogen stores.

In contrast to the more common hypoglycemia, some patients in poor metabolic control may experience a paradoxical rise in blood glucose with exercise as a result of absolute insulin deficiency. The deficiency leads to hyperglycemia (fasting blood glucose >300 mg/dl), frequent ketosis, and dehydration (see Fig. 42.4).[28,29] This is probably because the insulin deficiency and the associated excess of counterregulatory hormones cause an increased hepatic glucose and ketone body production that exceeds peripheral utilization. For practical purposes

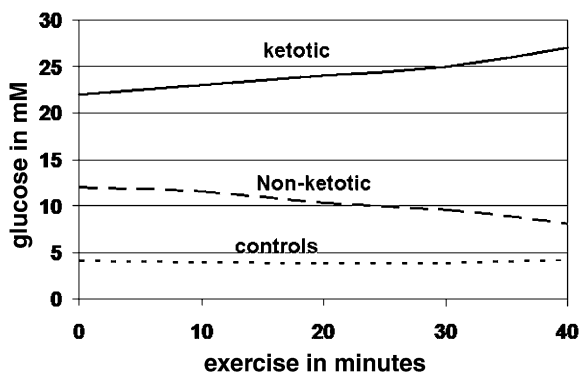

Fig. 42.4 Effects of exercise in severely insulin-deficient patients with type 1 diabetes mellitus – paradoxical hyperglycemia. Blood glucose in ketotic diabetic patients paradoxically increased with greater duration of exercise, unlike the control group and the non-ketotic diabetic group

patients with a *fasting* blood glucose >300 mg/dl or who have evidence of ketones are those at risk for paradoxical hyperglycemia. In these patients adequate insulinization needs to be achieved before exercise can exert beneficial effects.

Another situation where significant hyperglycemia may occur in patients with type 1 diabetes is following very high intensity exercise.[30] This is usually transient and results from brisk hepatic glycogenolysis at a time when peripheral tissues are relatively insulin resistant and are primarily using stored glycogen as an energy source. Unlike the situation in healthy individuals the hyperglycemia may be prolonged in patients with type 1 diabetes because increased endogenous insulin fails to compensate.

Type 2 Diabetes

The metabolic response to exercise in most patients with type 2 diabetes is similar to healthy individuals, and as noted above it will be modified by a number of factors including drug therapy and exercise intensity.

Patients with type 2 diabetes mellitus have a relatively low incidence of exercise-induced hypoglycemia. This is probably related to intact glucagon and epinephrine responses. However, hypoglycemia can occur in patients with type 2 diabetes treated with insulin or insulin secretagogues.

Benefits of Exercise Training

The potential benefits of regular physical activity in patients with diabetes are numerous and include improvements in insulin sensitivity and glycemic control, reduction in cardiovascular risk, improvements in blood pressure, lipid profile and coagulation factors, and weight loss (see Table 42.3).[31,32]

Table 42.3 Benefits of regular exercise in diabetes

– Improved insulin sensitivity
– Improved glycemic control in type 2 diabetes
– Decreased triglycerides
– Decreased numbers of small, dense LDL cholesterol particles
– Increased HDL cholesterol (with intensive exercise regimens)
– Decreased blood pressure
– Increased fibrinolytic activity
– Weight loss
– Decreased visceral adiposity
– Increased lean body mass
– Reduced cardiovascular risk
– Positive behavior modification
– Improved self-esteem and sense of well-being

Insulin Sensitivity

A number of studies have shown an improvement in glucose tolerance following a single exercise bout in normal individuals and patients with type 1 and 2 diabetes.[33–36] A single episode of exercise in patients with type 2 diabetes can typically improve insulin sensitivity at the liver and muscle for up to 16 h or longer.[37] Individuals undergoing long-term physical training regimens with an exercise frequency of three or more sessions per week have improved insulin-stimulated muscle glucose uptake and glucose tolerance and decreased insulin levels.[35,38–40] In most studies it is not clear to what extent these improvements are due to the summed effects of acute exercise bouts vs. the trained state per se. In one study after 6 months of physical training insulin sensitivity dramatically improved 12 h after the last exercise bout but had returned to baseline within a

week of subjects becoming sedentary, suggesting that acute exercise effects may predominate.[41] Certainly, more prolonged improvements in metabolic control could result indirectly through changes in body composition that occur during physical training such as decreased visceral fat and increased muscle mass.

The mechanisms underlying possible beneficial effects of the trained state include the following:

(a) Increased insulin-stimulated glucose disposal owing to increased skeletal muscle blood flow.[38]
(b) Increased insulin-responsive GLUT 4 glucose transporter availability in skeletal muscle with physical training.[12]
(c) Increased activity of mitochondrial enzymes involved in oxidation and storage of glucose in skeletal muscle.
(d) Increased conversion of type IIb to type IIa muscle fibers. (Type IIa fibers have higher concentration of glucose transporters, greater capillary density, and are more insulin responsive.)
(e) Decreased intra-abdominal and intramuscular fat stores.
(f) Increased muscle mass during programs of resistance training which may partially compensate for insulin insensitivity through the availability of an increased glucose storage space.[42]

Exercise and Glycemic Control

Type 2 Diabetes

There is substantial evidence that exercise training improves insulin sensitivity and decreases elevated blood glucose in patients with type 2 diabetes mellitus. Exercise programs performed at 50–70% VO_2max for 30–40 min, 3–4 times/week consistently show about a 10–20% drop in the HgA1c from baseline. Long-term studies have shown a sustained effect over as long as 5 years of regular exercise.[43,44] The maximum benefit is seen in patients with impaired glucose tolerance, mild type 2 diabetes, and those who are the most insulin resistant.[35,45] This is consistent with the effect of exercise training on insulin sensitivity. While the accumulated effects of individual exercise bouts are clearly a major contributor to improved overall blood glucose control, other factors such as changes in body composition, decreased visceral fat, and behavioral changes promoted by regular physical activity should not be underestimated.

Type 1 Diabetes

The beneficial effect of exercise on glycemic control in type 1 diabetic patients is less clear. Despite improvements in insulin sensitivity with decreased exogenous insulin requirements,[46] studies showing improved glucose control with regular exercise in large patient populations are lacking. One study noted a mild initial improvement in glucose control in 25 type 1 diabetic patients trained for >3 months that was lost by the third month of observation despite continued adherence to the exercise regimen.[47] The relatively high incidence of hypoglycemia during exercise in type 1 diabetic patients with resultant increased carbohydrate intake and decreased insulin dose probably offsets the benefit of the enhanced glucose disposal. Nevertheless, some patients with type 1 diabetes can achieve improved glucose control with exercise, although intensive self-monitoring and a predictable training regimen are usually required. More importantly, potential beneficial effects of physical training on body composition, psychological state, and cardiovascular risk factors can often be achieved along with a decrease in insulin requirements even in the absence of improvements in HgA1c. Hence exercise should not be discouraged but instead promoted in appropriate patients.

Exercise and Dyslipidemia

Type 2 diabetes is associated with a characteristic dyslipidemia related to an increased risk of premature atherosclerosis. Most often this consists of hypertriglyceridemia, low levels of HDL cholesterol, and normal or only modestly elevated levels of LDL cholesterol. Additional changes in the composition of LDL cholesterol

may also contribute to increased atherogenesis. The mechanisms by which exercise affects lipid metabolism are complex, but activation of lipoprotein lipase, changes in hepatic lipase activity, altered caloric balance, and changes in body composition and fat distribution may contribute.

Studies have shown that the most consistent effect of exercise training is a reduction in the plasma triglyceride levels, which fall up to 30% from baseline.[48–50] Some of the decrease in triglycerides seen with exercise may be transient and related to individual exercise bouts mirroring the effects of exercise on carbohydrate metabolism.[45]

Changes in LDL cholesterol with regular exercise have been less consistently demonstrated. There may be a decrease in the concentration of the small dense LDL particles, which are thought to be more atherogenic.[51] The effects are more pronounced in the patients who are more insulin resistant and have higher initial triglyceride levels. Many studies have not shown an increase in the HDL cholesterol with exercise even when the plasma triglyceride levels decrease. This could be due to the moderate intensity of the exercise regimens in the studies. In nondiabetic individuals, HDL cholesterol increases are seen only with high intensity exercise performed over a long period of time; many patients with type 2 diabetes are unable or unwilling to exercise to this intensity.

Patients with type 1 diabetes often have a lipid profile that differs from their counterparts with type 2 diabetes. When in good metabolic control HDL cholesterol levels may actually be elevated and major abnormalities of cholesterol and triglyceride measurements are unimpressive. Nevertheless, a very high incidence of premature CAD is found in these patients. Regular exercise has a favorable effect on the lipid profile in patients with type 1 diabetes similar to that seen in nondiabetic individuals.[5]

Exercise and Hypertension

Hypertension has been associated with the insulin resistance syndrome in patients with impaired glucose tolerance and type 2 diabetes. In trained subjects, both the resting pressure and the blood pressure response to exercise are reduced. Regular exercise in patients with type 2 diabetes may help improve hypertension especially in insulin-resistant/hyperinsulinemic patients.[45,47,52,53] Decreases of 5–10 mmHg of both systolic and diastolic pressure are typically found with exercise training in appropriate subgroups of patients.

Exercise and Fibrinolysis

Many patients with type 2 diabetes have an impaired fibrinolytic system with increased levels of plasminogen activator inhibitor-1 (PAI-1), the major inhibitor of tissue plasminogen activator. An acute exercise bout activates the fibrinolytic system, and there is an association of aerobic fitness with enhanced fibrinolytic activity. Some of this effect may be mediated indirectly through decreased levels of insulin and triglycerides.[41] Recent studies confirm that these improvements persist after years of regular exercise. Results from the Diabetes Prevention Program show modest but significant reductions in markers of coagulation and inflammation in those who exercised over an almost 3-year follow-up period.[54]

Exercise and Obesity

Weight loss has been shown to improve glucose control and insulin sensitivity, reduce blood pressure, and decrease cardiovascular risk. Even moderate weight loss (7–10% from baseline) is generally sufficient to improve glucose tolerance and reduce cardiovascular risk in patients with type 2 diabetes mellitus. Evidence suggests that in order to achieve weight loss, a combination of diet, exercise, and behavior modification is essential.[55,56] Exercise alone without dietary restriction is often not effective because of a compensatory increase in appetite and decrease in spontaneous activity. The combination of exercise and moderate caloric restriction is more effective than diet alone.[53,54,57,58] Exercise is also one of the strongest predictors of maintenance of weight loss.[53,54,56]

The beneficial effects of exercise in a weight-reducing program are often underestimated. Exercise increases lean body mass, which can obscure the loss of body fat when body weight is the criterion of success. In addition, exercise may cause a disproportionate loss of intra-abdominal fat, which has been most closely associated with the metabolic abnormalities in the insulin resistance syndrome. For weight reduction, an exercise frequency of at least 5–6 times a week, which burns 250–300 cal/session, is generally required. Initially this is difficult in most patients with type 2 diabetes because of their poor metabolic fitness. Studies from Blair et al. on the so-called obese fit individual suggest that overweight patients who maintain a substantial program of regular exercise have a risk factor profile and risk of cardiovascular events similar to that of normal weight individuals.[59]

In the last few years there has been heightened interest in resistance exercise as a weight loss tool. Greater muscle mass produced by resistance exercise results in an increased resting metabolic rate which could help with weight maintenance. Recent studies also suggest that the addition of resistance exercise to an aerobic exercise program potentiates the beneficial metabolic effects of the latter on insulin sensitivity.[77]

Exercise and Cardiovascular Disease

Insulin resistance is thought to be an important risk factor for premature atherosclerosis in most type 2 diabetic patients. Studies have shown that these patients are more sedentary compared with controls and have an unfavorable cardiovascular risk factor profile. The beneficial effects of physical training on those cardiovascular risk factors which are most common in patients with type 2 diabetes suggest that regular exercise might play an important role in diminishing their very high incidence of premature coronary artery disease.

Although there are no completed randomized controlled trials assessing reduction in cardiovascular events induced by physical activity in type 2 diabetes, available evidence supports the concept that physical activity may play an important role in reducing cardiovascular risk in type 2 diabetes (see Fig. 42.5).[60] Large nonrandomized studies of both men and women with type 2 diabetes and impaired glucose tolerance have found that physical activity is associated with a decreased risk for cardiovascular disease.[58] It also appears that the amount of physical activity is inversely associated with coronary events.[61,62]

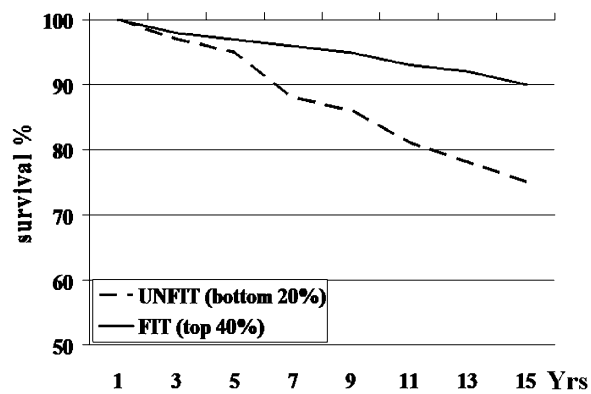

Fig. 42.5 Effects of fitness on cardiovascular mortality in patients with type 2 diabetes mellitus. Of 1263 men with type 2 diabetes, patients who scored in the lowest 20% (UNFIT) on a maximal exercise test had significantly greater mortality than those who scored in the top 40% (FIT) over the course of the study with average follow-up of 11.7 years (from Wei et al.[60])

The ongoing Look AHEAD trial, a large, randomized controlled study, aims to evaluate the long-term morbidity and mortality effects of intense lifestyle intervention in over 5000 patients with type 2 diabetes. It is scheduled to last over 11 years, and it will look specifically at changes in cardiovascular morbidity and mortality due to weight loss through physical activity, decreased caloric intake, and behavior modification. Although it is too soon for meaningful results in its primary outcomes, preliminary results show significant improvements in metabolic and disease markers.[63]

Table 42.4 Risks of exercise in diabetic patients

1. Metabolic
(a) Paradoxical hyperglycemia
(b) Hypoglycemia
2. Vascular
(a) Vitreous hemorrhage and traction retinal detachment
(b) Proteinuria
3. Neurologic
(a) Foot injury
(b) Excessive increases in blood pressure
(c) Postexercise hypotension
(d) Musculoskeletal injuries and degenerative joint disease

Risk of Exercise in Patients with Diabetes

The risks associated with exercise can be divided into metabolic, vascular, neurologic, and musculoskeletal and are summarized in Table 42.4.

Metabolic Derangements

Both hypoglycemia and paradoxical hyperglycemia are important complications of physical activity in patients with type 1 diabetes mellitus and in a smaller group of patients with type 2 disease. The mechanisms responsible for the surprisingly high incidence of hypoglycemia in these patients are discussed above. A number of options are available to avoid hypoglycemia in patients with type 1 diabetes and are summarized in Table 42.5. These should be individualized for each patient based on his/her response to exercise. Similar guidelines to avoid hypoglycemia have been advised for patients with type 2 diabetes taking insulin and some patients on sulfonylureas. Some of the measures recommended are as follows:

Table 42.5 Recommendations to avoid exercise-related hypoglycemia in patients with diabetes

1. Decrease dose of insulin prior to exercise (usually about 30–50%)
2. Avoid injecting short-acting insulin 1–2 h prior to exercise
3. Avoid injecting insulin directly over the exercising muscle
4. Ingest rapidly absorbable carbohydrates (about 15–30 g every 30 min) during exercise to avoid hypoglycemia during exercise
5. Ingest slowly absorbable carbohydrates and proteins to avoid delayed hypoglycemia

(a) Decreasing the dose of insulin taken prior to exercise. In general, reduction of about 30–50% in the insulin dose can be anticipated with moderate intensity exercise of >30-min duration. Greater reductions will be needed for more prolonged exercise. Because of their rapid onset and short duration of action, the newer very short-acting analogs of insulin are less likely to cause hypoglycemia.

(b) Avoiding injection of short-acting insulin into an area where the underlying muscles will be used during exercise within the next 1–2 h. For example, avoid injecting into the thigh if bicycling is planned.

(c) Consuming snacks of rapidly absorbable carbohydrates in the event that exercise is spontaneous and a dose of insulin has already been injected. About 15–30 g of carbohydrates ingested every 30 min is generally adequate for moderate intensity exercise. Larger amounts of carbohydrate are unlikely to be absorbed quickly and will only result in greater hyperglycemia later on.

(d) Exercising in the morning prior to the breakfast insulin dose, a time which appears to have the lowest risk of hypoglycemia. If possible, exercise should be avoided in the late evening, as this increases the risk of hypoglycemia in the early morning hours due to increased insulin sensitivity. Large meals preceding an

exercise session should be avoided as they place an additional stress on the cardiovascular system. Delayed hypoglycemia may be avoided by ingesting slowly absorbable carbohydrates and proteins at bedtime.[64] A high carbohydrate bedtime snack along with an agent which slows its absorption such as an intestinal sucrase inhibitor may also be useful. Use of the shorter acting insulin analogs, such as lispro, with evening food intake may also be helpful.

(e) Performing a brief burst of very high intensity exercise, which has a paradoxical hyperglycemic effect, in the event hypoglycemia develops during an exercise bout or at a time when carbohydrate is not readily available. For example, a 10 s maximal sprint can sometimes be used to temporarily restore glucose levels toward normal.[65]

The variability of the individual's response to physical activity in patients with type 1 diabetes cannot be overemphasized. As a result, self-monitoring of blood glucose (SMBG) by the patient done before, during, and after exercise is an essential step in developing personalized exercise recommendations.

When the *fasting* blood glucose is >250 mg/dl with ketones or >300 mg/dl with or without ketones, exercise should be delayed and such patients should be first adequately insulinized.

Microvascular Risks

While controlled studies are not available, observational evidence suggests that physical activity commonly precedes retinal hemorrhage in patients with advanced proliferative retinopathy. Most commonly, this is associated with hypoglycemia, rapid head movements which would increase shear forces, direct trauma to the eyes, or large swings in blood pressure. There is no evidence that regular exercise increases the risks of developing retinopathy or causes retinal hemorrhage in individuals with mild diabetic eye disease. In patients with more advanced retinopathy it is particularly important to avoid exercises that result in Valsalva maneuvers or levels of physical activity that cause a rise in the systolic blood pressure to >200 mmHg.

High intensity exercise increases the quantity of protein in the urine for hours after the exercise is completed. In as many as 30% of patients with diabetes whose baseline urine protein is normal, intense exercise creates a transient proteinuria. Assessments of quantitative urine protein excretion should be done at least 24 h after the last bout of exercise. Exercises that result in large increases in systolic blood pressure should probably also be avoided in patients with established nephropathy. Although no long-term studies of the effects of exercise on the progression of nephropathy are available, observational studies suggest that athletes do not have an increased risk of developing diabetic renal disease.

Neurological Risks

Patients with diabetes can be plagued by both peripheral and autonomic neuropathy. It is prudent to limit weight-bearing exercises in patients with significant peripheral neuropathy as repetitive exercise on insensitive feet will increase the risk for ulcerations and fractures. In addition, loss of proprioception can make some exercises dangerous, such as those involving free weights. Diabetic patients with autonomic neuropathy are at increased risk for excessive increases in blood pressure during exercise, postexercise hypotension, and sudden cardiac death. General measures to reduce the risks from exercise include maintaining adequate hydration during and after exercise and avoiding exercise in extremely hot or cold environments.

Exercise Recommendations

Compliance with exercise programs is a major problem. In a study of 255 diabetic patients in a diabetes education program that emphasized exercise, compliance with exercise fell from 80% at 6 weeks to <50% at 3 months

and <20% at 1 year.[45] To improve adherence to exercise programs, the activity should be enjoyable and convenient and the patient should be educated about the physiology of physical activity, its potential benefits, and risks. Quantitative indices of progress to provide feedback should be utilized, e.g., measurements of heart rate during submaximal exercise and measurements of body composition.[66] Also, the goals should be realistic. The guidelines and recommendations for exercise in diabetic patients are summarized in Table 42.7.[67,68]

Pre-exercise Evaluation

Prior to starting an exercise program all patients with diabetes should undergo a detailed history, physical examination, and appropriate studies with the focus on complications of diabetes affecting the eyes, heart, blood vessels, kidneys, and nervous system.[41] The goal of evaluating diabetic patients prior to starting a more intensive exercise program is to identify those patients who are at increased risk of having a serious adverse event with strenuous activity. As noted before, the response to exercise will be influenced by the type and intensity of exercise as well as the presence or absence of complications.

The most feared adverse effect of exercise in diabetic patients is sudden death due to arrhythmias or ischemia. Fortunately this is an extremely rare event. Cardiovascular risk prediction models based on the Framingham[69] or UKPDS studies,[70] or the risk assessment tool Diabetes PHD available at the American Diabetes Association (ADA) website, may be helpful in assessing a patient's risk. It has been suggested that any individual whose risk of cardiovascular disease exceeds 10% should undergo some form of formal cardiac exercise testing prior to initiating an exercise program. However, using a 10% cutoff would include an extremely high percentage of the population with type 2 diabetes mellitus. It therefore seems reasonable that individuals who will be exercising at an intensity similar to that which they experience during their activities of daily living probably do not need extensive formal cardiac evaluation. In contrast, in line with the updated 2002 guidelines from the American Heart Association/American College of Cardiology, a stress test evaluation is now more strongly recommended for those diabetic patients about to embark on a more vigorous exercise regimen.[71] Specific evidence-based studies evaluating risk stratification of diabetic patients prior to initiating an exercise regimen are lacking. Most completed and ongoing studies examine the broader categories of symptomatic patients (i.e., those with angina, anginal equivalents, shortness of breath, dyspnea on exertion, etc.) and asymptomatic patients. Unfortunately, the approach initially proposed by the ADA in its 1998 consensus position focusing heavily on the number of established cardiac risk factors has yet to be validated. The DIAD (Detection of Ischemia in Asymptomatic Diabetics) study found that the strongest predictors of abnormal adenosine stress SPECT myocardial perfusion imaging in asymptomatic patients were cardiac autonomic dysfunction (i.e., abnormal Valsalva), male sex, and diabetes duration.[72]

There are a number of noninvasive approaches to evaluate a patient for underlying cardiovascular disease. Exercise electrocardiography, stress myocardial perfusion imaging, and stress echocardiography can detect myocardial ischemia. The sensitivity, specificity, and positive and negative predictive values for the diagnosis of coronary artery disease in symptomatic diabetic patients is presented in Table 42.6; there is limited data for

Table 42.6 Sensitivity, specificity, and predictive values for the diagnosis of coronary artery disease in symptomatic patients with diabetes

Type of test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Exercise ECG stress test[a]	47	81	85	41
Dobutamine stress echocardiography[b]	82	54	84	50
Nuclear stress test[c]	86	56	n/a	n/a

[a]Lee et al.[97]
[b]Hennessy et al.[98]
[c]Kang et al.[99]

Table 42.7 Guidelines and recommendations for exercise in diabetic patients

1. Pre-exercise evaluation
   A. Detailed history, physical examination, and appropriate studies with focus on complications of diabetes affecting eyes, heart, blood vessels, kidneys, and nervous system
   B. Exercise stress test: for those starting a moderate to high intensity exercise program and those judged to have an increased risk for ischemic heart disease including
      (a) Type 2 diabetes of >10 years duration
      (b) Type 1 diabetes >15 years duration
      (c) Presence of peripheral vascular disease
      (d) Autonomic neuropathy
      (e) Nephropathy
      (f) Presence of multiple traditional risk factors
2. Aerobic exercise involving large muscle groups
   A. Frequency: minimum 3–5 times a week
   B. Intensity: 40–60% VO_2max
   C. Duration: >10 min/session; >150 min cumulatively per week
3. Resistance exercise, in those without contraindication, targeting all major muscle groups
   A. Frequency: three times a week
   B. Intensity: a resistance that can be overcome for 15 repetitions
   C. Duration: three sets of 8–10 repetitions

asymptomatic diabetic patients. Although the recently completed DIAD study mentioned above failed to show any morbidity or mortality benefit to routine screening of asymptomatic diabetic patients with myocardial perfusion imaging, there was a lower than expected event rate and therefore further investigation is still required. Newer imaging studies like CT angiography, cardiac magnetic resonance imaging, and coronary artery calcium scoring are also being studied to assist in the risk stratification of diabetic patients, although data on these techniques are more limited. Because currently there is not enough information available to support a specific evidence-based approach to identify potential significant cardiovascular disease, the general guidelines proposed by the ADA in a 2007 Consensus Statement are based on clinical judgment. Patients whom a clinician may judge to be most likely at risk for cardiovascular disease may include those with cerebrovascular or peripheral vascular disease, renal disease, autonomic neuropathy, an abnormal ECG, and traditional cardiovascular disease risk burden. The role, if any, for a cardiac CT to obtain a coronary artery calcium score is still controversial, and further research is needed to clarify the use of newer technologies in evaluating diabetic patients for cardiovascular risk and to identify the benefits, if any, of earlier intervention.[73]

Type of Exercise

Recommendations for the type, intensity, and duration of exercise depend on the risks for the individual patient and the desired benefit/outcome such as athletic training, improvements in insulin sensitivity, weight loss, and changes in body composition or enhancing muscle strength and flexibility.

The ADA recommends repetitive aerobic exercise involving large muscle groups that can be maintained for a prolonged period in patients with diabetes mellitus.[41] Examples of such exercise include brisk walking, jogging, swimming, rowing, dancing, cycling, and other endurance activities. The benefits of exercise for a given level of energy expenditure are not dependent on the mode of exercise. Hence, the type of aerobic activity should be determined by patient preference and risks based on complications of diabetes. For example, a patient with severe peripheral neuropathy would be wise to avoid jogging and instead consider exercises such as swimming or cycling.

In addition to aerobic exercise recent research has suggested the benefit of resistance training of a sufficient intensity to build and maintain muscle strength, endurance, and fat-free mass in healthy individuals.[74] In patients with diabetes, resistance training has been shown to improve insulin sensitivity in the absence of changes in

maximal oxygen uptake (VO_2max).[40,75,76] A number of recent randomized, controlled trials have consistently demonstrated a decrease in the HgA1c ranging from 0.5 to 1.2% with resistance training. Recent studies also indicate that resistance training is likely to potentiate the beneficial effects of aerobic exercise.[77] Well-designed resistance training programs with careful monitoring are safe[40,78] and light weights with high repetitions can be used to enhance upper body muscle strength in almost all patients including healthy older individuals. However, resistance exercise may not be advisable for some patients with long-standing diabetes and increased risk for ischemic heart disease and patients with diabetic nephropathy and proliferative retinopathy.

Frequency

Because much of the improvement in insulin sensitivity following a bout of exercise is transient, it is recommended that patients with diabetes engage in aerobic exercises at least every other day or 3–5 days each week. There should not be more than two consecutive days without physical activity. It is not yet clear if multiple shorter bouts of activity throughout the day will result in similar improvements in glucose control. The optimal training regimen to achieve glycemic and cardiovascular improvements will vary depending on a patient's baseline fitness, pre-existing risk factors, and desired goals of therapy. Several organizations including the AHA, American College of Sports Medicine (ACSM), and the ADA have advocated inclusion of both moderate to vigorous intensity aerobic exercises most days of the week and resistance training at least 2–3 times/week to a regular schedule of physical activity.

Intensity

The intensity of exercise is usually given to the patient in the form of a recommendation for a specific target heart rate during activity. Most of the studies that show metabolic benefit, i.e., improved glucose disposal and insulin sensitivity, are seen with an exercise intensity of 50–75% of an individual's VO_2max. Also, the AHA recommends engaging in activities that use between 700 and 2000 cal/week.[79] Lower intensity exercise (<50% VO_2max), which may be associated with improved patient adherence, may also have beneficial cardiorespiratory and circulatory effects, but beneficial effects on insulin sensitivity may not occur.[80,81] On the other hand, higher intensity exercise (>75% VO_2max) may be associated with increased cardiovascular risk, musculoskeletal injuries, and decreased patient adherence. While most programs emphasize exercises that improve fitness as demonstrated by an increased maximal oxygen uptake, recent studies suggest that regular participation in low to moderate intensity physical activity may reduce the risk of type 2 diabetes, hypertension, and coronary artery disease despite suboptimal effects on the VO_2max.[55,82,83]

Heart rate during exercise is linearly related to exercise intensity. If one knows the basal and maximal heart rate, it is possible to estimate a percent of VO_2max based on an individual's heart rate during a given activity. Most exercise prescriptions are given as a recommended exercise heart rate. Most patients can learn to measure their own heart rate and for those who cannot, inexpensive devices are available for use during exercise. The HR_{max} should ideally be determined during formal exercise testing. If the true HR_{max} is not known then one can estimate it from the following equation: $HR_{max} = 220 - \text{patient age (years)}$.

Fifty percentage of a maximum heart rate can be estimated by the following equation:

$$0.5(HR_{max} - HR_{rest}) + HR_{rest}$$

where HR_{rest} is the basal heart rate which is determined before arising in the morning. Another commonly used approach to prescribing exercise makes use of the rating of perceived exertion. This analog scale can be used by patients to estimate their relative workload with acceptable accuracy after some training. Resistance exercise programs emphasize what is called high volume resistance exercise. Patients perform a series of activities involving different muscle groups with a short rest period between each set. One approach is to determine a level

of resistance which can be performed 15 times without significant discomfort. The patient is then instructed to perform 8–12 repetitions of this activity two to three times with a brief rest period (less than 90 s) between each set. Resistance exercise of this intensity results in changes of pulse and blood pressure similar to the aerobic exercise recommended above and appears to be equally safe for most patients with diabetes.

To reduce the risk of musculoskeletal injuries and prepare the cardiorespiratory system and skeletal muscles for the progressive increase in exercise intensity, a warm up of 5–10 min is recommended. The warm-up period involves low intensity aerobic exercise such as walking. Stretching exercises (but not with breath holding) are quite useful in patients with diabetes who often complain of decreased flexibility. Stretching should be done following a brief aerobic warm up to avoid muscle injury. A cooldown period similar to the warm up should be done at the end of the exercise session. This usually involves 10 min of activity at an intensity of 30–40% of that done during the exercise session. This will help gradually reduce the heart rate down to the pre-exercise level and may reduce the risk of postexercise hypotension and arrhythmias.

Duration

Depending on the intensity of the exercise regimen, the duration of each session will vary in order to provide the optimal benefit. Exercise done at 40–60% VO_2max, 3–5 times per week, should last at least 20 min/session and cumulatively at least 150 min/week. In addition to, or instead of, this regimen a patient may perform at least 90 min/week of vigorous intensity exercise at >60% VO_2max. Approaches using two or more short exercise sessions of, for example, 10 min may be beneficial, but the effectiveness of this approach for improving metabolic control is still unclear.

Exercise and the Prevention of Type 2 Diabetes Mellitus

Decreased physical activity, independent of obesity, is a well-established risk factor for the development of type 2 diabetes in high-risk individuals. Insulin resistance and visceral adiposity play an important role in the development of impaired glucose tolerance and frank type 2 diabetes. Therefore, physical activity, by decreasing insulin resistance and visceral adiposity in these high-risk patients, is likely to be useful to prevent or delay the development of type 2 diabetes.

Individuals at high risk for the development of type 2 diabetes mellitus include those with a family history, members of high-risk ethnic groups such as Native Americans and individuals from the Indian subcontinent, a history of gestational diabetes,[84,85] patients with the polycystic ovary syndrome, and any individual with android-type obesity and the cluster of risk factors that make up the metabolic syndrome (see below). Various types of studies have supported the hypothesis that regular physical activity may prevent or substantially delay the onset of type 2 diabetes. These include cross-cultural, migrant, and other observational studies[86–88] and prospective studies in subjects at high risk for developing type 2 diabetes.[89–91] Recently, large interventional trials have reinforced the benefits of exercise in reducing the risk for type 2 diabetes. These include the Malmo study from Sweden,[48] the Da Quing study from China[92], and the Finnish Diabetes Prevention Study.[93] These prospective but not randomized studies show a reduction in the risk of type 2 diabetes of between 15 and 60% with similar benefits for older and younger individuals and for men and women.

The results of the Diabetes Prevention Program, a large randomized controlled trial in the United States, confirmed the benefit of exercise in the prevention or delay in onset of type 2 diabetes. Over 3000 nondiabetic patients at risk for developing diabetes underwent either intense lifestyle modification including 150 h of moderate intensity exercise with diet training and a goal of 7% weight loss, metformin treatment twice daily, or placebo. After an average 2.8-year follow-up, intense lifestyle modification reduced the incidence of diabetes by 58%, significantly greater than the 31% reduction by metformin therapy.[94] Significant improvements were also noted in insulin sensitivity, markers of inflammation (i.e., C-reactive protein), and coagulation. There is some concern regarding the sustainability of the intervention in light of the fact that only 58% continued to achieve

the goal activity level by the end of the study. In addition, some analyses suggest that the cost of implementing the program may be prohibitively high.[95]

Exercise and the Metabolic Syndrome

The metabolic syndrome is a constellation of metabolic abnormalities that predicts an increased risk for type 2 diabetes and/or cardiovascular disease. Current theories attempting to explain the underlying pathophysiology highlight a combination of insulin resistance, fat repartitioning, and a pro-inflammatory state. Although the specific criteria for the syndrome have been debated by several organizations such as the World Health Organization and the International Diabetes Foundation, the general components are similar. These include abdominal obesity, glucose intolerance (impaired fasting glucose, impaired glucose tolerance, or overt type 2 diabetes), dyslipidemia (both hypertriglyceridemia and low HDL cholesterol), and hypertension. As the role for regularly scheduled, moderate to severe intensity exercise has become more established for the treatment and prevention of diabetes, guidelines for the treatment of the metabolic syndrome also have come to include regular routines of moderate physical activity. The Look AHEAD study mentioned above will also have important ramifications for both the consequences and the treatment of the metabolic syndrome.[96]

Summary

Exercise has been shown to be a useful tool in the treatment of diabetes mellitus. Improvements of HgA1c levels of 1–2% are generally found in patients with type 2 diabetes mellitus undergoing a modest exercise program three to five times per week. In addition, exercise has beneficial effects on body composition and a variety of cardiovascular risk factors and is associated with a decreased risk of premature coronary artery disease. The benefits of exercise on glucose control are more difficult to attain in patients with type 1 diabetes, but beneficial effects on cardiovascular risk factors are likely to be valuable. Aerobic exercises of moderate intensity are generally recommended for patients with diabetes but high volume resistance exercises are also of benefit and should be included for appropriate patients. While the mechanisms remain incompletely understood it is clear that exercise on a regular basis acts through improved insulin sensitivity in liver and skeletal muscle as well as changes in body composition. The risks of initiating a moderate intensity exercise program for most patients with diabetes are minimal. Patients with neurologic and vascular complications of diabetes may need to limit certain activities. Patients treated with insulin and some oral agents are at risk of hypoglycemia related to exercise. These patients require special education and a regimen based on frequent home blood glucose monitoring. In addition to improving the clinical status of patients with established diabetes, exercise may play an even more important role in prevention of type 2 diabetes in high-risk populations. A safe and effective exercise program can be devised for the great majority of patients with diabetes mellitus and should be a part of every comprehensive treatment regimen.

Internet Resources

http://www.diabetes.org/diabetesphd/default.jsp
http://www.mayoclinic.com/health/diabetes/DA00123
http://www.dtu.ox.ac.uk/index.php?maindoc=/riskengine/
http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof

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