Physical Activity/Exercise and Type 2 Diabetes

RONALD J. SIGAL, MD, MPH[1,2,3]
GLEN P. KENNY, PHD[2,3]

DAVID H. WASSERMAN, PHD[4]
CARMEN CASTANEDA-SCEPPA, MD, PHD[5]

For decades, exercise has been considered a cornerstone of diabetes management, along with diet and medication. However, high-quality evidence on the importance of exercise and fitness in diabetes was lacking until recent years. The last American Diabetes Association (ADA) technical review of exercise and type 2 diabetes (formerly known as non–insulin dependent diabetes) was published in 1990. The present work emphasizes the advances that have occurred since the last technical review was published.

Major developments since the 1990 technical review include:

- Advances in basic science, increasing our understanding of the effects of exercise on glucoregulation.
- Large clinical trials demonstrating that lifestyle interventions (diet and exercise) reduce incidence of type 2 diabetes in people with impaired glucose tolerance (IGT).
- Meta-analyses of structured exercise interventions in type 2 diabetes showing: *1*) effectiveness of exercise in reducing HbA$_{1c}$, independent of body weight; and *2*) association between exercise training intensity and change in HbA$_{1c}$.
- Large cohort studies showing that low aerobic fitness and low physical activity level predict increased risk of overall and cardiovascular disease (CVD) mortality in people with diabetes.
- Clinical trials showing effectiveness of resistance training (such as weight lifting) for improving glycemic control in type 2 diabetes.
- New data on safety of resistance training in populations at high risk for CVD.

Based on this new evidence, we have refined the recommendations on the desired types, amounts, and intensities of aerobic physical activity for people with diabetes. Resistance training will now be recommended in a broader group of patients and at a broader range of intensity than done previously. There are other areas in which new evidence is lacking, but we feel that previous recommendations may have been more conservative than necessary. These areas include indications for exercise stress test before beginning an exercise program and precautions regarding exercise in the presence of some specific complications or suboptimal metabolic control. The levels of evidence used are defined by the ADA (see Ref. 1).

A new *Handbook of Exercise* was published in 2002 by the ADA, including 40 articles by leading experts on specific topics related to exercise and diabetes. Space limitations do not allow the present work to be comprehensive and, where appropriate, we refer the reader to chapters in the *Handbook of Exercise* and other review articles for additional details. The present review focuses on type 2 diabetes. Issues primarily germane to type 1 diabetes will be covered in a subsequent technical review.

Definitions

The following definitions are based on those outlined in "Physical Activity and Health," the 1996 report of the Surgeon General (2).

Physical activity. Bodily movement produced by the contraction of skeletal muscle that requires energy expenditure in excess of resting energy expenditure.

Exercise. A subset of physical activity: planned, structured, and repetitive bodily movement performed to improve or maintain one or more components of physical fitness. In the present review, the terms "physical activity" and "exercise" will be used interchangeably.

Physical fitness. This includes cardiorespiratory fitness, muscular fitness, and flexibility.

Cardiorespiratory fitness (also known as cardiorespiratory endurance or aerobic fitness). The ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity. The gold standard for measurement of cardiorespiratory fitness is a test of maximal oxygen uptake ($\dot{V}O_{2max}$), typically performed using indirect calorimetry on a treadmill or bicycle ergometer. Cardiorespiratory fitness can be estimated accurately using graded maximal exercise testing on standard treadmill or bicycle ergometer protocols without indirect calorimetry (3).

Aerobic exercise. This consists of rhythmic, repeated, and continuous movements of the same large muscle groups for at least 10 min at a time. Examples include walking, bicycling, jogging, continuous swimming, water aerobics, and many sports. When performed at sufficient intensity and frequency, this type of exercise increases cardiorespiratory fitness.

Intensity of aerobic exercise. This will be described as "moderate" when it is at 40–60% of $\dot{V}O_{2max}$ (~50–70% of maxi-

Figure 1—*Potential impact of impaired EGP on glucose homeostasis during exercise. If EGP is not coupled to the increase in glucose utilization, hypoglycemia may result.*

mum heart rate) and "vigorous" when it is at >60% of $\dot{V}_{O_{2max}}$ (>70% of maximum heart rate).

Muscular fitness. This refers to strength (the amount of force a muscle can exert) and muscular endurance (the ability of the muscle to continue to perform without fatigue).

Resistance exercise. Activities that use muscular strength to move a weight or work against a resistive load. Examples include weight lifting and exercises using weight machines. When performed with regularity and moderate to high intensity, resistance exercise increases muscular fitness.

Intensity of resistance exercise. This will be described as "high" if the resistance is ≥75% of the maximum that can be lifted a single time (≥75% of 1-RM [repetition maximum]) and "moderate" if resistance is 50–74% of 1-RM.

Flexibility. This term refers to the range of motion available at joints.

Flexibility exercise. This is exercise (typically stretching) aimed at increasing or maintaining range of motion at joints.

MET (metabolic equivalent). A MET is a unit of intensity equal to energy expenditure at rest. Physical activity at 3 METs uses three times as much energy as stationary sitting. MET-hours are units of exercise volume in which intensity in METs is multiplied by duration of the activity in hours.

PHYSIOLOGY OF FUEL METABOLISM DURING EXERCISE

For more detailed reviews of the physiology and basic science of exercise, see Refs. 4–6.

Exercise results in a shift in fuel usage by the working muscle from primarily nonesterified fatty acids (NEFAs) to a blend of NEFAs, glucose, and muscle glycogen. Muscle glycogen is the chief source of energy during the early stages of strenuous exercise, while with increasing exercise duration the contribution of circulating glucose and particularly NEFAs become more important as muscle glycogen gradually depletes. The origin of circulating glucose also shifts from hepatic glycogenolysis to gluconeogenesis. With increasing exercise intensity the balance of substrate usage shifts to greater carbohydrate oxidation. Although the metabolic response to exercise is influenced by numerous factors (e.g., nutrition, age, type of exercise, and physical condition), the most important factors affecting fuel utilization are generally work intensity and duration.

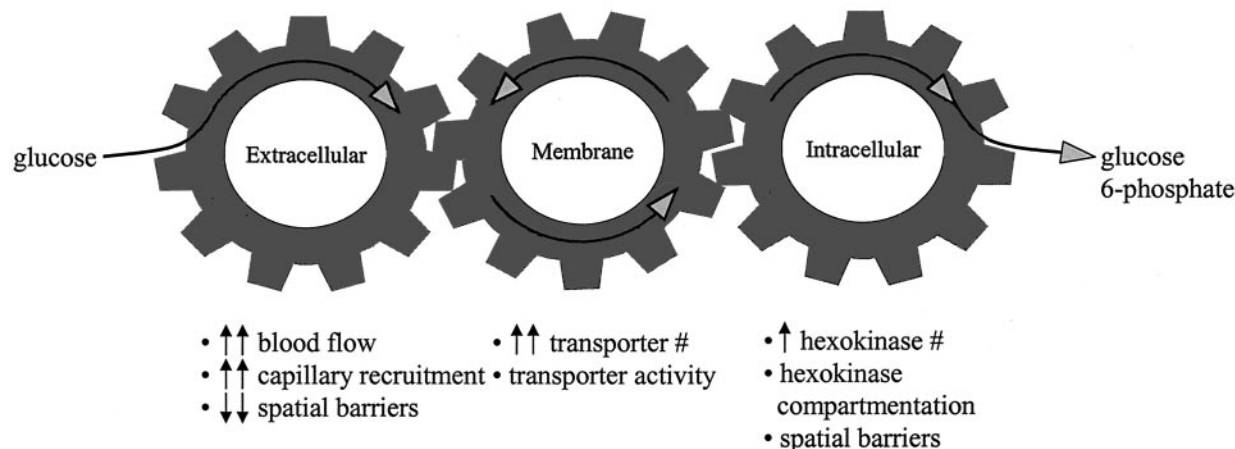### Regulation of fuel mobilization during aerobic exercise

Fuel mobilization is controlled during aerobic exercise largely by the neuroendocrine system. If exercise is sustained, a decrease in insulin secretion and in-

creases in glucagon, catecholamines, cortisol secretion, and other hormones are observed. Postulated signals causing these hormonal and neural changes may be related to deficits in fuel availability, neural feed-forward mechanisms, or increased afferent nerve activity from the working limb, splanchnic bed, or carotid sinus (7,8). In addition to neuroendocrine factors, other parameters such as blood-flow shifts and subtle changes in glycemia or metabolic state play a role in the control of fuel metabolism during exercise.

Endogenous glucose production. Endogenous glucose production (EGP) is closely coupled to the increase in muscle glucose uptake during moderate exercise. Studies conducted in animal models and human subjects have defined the importance of insulin and glucagon in the stimulation of EGP during light- and moderate-intensity aerobic exercise (7). The exercise-induced increment in glucagon stimulates glycogenolysis and gluconeogenesis (7). Glucagon also stimulates hepatic amino acid metabolism (9) and fat oxidation (7), providing precursors for gluconeogenesis and energy to fuel it. The decrease in insulin during exercise is necessary for the full glycogenolytic response (7). When the decline in portal vein insulin is eliminated, the increase in EGP is reduced by ~50%. The importance of the exercise-induced increase in EGP to whole-body glucose homeostasis is illustrated in Fig. 1. If the liver did not release more glucose in response to exercise, hypoglycemia would result.

In contrast, in very intense aerobic exercise (>80% of $\dot{V}_{O_{2max}}$), the catecholamines likely play a more important role. In this situation, norepinephrine and epinephrine levels rise as much as 15-fold from baseline, and glucose production in young fit subjects rises about 7-fold during exercise (10–12). In intense exercise under islet cell clamp, where the glucagon-to-insulin ratio does not rise, glucose production increases as much as it does without islet cell clamp (12). Infusion of norepinephrine (13), epinephrine (14), or both (15) during moderate exercise induces glucose production similar to that characteristic of intense exercise. Studies of intense exercise during β-adrenergic blockade with propranolol in normal (11) and type 1 diabetic (16) subjects found that glucose production during exercise

Control of Glucose Uptake by the Working Muscle

- ↑↑ blood flow
- ↑↑ capillary recruitment
- ↓↓ spatial barriers

- ↑↑ transporter #
- transporter activity

- ↑ hexokinase #
- hexokinase compartmentation
- spatial barriers

Figure 2—*Schematic representation of the control of muscle glucose uptake during exercise. Control of glucose is distributed between three serial steps. These are extracellular glucose delivery from blood to muscle membrane, muscle membrane glucose transport, and intracellular glucose phosphorylation. Below each gear are known mechanisms of regulation. Arrows associated with those mechanisms reflect exercise adaptations. Note that acute exercise increases hexokinase II protein; however, this adaptation is slow in onset. Modified from Wasserman and Halseth (47).*

was greater than that in subjects exercising without β-blockade. Conversely, another study (17) found that subjects performing intense exercise during α-adrenergic blockade with phentolamine had slightly less glucose production than subjects exercising at similar intensity without adrenergic blockade. No study has used combined β- and α-adrenergic blockade during very intense exercise. These studies are difficult to interpret due to the lack of specificity of these pharmacological blockers. A method was developed in the dog that uses intraportal propranolol and phentolamine infusion to selectively block hepatic adrenergic receptors (18). Results obtained in this model were consistent with those using systemic adrenergic blockade, showing that EGP was not reliant on hepatic adrenergic receptor stimulation during heavy exercise (18). In normal subjects, plasma insulin doubles soon after the end of a very intense exercise session, restoring glycemia to baseline within an hour (10). In contrast, in type 1 diabetes, in which endogenous insulin cannot increase, hyperglycemia after very intense exercise lasts at least several hours (19,20).

Type 2 diabetic patients with a mild to moderate elevation in glucose levels may experience a fall in glucose during exercise due to impaired endogenous glucose output. This population, when maintained on diet therapy alone or diet and sulfonylurea therapy with postabsorptive plasma glucose in excess of 200 mg/dl and normal basal insulin, shows a fall in glycemia of ~50 mg/dl during a 45-min exercise bout (21). High-intensity intermittent exercise performed in postprandial type 2 diabetic subjects (22) has the same plasma glucose– and insulin-lowering effect as moderate-intensity exercise of equivalent caloric requirement (22).

Fat metabolism. Moderate exercise is associated with an ~10-fold increase in fat oxidation. This is due to increased energy expenditure coupled with greater fatty acid availability. The increase in fatty acid availability is due both to an increase in lipolysis and decreased re-esterification of NEFA to triglycerides (23). Acute NEFA release from adipose tissue is regulated primarily by the actions of insulin and the catecholamines. When the exercise-induced fall in insulin is prevented, the increase in NEFA levels is prevented (7). NEFA levels are diminished during exercise by β-blockade, presumably due to a suppression of lipolytic activity. Not only are catecholamines increased by exercise, but adipocytes taken following exercise have increased lipolytic responsiveness to β-adrenergic actions of the catecholamines (24). Besides fat mobilization from adipocytes, there is evidence (25,26) that intramuscular triglycerides represent an important fuel for working muscle. Metabolism of fats during exercise is quantitatively different in obese type 2 diabetic subjects in relation to healthy subjects. In this population, utilization of plasma free fatty acids is reduced, while intramuscular triglyceride utilization is increased (27). Interestingly, lean type 2 diabetic individuals do not have this adaptation to exercise (28).

Muscle glycogenolysis. Glycogen breakdown is regulated by glycogen phosphorylase. It is interesting that although muscle glycogenolysis increases with increasing work rate, phosphorylase transformation to its active phosphorylated form is not (29). This suggests that allosteric regulators may be important activators of glycogen phosphorylase during exercise (30). β-Adrenergic receptor stimulation by catecholamines plays a major role in the mobilization of muscle glycogen during exercise (7).

Exercise-induced muscle glucose uptake

Muscle glucose uptake requires three serial steps (Fig. 2). These are the delivery of glucose from the blood to the muscle, transport of glucose across the muscle membrane, and phosphorylation of glucose within the muscle. The effect of exercise on these specific steps that comprise muscle glucose uptake is discussed below and illustrated in Fig. 1.

Glucose delivery from blood to muscle. Muscle interstitial glucose would fall precipitously and the glucose transport gra-

dient would be insufficient to sustain glucose uptake if it were not for the marked increase in blood flow to working muscle. The exercise-induced increase in glucose delivery is so effective at maintaining interstitial glucose that an increase in muscle fractional glucose extraction is not required for the increase in muscle glucose uptake (31). The importance of glucose supply is supported by the close correlation of muscle blood flow to glucose uptake by the working limb (32). In addition, an increase in perfusion of the isolated rat hindlimb is necessary for full contraction-induced glucose uptake (33).

Membrane glucose transport. Exercise increases glucose transport by stimulating GLUT4 translocation to the muscle cell surface (34). A possible mechanism involves sensing of an increase in muscle AMP, which stimulates AMP kinase, causing a number of metabolic changes, including increased glucose transport (35). Muscle AMP kinase measurements are, in fact, consistent with stimulation by exercise (36,37). Such a role for this enzyme is supported by the demonstration that pharmacological activation of AMP kinase stimulates GLUT4 translocation (38) and glucose uptake (36,39,40) and is linked to other changes in enzyme activities (35,41) and gene transcription (42,43) associated with exercise. AMP kinase activation is not the sole mechanism of contraction-stimulated muscle glucose uptake (40). In addition to AMP kinase activation, data suggest that nitric oxide (NO) may mediate contraction-induced glucose uptake. Electrical stimulation increases muscle NO synthesis, and pharmacologic inhibition of NO synthesis decreases uptake of a glucose analog (44). Another study (45) showed that NO synthase inhibition at the working leg caused a reduction in leg glucose uptake without affecting blood flow. NO synthase has also been implicated as a mediator of AMP kinase–induced glucose uptake (46).

Muscle glucose phosphorylation. The first step in glucose metabolism is phosphorylation by a hexokinase. There is evidence that glucose phosphorylation is the primary limitation to glucose uptake during exercise (47). Hexokinase II overexpression improves the ability to consume glucose in mice, and reducing the glucose 6-phosphate pool by a glycogen-depleting fast enhances uptake of glucose even further (48). In contrast to the extensive work on glucose transport, very little

is known regarding the effects of exercise on hexokinases. The percentage of hexokinase activity associated with mitochondria, where its specific activity is greater, does not appear to be increased with exercise in human muscle (49,50). Exercise has been shown to stimulate muscle hexokinase II gene transcription (51), leading to an increase in its protein (50). The increase in hexokinase activity lags behind the increase in hexokinase II mRNA (51) and may be more significant to the persistent increase in insulin action following exercise or adaptations that occur with training.

Insulin-independent and insulin-sensitive muscle glucose uptake during exercise

The preceding section described the steps required for muscle glucose uptake. The flux through these steps is controlled by insulin-independent signals generated within working muscle, but can be greatly modified by actions of circulating insulin. Exercise increases both insulin-independent muscle glucose uptake and insulin sensitivity. The focus below is on these two important characteristics of exercise.

Insulin-independent glucose uptake. The cell signaling pathway of contraction-stimulated glucose transport is distinct from that for insulin-stimulated glucose transport (52,53). Although the increase in membrane transporters in response to both insulin and exercise result from an increase in GLUT4 translocation, these stimuli recruit GLUT4 from different intracellular pools (54). Evidence that cell signaling for glucose uptake is different for exercise and insulin is supported by the demonstration that muscle contraction does not increase phosphorylation of insulin receptor substrate (IRS)-1 and -2 or phosphatidylinositol I (PI) 3-kinase (55), all of which are involved in insulin signaling. In addition, wortmannin, an inhibitor of PI 3-kinase, eliminates insulin-stimulated glucose uptake but not glucose transport in isolated contracting muscle (34). The importance of insulin-independent mechanisms in control of exercise-stimulated muscle glucose uptake is further exemplified by studies in type 2 diabetic individuals. Although type 2 diabetic individuals are usually insulin resistant, they are not resistant to the stimulatory effects of exercise on glucose utilization. Type 2 diabetic subjects retain

the capacity to translocate GLUT4 to the sarcolemma in response to exercise (56). The functional recruitment of GLUT4 transporters coupled to elevated circulating glucose levels can actually lead to a greater rate of glucose utilization by muscle of people with type 2 diabetes.

Insulin-dependent glucose uptake (insulin sensitivity). Exercise and insulin stimulate glucose utilization synergistically (7). The primary route of insulin-mediated glucose metabolism at rest and in the postexercise state is nonoxidative metabolism (7). Exercise, however, shifts the route of insulin-stimulated glucose disposal so that all glucose consumed by muscle is oxidized (7). The effects of this increase in insulin action are probably most important in the postprandial state and in the intensively treated diabetic state, when insulin levels are higher than those that normally accompany exercise. Several mechanisms have been proposed to explain how exercise enhances insulin action (6,57,58). Hemodynamic adjustments increase capillary surface area in working muscle, increasing the availability of insulin. Exercise may also increase insulin-stimulated glucose utilization by a mechanism secondary to insulin's suppressive effect on non-NEFAs. Insulin action is also directly enhanced at working muscle by activation of postinsulin receptor signaling (32).

Carbohydrate ingestion and exercise

Glucose feeding has been shown (7) to improve exercise endurance. The underlying mechanism for this improvement is probably related to increased glucose availability to working muscle. The amount, form, and timing of an oral carbohydrate load, along with the duration and intensity of exercise, will determine how effective glucose ingestion is at sustaining glucose availability to the working muscle.

Carbohydrate ingestion slows the mobilization of endogenous fuels during prolonged exercise. It also slows the rate of fall of circulating glucose that would otherwise occur or leads to an overt increase in circulating glucose (7). At least two important endocrine changes accompany the increase in glucose availability. The exercise-induced fall in insulin and rise in glucagon are attenuated or eliminated altogether. The absence of the fall in insulin attenuates the increases in lipolysis and EGP, whereas a reduction in glu-

cagon will reduce the latter (7). Although insulin acts to suppress glycogen breakdown, multiple signals are present in working muscle, and glycogen is generally not spared by carbohydrate ingestion (59).

The metabolic availability of ingested carbohydrate depends on the composition and quantity of the substrate load. In addition, exercise parameters (i.e., work intensity, duration, and modality) also determine the availability of ingested glucose. As a consequence, it is difficult to ascribe an exact metabolic efficiency of ingested glucose. In any case, a reasonable estimate might be that ~40% of a 50-g glucose load, ingested at the start of moderate exercise, is metabolized during the first hour (60). There is probably little difficulty in delivering adequate amounts of ingested glucose to the muscle during light exercise. Because glucose oxidation by muscle increases at higher work rates, it may no longer be possible to absorb adequate amounts of ingested glucose. As a consequence, limitations to the oxidation of ingested glucose may shift at different work intensities: low muscle demand limits glucose oxidation at light work rates, whereas absorption from the gastrointestinal tract limits it at high work rates (61). In humans, the maximum absorption rate of carbohydrate in the gut during exercise is about 1 g/min (62).

Postexercise glucose metabolism

Exercise leads to diverse adaptations that have significant impact on glucoregulation, even after the cessation of exercise. These adaptations largely share the common purpose of replenishing fuel stores, particularly muscle and liver glycogen.

Muscle. Stimulation of muscle glucose uptake persists well after exercise. The added glucose taken up after exercise is channeled into glycogen (32). Glycogen repletion is characterized by a marked and persistent increase in insulin action (32). This increase in insulin action occurs without increasing the tyrosine phosphorylation of the insulin receptor, IRS-1, IRS-2, and shc (63,64). Moreover, PI 3-kinase activity is not increased (65). The presence of the muscle insulin receptor may not even be necessary for the increased effects of insulin on muscle glucose uptake and glycogen synthase after exercise (66). This implies that the effects of prior exercise are mediated by

nonmuscle cells or by downstream signaling (66). It has also been proposed that a postreceptor modification may be linked to the glycogen depleting effect of exercise. However, the improved effect of insulin on glucose uptake can persist after exercise, even when pre-exercise glycogen levels have been restored (32). The cellular basis for the persistent increase in insulin sensitivity may, at least in part, relate to increases in skeletal muscle GLUT4 (67), glycogenin (68), and hexokinase II (51) during exercise recovery. It is noteworthy that AMP kinase activation leads to a subsequent increase in insulin sensitivity, much like exercise (69).

Muscle contraction activates a number of signaling pathways, in addition to those involved with glucose transport, in a manner that is influenced by the intensity and duration of work (70,71). These include the activation of the mitogen-activated protein (MAP) kinase (64,72), Akt (71), and p70^{s6k} (70) pathways. Contraction inhibits the glycogen synthase kinase-3 pathway, at least in rodent muscle (73), promoting glycogen synthesis. It is likely that the activation of some of these signaling cascades are important to the persistent adaptations to exercise and not the acute metabolic response. Activation of MAP kinase, Akt, p70^{s6k}, and AMP kinase pathways and deactivation of the glycogen synthase kinase-3 pathway all are capable of stimulating gene transcription or protein synthesis (53).

Liver. It was recently shown (74) that prior exercise increases the capacity of the liver to consume glucose. These data are consistent with studies (75) using ^{13}C magnetic resonance spectroscopy that showed that ingestion of glucose immediately after prolonged exercise increased liver glycogen resynthesis. The liver, like muscle, is more insulin sensitive after exercise (76). Also like muscle, a greater fraction of glucose taken up by the liver after exercise is nonoxidatively metabolized (77).

Metabolic adaptations to regular physical activity

Adaptations to chronic exercise depend on the exercise parameters (intensity, duration, frequency, and mode) and the characteristics of the individual (presence of disease, fitness, and genetic determinants). Endurance and resistance exercise lead to biochemical adaptations specific

to the training regimen. Adaptations to endurance exercise enable the muscle to use O_2 and blood-borne fuels, whereas those for resistance exercise lead to improved force generation (e.g., hypertrophy, contractile properties). Of specific interest to people with diabetes are those adaptations that directly affect the metabolism of glucose.

The adaptation of the pancreatic β-cell to exercise training has been the most widely assessed of the endocrine organs. Basal and glucose-stimulated insulin levels are both reduced in response to regular exercise due to reduced secretion (7). Training results in decreases in the mRNA for proinsulin and glucokinase in the pancreas (78). This suggests that there are at least two potential cellular mechanisms for decreased insulin secretion. First, the reduction in proinsulin mRNA suggests that the synthesis of insulin is reduced. Second, because glucokinase is necessary for glucose sensing in the pancreas, the reduction in glucokinase mRNA may explain the decreased sensitivity of the β-cell to glucose.

Exercise training, whether endurance (79) or resistance (80), leads to increased muscle GLUT4. This increase in GLUT4 probably contributes to the increased capacity for insulin-stimulated glucose transport in trained subjects. This, of course, has important therapeutic implications for people with insulin resistance. Exercise training has been shown to stimulate insulin-stimulated PI 3-kinase in muscle (81–83). There is evidence that this increase is due to IRS-1–associated PI 3-kinase activity (81,83). Because PI 3-kinase is an important step in the recruitment of GLUT4 by insulin to the muscle cell surface, it is reasonable to postulate that this is one site at which regular physical activity may affect insulin signaling. Regular physical activity leads to an increase in basal and insulin-stimulated MAP kinase pathway activity (84). Although an increase in the activity of this signaling pathway is not thought to be necessary for the exercise-induced increase in insulin-stimulated glucose uptake, it may be associated with other adaptive changes in muscle. The mechanisms through which aerobic and resistance exercise increase glucose disposal are similar (85). Although resistance exercise has greater propensity than aerobic exercise to increase muscle mass and thereby glucose storage space (5), this is

only one of many factors explaining its effects on glucose disposal (85).

Trained subjects have an increased ability to mobilize and store NEFAs (86). The increased ability to mobilize NEFAs occurs at least in part due to increased adipocyte catecholamine sensitivity and is mediated by an increased formation and/or improved effectiveness of cAMP (87). Training increases the capacity of muscle to extract NEFAs from the blood and oxidize them (7). The mechanism for this adaptation may pertain to the enhanced capacity of trained muscle to oxidize fat (88,89) or to increased number or function of muscle fatty acid transport or binding proteins (89,90). It has been hypothesized that an excess accumulation of intramuscular lipid is associated with insulin resistance. This concept is inconsistent with results from exercise-trained subjects. Compared with sedentary control subjects, athletes with high aerobic fitness have increased intramuscular lipids, but are more insulin sensitive, not less (91).

EVALUATION OF THE DIABETIC PATIENT BEFORE RECOMMENDING AN EXERCISE PROGRAM

For a more detailed review on this subject, see Ref. 92.

Before beginning a program of physical activity more vigorous than brisk walking, people with diabetes should be assessed for conditions that might contraindicate certain types of exercise or predispose to injury (e.g., severe autonomic neuropathy, severe peripheral neuropathy, or preproliferative or proliferative retinopathy), which require treatment before beginning vigorous exercise, or that may be associated with increased likelihood of CVD. The patient's age and previous physical activity level should be considered.

One potential area of controversy is the circumstances under which a graded exercise electrocardiogram (ECG) stress test should be considered medically indicated. We unfortunately did not find any randomized trials or large cohort studies evaluating the utility of exercise stress testing specifically in people with diabetes; the lack of such studies is an important gap in the literature. Previous ADA guidelines (93) have suggested that before beginning a vigorous or moderate exercise program, an exercise ECG stress test should be done in all diabetic individuals

aged >35 years and in all individuals aged >25 years in the presence of even one additional CVD risk factor (diabetes duration >10 years for type 2 diabetes or >15 years for type 1 diabetes, hypertension, dyslipidemia, smoking, proliferative retinopathy, nephropathy including microalbuminuria, peripheral vascular disease, or autonomic neuropathy). If this previous recommendation were followed strictly, the great majority of people with diabetes, including a large number of younger individuals with very low absolute risk of CVD, would require formal exercise stress testing before beginning even a moderate-intensity exercise program. The costs of such widespread stress testing might be prohibitive (92). The prevalence of both symptomatic and asymptomatic coronary artery disease (CAD) is higher in both type 1 and type 2 diabetic individuals compared with nondiabetic individuals of the same age-group. However, many younger diabetic patients have relatively low absolute risk for a coronary event. For example, a 38-year-old Caucasian nonsmoking man with diabetes for 5 years, HbA$_{1c}$ 7.5%, systolic blood pressure 130 mmHg, total cholesterol 5.2 mmol/l, and HDL cholesterol 1.1 mmol/l would have a 10-year CAD risk of only 7.3% or ~0.7% per year, calculated using the U.K. Prospective Diabetes Study (UKPDS) Risk Engine (94) (www.dtu.ox.ac.uk/riskengine/download.htm). The lower the absolute CAD risk, the higher the likelihood of a false-positive test. A recent systematic review for the U.S. Preventive Services Task Force came to the conclusion that stress tests should usually not be recommended to detect ischemia in asymptomatic individuals at low CAD risk (<10% risk of a cardiac event over 10 years) because the risks of subsequent invasive testing triggered by false-positive tests outweighed the expected benefits from the detection of previously unsuspected ischemia (95,96).

There is, however, some value to performing a maximal aerobic exercise test in a broader range of individuals. In addition to screening for exercise-induced ischemia, a maximal exercise test can provide useful information regarding maximal heart rate and blood pressure responses to different exercise levels, initial performance status, and prognosis, and therefore is potentially of some benefit to any individual, diabetic or otherwise. With-

out a maximal exercise test, one cannot know a given individual's maximum heart rate or the heart rate associated with a given percentage of the maximum. Use of the Borg scale (Rating of Perceived Exertion [97]), with target perceived intensities of "moderate," "somewhat hard," or "hard," is sometimes recommended as a possible alternative to heart rate–based targets based on maximal exercise testing. A large long-term cohort study found that exercising habitually at perceived intensity of "moderate," "somewhat strong," "strong," or more intense than "strong" were associated with adjusted relative risks for coronary heart disease of 0.86, 0.69, and 0.72, respectively, compared with exercising at perceived intensity of "weak" or less intense (98). However, there is a great deal of variability among individuals in terms of the perceived exertion associated with performing the same exercise at the same objectively defined exercise intensities (99). Likewise, the same individuals often have different ratings of perceived exertion when performing different exercises at the same intensities (e.g., running or bicycling at the same percentage of heart rate reserve) and even at equivalent stages of different treadmill protocols (Bruce versus Balke) (100).

Therefore, available clinical evidence does not support any specific definitive recommendations regarding which individuals should undergo stress testing. Potential benefits must be weighed against risks and costs. Our recommendations should be considered in this context.

A stress test is most useful in terms of positive predictive value for coronary ischemia when the probability of CAD is at least moderate. When the probability of CAD is low (e.g., <10% over 10 years), the number of false-positive tests is likely to be substantially greater than the number of true-positive tests.

Therefore, we propose the following revised criteria for deciding when a stress test is indicated for detection of ischemia. These criteria would encompass virtually all people with diabetes with a 10-year CAD risk of at least 10% (1% per year).

Recommendations: indications for graded exercise test with ECG monitoring

In the absence of contraindications (101,102), maximal exercise testing could be considered in all diabetic indi-

viduals in order to assess maximal heart rate, set exercise intensity targets, and assess functional capacity and prognosis. A graded exercise test with ECG monitoring should be seriously considered before undertaking aerobic physical activity with an intensity exceeding the demands of everyday living (more intense than brisk walking) in previously sedentary diabetic individuals whose 10-year risk of a coronary event is ≥10%. This risk could be estimated directly using the UKPDS Risk Engine (www.dtu.ox.ac.uk/riskengine/download.htm) (94) and would correspond approximately to meeting any of the following criteria:

- Age >40 years, with or without CVD risk factors other than diabetes
- Age >30 years and
  - Type 1 or type 2 diabetes of >10 years' duration
  - Hypertension
  - Cigarette smoking
  - Dyslipidemia
  - Proliferative or preproliferative retinopathy
  - Nephropathy, including microalbuminuria
- Any of the following, regardless of age
  - Known or suspected CAD, cerebrovascular disease, and/or peripheral vascular disease
  - Autonomic neuropathy
  - Advanced nephropathy with renal failure

The above should not be construed as a recommendation against stress testing for individuals without the above risk factors or for those who are planning less-intense exercise.

Level of evidence: E.

PHYSICAL ACTIVITY AND PREVENTION OF TYPE 2 DIABETES

Recent clinical trials, and a number of large cohort studies, provide strong evidence for the value of physical activity in reducing the incidence of type 2 diabetes. The Da Qing IGT and Diabetes Study (103) was the first randomized trial evaluating lifestyle interventions for the prevention of type 2 diabetes. In this study, 577 people with IGT from 33 clinics were randomized, by clinic, to diet only, exercise only, diet plus exercise, or control. After 6 years of follow-up, cumulative in-

cidence of type 2 diabetes was 68% in control, 44% in diet only, 41% in exercise only, and 46% in diet plus exercise groups. This study provides evidence that both diet and exercise can be effective diabetes prevention modalities, although their effects were not additive. The Da Qing study's subjects were far leaner (mean BMI ~23 kg/m^2) than most people with IGT in the western world.

More compelling evidence for the effectiveness of lifestyle interventions comes from two randomized controlled trials: the Finnish Diabetes Prevention Study (104,105) and the U.S. Diabetes Prevention Program (DPP) (106,107). In the Finnish Diabetes Prevention Study (104,105), 522 overweight subjects, aged 40–65 years, with IGT were randomly assigned to a lifestyle intervention or control group. The goals were to reduce weight by at least 5%; perform moderate-intensity exercise at least 30 min/day; limit total and saturated fat intake to <30 and <10%, respectively, of energy consumed; and increase fiber intake to ≥15 g/1,000 kcal. Intervention group subjects had 1-h meetings with a dietitian seven times in the first year and every 3 months subsequently. Subjects in the intervention group were also offered an individualized exercise plan, thrice-weekly supervised facility-based aerobic and resistance exercise for 6–12 months free of charge, but the proportion of subjects participating in this facility-based training was not stated in the publications. The cumulative incidence of type 2 diabetes was 11% in the intervention group and 23% in the control group. In the DPP (106,107), 3,234 individuals with IGT aged ≥25 years were randomly allocated to intensive lifestyle intervention, metformin, or placebo. (A fourth arm, troglitazone, was terminated early when troglitazone was withdrawn from the market.) Subjects in the intensive lifestyle group followed an individually supervised program aimed at achieving and maintaining a ≥7% weight loss through a low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for ≥150 min/week. A 16-lesson curriculum was taught by case managers one-on-one during the first 24 weeks, and individual and group sessions occurred at least monthly for the remainder of the program. After a mean of 2.8 years of follow-up, the incidence of diabetes was 11.0, 7.8, and 4.8 cases/100

person-years in the placebo, metformin, and lifestyle groups, respectively. Relative risk reductions in the Finnish Diabetes Prevention Study and the DPP were identical at 58% with lifestyle interventions compared with usual care or placebo. The DPP was notable because it included a large, racially and socioeconomically diverse sample.

In the Malmo study (108,109), a nonrandomized trial, 161 people with IGT who participated in a diet-and-exercise intervention were compared after 6 years with 56 individuals with IGT who were offered the same intervention and declined. The cumulative 6-year incidence of type 2 diabetes was 11% in the intervention group and 21% in the control group (108). After 12 years of follow-up in the Malmo study, overall mortality among IGT subjects was 6.5 per 1,000 person-years in the lifestyle intervention group, less than one-half of the 14.0 per 1,000 person-years in the IGT/no lifestyle intervention (109). Large cohort studies (110–118) have consistently found that higher levels of physical activity and/or cardiorespiratory fitness were associated with reduced risk of developing type 2 diabetes. This was true in most studies, regardless of the presence or absence of additional risk factors for diabetes such as hypertension, parental history of diabetes, and obesity. Comparable magnitudes of risk reduction were seen with walking compared with more vigorous activity when total energy expenditures are similar (114).

Therefore, there is firm and consistent evidence that programs of increased physical activity and modest weight loss reduce the incidence of type 2 diabetes in individuals with IGT. The two strongest studies, the Finnish Diabetes Prevention Study (104) and the U.S. DPP (106), do not permit one to determine the relative importance of physical activity versus diet.

Recommendations: lifestyle measures for prevention of type 2 diabetes

In people with IGT, a program of weight control is recommended, including at least 150 min/week of moderate to vigorous physical activity and a healthful diet with modest energy restriction.

Level of evidence: A (104–107).

AEROBIC FITNESS AND AEROBIC EXERCISE IN TYPE 2 DIABETES

Effects of structured exercise interventions on glycemic control and body weight in type 2 diabetes

For details of the individual aerobic exercise clinical trials, see Ref. 119.

Most clinical trials on the effects of physical activity interventions in type 2 diabetes have had small sample sizes and therefore inadequate statistical power to determine the effects of exercise on glycemic control and body weight. Boulé et al. (119) undertook a systematic review and meta-analysis on the effects of structured exercise interventions in clinical trials of duration ≥ 8 weeks on HbA_{1c} and body mass in people with type 2 diabetes. Twelve aerobic training studies and two resistance training studies were included (totaling 504 subjects), and the results were pooled using standard meta-analytic statistical methods. The exercise and control groups did not differ at baseline in HbA_{1c} or body weight. Postintervention HbA_{1c} was significantly lower in exercise than control groups (7.65 vs. 8.31%, weighted mean difference -0.66%; $P < 0.001$). In contrast, postintervention body weight did not differ between exercise and control groups. Meta-regression confirmed that the beneficial effect of exercise on HbA_{1c} was independent of any effect on body weight. Therefore, structured exercise programs had a statistically and clinically significant beneficial effect on glycemic control, and this effect was not mediated primarily by weight loss.

Although the significant effect of exercise on HbA_{1c} in these studies is encouraging, the lack of overall effect of exercise on body weight in these studies is disappointing but not surprising. The exercise volumes and program durations (mean 53 min/session, mean 3.4 sessions/week, mean duration 15 weeks) may have been insufficient to achieve the energy deficit necessary for major weight loss. Most of these studies did not examine body composition, and loss of fat might have been partially offset by increased lean body mass (119a).

Boulé et al. (120) later undertook a meta-analysis of the interrelationships among exercise intensity, exercise volume, change in cardiorespiratory fitness, and change in HbA_{1c}. This analysis was restricted to aerobic exercise studies in which $\dot{V}O_{2max}$ was either directly measured or estimated from a maximal exercise test using a validated equation. Exercise intensities during training ranged from $\sim 50\%$ of $\dot{V}O_{2max}$ to $>75\%$ of $\dot{V}O_{2max}$, exercise volume 8.75–24.75 MET-hours/week. Meta-analysis revealed a clinically significant 11.8% increase in $\dot{V}O_{2max}$ in exercising groups, compared with a 1% decrease in control groups. Exercise intensity predicted postintervention weighted mean difference in HbA_{1c} ($r = -0.91$, $P = 0.002$) to a larger extent than exercise volume ($r = -0.46$, $P = 0.26$).

Consistent with the above, the greatest effect of exercise on HbA_{1c} (mean absolute postintervention HbA_{1c} difference of 1.5% between exercise and control groups) was seen in the single study with the highest exercise intensity (121). In this study, subjects exercised at 75% of $\dot{V}O_{2max}$, with intervals at even higher intensity, for 55 min three times a week, including 5 min of warm-up and 5 min of cool down. $\dot{V}O_{2max}$ increased 41% in the exercising subjects versus 1% in control subjects. Abdominal visceral fat assessed by magnetic resonance imaging was reported to decline by 48% and abdominal subcutaneous fat by 18% in the exercising group in this study, which are much larger fat losses than seen in most exercise studies and surprising in light of the relatively moderate total energy expenditure on exercise.

This meta-analysis provides support for higher-intensity aerobic exercise in people with type 2 diabetes as a means of improving HbA_{1c}. The analysis, however, is limited by the fact that only one study (121) featured an unequivocally high-intensity exercise program at 75% of $\dot{V}O_{2max}$. This intensity might be difficult to sustain or even hazardous for many previously sedentary people with type 2 diabetes. Nevertheless, there was a strong dose-response relationship between exercise intensity across studies and both cardiorespiratory fitness and HbA_{1c} change. These results would provide support for encouraging type 2 diabetic individuals who are already exercising at moderate intensity to consider increasing the intensity of their exercise to obtain additional benefits in both aerobic fitness and glycemic control.

Physical activity, aerobic fitness, and risk of cardiovascular and overall mortality

The effects of exercise on glycemic control, while statistically and clinically significant, might be perceived as modest in relation to the time and effort involved. After all, a similar degree of glucose lowering could be achieved in many cases by adding a single oral hypoglycemic medication. The effects of aerobic exercise on lipids and blood pressure are also relatively modest. However, large cohort studies have found that higher levels of habitual aerobic fitness and/or physical activity are associated with significantly lower subsequent cardiovascular and overall mortality, to a much greater extent than could be explained by glucose lowering alone.

Wei et al. (122) reported on 1,263 type 2 diabetic men, a subsample of >20,000 men in the Aerobics Center Longitudinal Study who underwent a detailed examination, including a maximal treadmill exercise test with ECG monitoring, physical exam, blood tests, and extensive health and lifestyle questionnaires between 1970 and 1993 and followed for mortality through 31 December 1994 using the National Death Index. Cardiorespiratory fitness was classified as low when treadmill time was at the bottom 20% of the overall cohort (including nondiabetic subjects) for the subject's age-group (30–39 years, 40–49 years, etc.), moderate if performance was in the 21st to 60th percentile for age-group, and high if in the highest 40% for age-group. Among the diabetic subjects, 42% were classified as "low fit" and 58% as "moderate" or "high-fit." The 50% of diabetic subjects who reported any participation in walking, jogging, or other aerobic exercise programs in the previous 3 months were classified as "active," and the other 50% were classified as "inactive." After a mean of 11.7 years of follow-up, there were 180 deaths. Mortality in the moderate-fit men was $\sim 60\%$ lower than in low-fit men. Even after adjustment for age, examination year, baseline CVD, hypercholesterolemia, hypertriglyceridemia, BMI, hypertension, parental CVD, smoking, and baseline fasting glucose levels, low-fit diabetic men had a 2.2-fold greater mortality risk compared with men with moderate or high fitness (95% CI 1.6–3.2). Similarly, after adjusting for the same list of confounders, mortality in di-

Table 1—*Clinical trials of resistance exercise with people with diabetes*

Source	Sessions per week	Duration	No. of exercises	No. of sets, rest interval, and intensity of exercise	HbA$_{1c}$ (mean ± SD)
Eriksson et al., 1997 (152)	2	13 weeks	11 (including both upper and lower body, performed at stations arranged in a circuit)	1 set, maximum 30-s rest interval between each exercise, 15–20 repetitions performed at >50% of maximal exertion.	No control group Intervention: 8.8 ± 1.4 to 8.2 ± 1.4%*
Honkola et al., 1998 (154)	2	5 months	8–10 (including both upper and lower body)	2 sets, total of 16–20 sets performed, rest interval between sets was <60 s, 12–15 repetitions performed at a moderate intensity.	Control (type 2 diabetes): 7.7 ± 0.3 to 8.1 to 0.3%† Intervention group (type 2 diabetes): 7.5 ± 0.3 to 7.5 ± 0.3%
Ishii et al., 1998 (153)	5	4–6 weeks	4 (lower body) and 5 (upper body)	2 sets, rest interval between sets of <1 min, 10 and 20 repetitions for upper and lower body exercises, respectively, performed at 40–50% of 1-RM.	Control group (type 2 diabetes): 8.8 ± 2.1 to 7.6 ± 1.9% Intervention group (type 2 diabetes): 9.6 ± 2.8 to 7.6 ± 1.3% (All subjects were hospitalized.)
Dunstan et al., 1998 (155)	3	8 weeks	3 (lower body) and 7 (upper body)	3 sets; rest interval between sets 30 s, with active recovery on cycle ergometer; 10–15 repetitions performed at 50–55% of 1-RM.	Control group (type 2 diabetes): 8.1 ± 0.6 to 8.3 ± 0.7% Intervention group: 8.2 ± 0.5 to 8.0 ± 0.8%
Maiorana et al., 2002 (156)	3	8 weeks	7 (lower and upper body exercises)	Number of sets was increased from 1 to 3; rest interval between sets of 45 s, with active recovery on a cycle ergometer or treadmill; resistance training intensity commenced at 55% of 1-RM and increased to 65% of 1-RM by week 4. Aerobic exercise was performed at 70% of peak heart rate, increasing to 85% by week 6.	Control group (type 2 diabetes): 8.0 ± 0.5 to 8.4 ± 0.6% Intervention group (type 2 diabetes): 8.5 ± 0.4 to 7.9 ± 0.3%
Dunstan et al., 2002 (159)	3	26 weeks	8–10 (including both upper and lower body)	Intervention group: Initial 3 sessions involved 2 sets, 8–10 repetitions performed at 50–60% of 1-RM and increased to 3 sets in the subsequent 3 sessions. 3 sets, 8–10 repetitions performed at 75–85% of 1-RM was performed for the duration of the intervention. Control group: placebo exercise training program for 3 days/week, incorporating 18 different stretching/flexibility exercises.	Control group (type 2 diabetes, placebo exercise): 7.5 ± 1.1 to 7.1 to 0.8% Intervention group (type 2 diabetes): 8.1 ± 0.9 to 6.9 ± 0.9% (All subjects followed a moderate energy-restriction diet.)
Castaneda et al., 2002 (160)	3	16 weeks	3 (lower body) and 2 (upper body)	3 sets of 8–10 repetitions, progression to 75% of 1-RM, 2–3 min of rest between sets.	Control group (type 2 diabetes): increased 0.4 ± 1.2% Intervention group (type 2 diabetes): decreased 1.0 ± 1.1%‡ (All subjects were Hispanic.)

Table 1—Continued

Source	Sessions per week	Duration	No. of exercises	No. of sets, rest interval, and intensity of exercise	HbA$_{1c}$ (mean ± SD)
Cuff et al., 2003 (158)	3	16 weeks	Control group: no exercise; usual care.	Control group: usual care.	Control group (type 2 diabetes): decreased 0.03 ± 0.43
			Combined aerobic and resistance group: warm up, aerobic phase (continuous aerobic activity), resistance phase (three lower body and two upper body exercises), and cool down.	Combined aerobic and resistance group: total duration of sessions, 75 min. Strength component comprised 2 sets, 12 repetitions, light initial intensity that increased thereafter, technique permitting.	Combined group (type 2 diabetes): decreased 0.1 ± 1.4%
			Aerobic only group: warm up, aerobic phase (continuous aerobic activity), warm down.	Aerobic component comprised 60–75% heart rate reserve (progression not defined). Aerobic only group: total duration of session was 75 min. Aerobic component comprised 60–75% heart rate reserve (progression not defined). Low-impact, low-intensity aerobic activity was used during the time period allocated for the resistance phase in the combined treatment group.	Aerobic only group (type 2 diabetes): decreased 0.1 ± 1.6%

*$P < 0.05$ vs. baseline; †$P < 0.001$ vs. baseline; ‡$P = 0.0001$ vs. control group.

abetic men reporting no physical activity participation in the previous 3 months was 1.8-fold higher than in those reporting any participation in such activity (95% CI 1.3–2.5). Low cardiorespiratory fitness was at least as strong a risk factor for mortality as smoking, hypertension, hypercholesterolemia, and any of the other listed risk factors. The same research team has now published an updated study (123) with more subjects and longer follow-up. This later analysis found that moderate or high cardiorespiratory fitness was associated with lower mortality than low fitness independently of body composition and that essentially all of the association between higher BMI and higher mortality was explained by confounding with cardiorespiratory fitness.

Because moderate fitness was associated with vastly lower mortality than low fitness, it is of interest to know the activity levels associated with moderate fitness. Over 17,000 mainly nondiabetic participants in the Aerobic Center Longitudinal Study completed detailed physical activity logs and a maximal exercise test. Among moderately fit subjects (21st to 60th percentile for age) whose only exercise was walking, the mean time spent per week on exercise was 130 min for men and 148 min/week for women. These times are consistent with recommendations from the U.S. Surgeon General (124) and other respected bodies (125–127) to accumulate about 150 min/week of moderate-intensity exercise. Moderately fit subjects whose only exercise was jogging or running reported a mean of 90 min/week for men and 92 min/week for women. These times are consistent with an alternative and equally valid recommendation for vigorous activity 30 min three times a week.

Hu et al. (128) reported on 5,125 female nurses with type 2 diabetes who completed detailed health questionnaires every 2 years, of whom 323 developed new CVD events over 14 years of follow-up. Age-adjusted relative risks according to average hours per week of moderate or vigorous activity were 1.0 for <1 h (reference group), 0.93 for 1–1.9 h, 0.82 for 2–3.9 h, 0.54 for 4–6.9 h, and 0.52 for ≥7 h. There was little change with adjustment for BMI, smoking, and other CVD risk factors (relative risks 1.0, 1.02, 0.87, 0.61, and 0.55 for <1, 1–1.9, 2–3.9, 4–6.9, and ≥7 h/week, respectively). Faster usual walking pace was associated with reduced CVD risk, independently of total physical activity score. Therefore, there was some cardioprotection associated with 2–3.9 h/week of physical activity, but a greater degree of cardioprotection associated with at least 4 h/week of such activity.

Myers et al. (129) reported on 6,213 consecutive men referred for treadmill exercise testing for clinical reasons, including ~500 with diabetes (J. Myers, e-mail communication, August 2003). They found that in people with and in those without baseline CVD, absolute exercise capacity was a better predictor of mortality risk than percentage of age-predicted exercise capacity. Every 1-MET increment in treadmill performance was associated with 12% greater probability of survival.

To our knowledge, no meta-analysis of the effects of exercise training on lipids

or blood pressure in people with diabetes has been published. In the general, predominantly nondiabetic population, the effects of exercise training on blood pressure and lipids are relatively modest. A meta-analysis of the effects of aerobic exercise training on blood pressure (130) (54 trials, total 2,419 participants) found a weighted mean blood pressure change through exercise interventions of −3.84 mmHg systolic and −2.58 mmHg diastolic. A review of the effects of supervised, structured aerobic exercise training on lipids (51 trials of duration ≥12 weeks, ~4,700 subjects) (131) found a mean increase in HDL cholesterol of 4.6% ($P < 0.05$), and reductions in plasma triglycerides and LDL and total cholesterol of 3.7% ($P < 0.05$), 5.0% ($P < 0.05$), and 1.0% (NS), respectively. Greater increases in HDL cholesterol and decreases in plasma triglycerides have been seen with exercise programs that are more rigorous in terms of both volume and intensity than those that have been evaluated in diabetic subjects (132). Aerobic exercise training increases lipoprotein lipase activity and reduces the number of apolipoprotein B–containing particles (133–136).

Potential mechanisms through which exercise could improve cardiovascular health were reviewed recently by Stewart (137). These include decreased systemic inflammation, improved early diastolic filling (reduced diastolic dysfunction), improved endothelial vasodilator function, and decreased abdominal visceral fat accumulation.

Frequency of exercise

The U.S. Surgeon General's report recommended that most people accumulate ≥30 min of moderate intensity activity on most, ideally all, days of the week. However, most clinical trials evaluating exercise interventions in people with type 2 diabetes have used a three times per week frequency (119), and many people find it easier to schedule fewer longer sessions rather than five or more weekly shorter sessions. The effect on insulin sensitivity of a single bout of aerobic exercise lasts 24–72 h, depending on the duration and intensity of the activity (138). Because the duration of increased insulin sensitivity is generally not >72 h, we recommend that the time between successive sessions of physical activity be no more than 72 h (i.e., there should not be more than 2 con-

secutive days without aerobic physical activity). There is some evidence that the effect of resistance exercise training on insulin sensitivity is somewhat longer (139), perhaps because some of its effects are mediated by increases in muscle mass.

Exercise for weight loss and weight maintenance

The most successful programs for long-term weight control have involved combinations of diet, exercise, and behavior modification (140). University-based obesity research programs using combinations of diet, exercise, and behavior modification have typically produced weight losses of 9–13.6 kg after 20 weeks, and ~60% of this weight loss is maintained over 1 year of follow-up (140). Exercise alone, without concomitant dietary caloric restriction and behavior modification, tends to produce only modest weight loss of ~2 kg. Weight loss is typically this small primarily because obese people often have difficulty performing sufficient exercise to create a large energy deficit, and it is relatively easy to counterbalance increased energy expenditure through exercise by eating more or becoming less active outside of exercise sessions (140). However, in a randomized trial, high-volume aerobic exercise (700 kcal/day, about 1 h/day of moderate-intensity aerobic exercise) produced at least as much fat loss as the equivalent degree of caloric restriction (141). Furthermore, exercise-induced weight loss resulted in greater improvements in insulin sensitivity than diet-induced weight loss (141).

The optimal volume of exercise to achieve sustained major weight loss is probably much larger than that needed to achieve improved glycemic control and cardiovascular health. In the National Weight Control Registry (142), a study of individuals who lost at least 13.6 kg (mean 30 kg) and maintained the weight loss for at least 1 year (mean 5 years), the average self-reported energy expenditure on exercise was 2,545 kcal/week among women and 3,293 kcal/week among men. These amounts would correspond to ~7 h/week of moderate-intensity exercise. Similarly large amounts of exercise have been associated with long-term maintenance of weight loss in other studies (143–146).

Recommendations: aerobic exercise

The amount and intensity recommended for aerobic exercise vary according to goals.

- To improve glycemic control, assist with weight maintenance, and reduce risk of CVD, we recommend at least 150 min/week of moderate-intensity aerobic physical activity (40–60% of $V_{O_{2max}}$ or 50–70% of maximum heart rate) and/or at least 90 min/week of vigorous aerobic exercise (>60% of $V_{O_{2max}}$ or >70% of maximum heart rate). The physical activity should be distributed over at least 3 days/week and with no more than 2 consecutive days without physical activity.
- Performing ≥4 h/week of moderate to vigorous aerobic and/or resistance exercise is associated with greater CVD risk reduction compared with lower volumes of activity (128).
- For long-term maintenance of major weight loss (≥13.6 kg [30 lb]), larger volumes of exercise (7 h/week of moderate or vigorous aerobic physical activity per week) may be helpful.

Levels of evidence: A, for improved glycemic control (119,120); B, for CVD prevention (122,128); and B, for long-term maintenance of major weight loss (142–146).

RESISTANCE EXERCISE

For more detailed reviews on this topic, see Refs. 148 and 149.

The proven value of aerobic exercise notwithstanding, it does have some limitations. Some find aerobic exercise monotonous. Most forms of aerobic exercise would not be advisable with advanced peripheral neuropathy and are challenging in people with severe obesity. Resistance exercise training, by increasing muscle mass and endurance, often causes more rapid changes in functional status and body composition than aerobic training and might therefore be more immediately rewarding. Because each session involves many different resistance exercises, some find it less monotonous than aerobic exercise. Resistance exercise improves insulin sensitivity to about the same extent as aerobic exercise (150).

Because of the increased evidence for health benefits from resistance training during the past 10–15 years, the American College of Sports Medicine (ACSM)

Table 2—*The positions of other major professional associations on the recommended types and amounts of physical activity*

Reference	Aerobic training			Resistance training		
	Frequency	Intensity	Duration/mode	Frequency	No. of exercises	Sets/repetitions
Healthy adults						
1995 CDC/ACSM Public Health Statement (126)	Daily	Moderate	Accumulate 30 min/day continuous physical activity	—	Addressed but not specified	—
1996 U.S. Surgeon General's Report (2)	Near daily	Moderate/intense	Accumulate ≥30 min	2 days/week	8–10 exercises involving major muscle groups	1–2 sets, 8–12 reps
1998 Health Canada (186)	Daily	Light/moderate	Accumulate 60 min/day with light physical activity; can decrease to 30 min with moderate intensity	2–4 days/week	Involve all major muscle groups	2–4 sets, 10–15 reps
2000 ACSM Position Stand (127)	3–5 days/week	65–90% HR_{max} or 50–85% $\dot{V}o_{2max}$ or HR_{max} reserve; start at lower intensity if initially unfit or sedentary	20–60 min continuous aerobic activities; 20–30 min minimum	2 days/week	8–10 exercises involving major muscle groups	1 set, 8–12 reps
Elderly people (aged ≥65 years)						
1998 ACSM Position Stand (151)	3–5 days/week	50–85% $\dot{V}o_{2max}$ or 40–80% HR_{max} reserve	30–60 min continuous aerobic activity	2 days/week	8–10 exercises involving major muscle groups	1 set, 10–15 reps
Cardiac patients						
1995 AHA Exercise Standards (187)	Minimum of 3 days/week	50–60% $\dot{V}o_{2max}$ or HR_{max} reserve	Minimum of 30 min continuous physical activity	2–3 days/week	8–10 exercises involving major muscle groups	1 set, 10–15 reps
1999 AACVPR (188)	3–5 days/week	50–60% $\dot{V}o_{2max}$ or HR_{max} reserve	30–45 min of continuous or intermittent aerobic activity	2–3 days/week	Incorporate all major muscle groups	1 set, 10–15 reps
Individuals with type 2 diabetes						
2003 Canadian Diabetes Association (189)*	At least 3 nonconsecutive days/week	Moderate or intense	Accumulate at least 150 min/week (≥ h/week, if willing)	3 days/week	~8 exercises involving major muscle groups	Initially 1 set, 10–15 reps; Progress to 3 sets, 8–12 reps
2000 ACSM Position Stand (127)	At least 3 nonconsecutive days/week	40–70% $\dot{V}o_{2max}$	10–15 min continuous physical activity in early stages, gradually increased to 30 min. Sessions can be divided into three 10-min sessions	At least 2 days/week	Minimum of 8–10 exercises involving major muscle groups	Minimum of 1 set, 10–15 reps
Previous ADA guidelines (190)	3–5 days/week	55–79% of HR_{max} or 40–74% HR_{max} reserve	20–60 min continuous or intermittent aerobic activity (min of 10-min bouts)	High resistance exercise using weights may be acceptable for young individuals or those with longstanding diabetes. Moderate weight training programs that utilize light weights and high repetitions can be used for maintaining or enhancing upper body strength in nearly all patients with diabetes		

*The 2003 Canadian Diabetes Association Clinical Practice Guidelines, published in December 2003, were drafted by two of the authors of the present technical review and reviewed by the Canadian Diabetes Association Expert Committee. The Canadian Diabetes Association guidelines are based on some of the same authors examining the same updated-evidence reviewed in the present work, and therefore the recommendations are similar to the new proposed ADA recommendations. AHA, American Heart Association; AACVPR, American Association of Cardiovascular and Pulmonary Rehabilitation; CDC, U.S. Centers for Disease Control and Prevention; HR, heart rate.

now recommends resistance training be included in fitness programs for healthy young and middle-aged adults (125), older adults (151), and adults with type 2 diabetes (127). With increased age, there is a tendency to progressive declines in muscle mass, leading to "sarcopenia," decreased functional capacity, decreased resting metabolic rate, increased adiposity, and increased insulin resistance, and resistance training can have a major positive impact on each of these (151).

Studies of resistance exercise in type 2 diabetes

Notwithstanding the above, the previous ADA Position Statement on physical activity and exercise took a conservative view on resistance exercise, stating that high-intensity resistance training with weights might be appropriate for younger diabetic patients but not for older patients or those with longstanding disease; instead lower-intensity resistance exercise with light weights was endorsed (93). This was due to a lack of published studies on high-intensity resistance exercise in older diabetic individuals and concerns about the safety of this type of exercise in the absence of published data (Table 1).

Before 1997 there were no published studies of resistance exercise in type 2 diabetic subjects. The first such published experiment was by Eriksson et al. (152), who studied eight moderately obese type 2 diabetic patients aged 55 ± 9 years ($\pm$SD) before and after a 3-month program of moderate-intensity weight training. Muscle endurance increased by 32%. HbA$_{1c}$ decreased from 8.8 to 8.2% ($P < 0.05$), and there was a strong negative correlation between HbA$_{1c}$ and muscle cross-sectional area ($r = -0.73$). There was no control group. Ishii et al. (153) studied nine nonobese middle-aged type 2 diabetic subjects before and after 4–6 weeks of high-volume, moderate-intensity weight training. They were compared with control subjects unable to exercise because of orthopedic disorders. Insulin sensitivity rose 48% in exercisers but remained unchanged in control subjects. HbA$_{1c}$ declined from 9.6 to 7.6% in the weight training group, but also inexplicably declined from 8.8 to 7.6% in the sedentary subjects. In a nonrandomized trial (154), 18 subjects with type 2 diabetes (12 men and 6 women; mean age 62 years) underwent 5 months of moderate-intensity resistance training and were

compared with 5 men and 15 women (mean age 67 years) with type 2 diabetes who did not exercise during this time. HbA$_{1c}$ in the exercise group was 7.5% at baseline and 7.4% at 20 weeks, whereas HbA$_{1c}$ in control subjects increased from 7.7 to 8.1% ($P < 0.05$ between groups). Interpretation of this study is complicated by a lack of randomization and imbalances at baseline in age and sex between the exercisers and control subjects. The first randomized controlled trial evaluating resistance training on glycemic control in type 2 diabetic patients was done by Dunstan et al. (155) in which 27 type 2 diabetic patients were randomized to nonexercise control or 8 weeks of circuit training in which subjects alternated between 30 s at a time of moderate-intensity weight lifting and 30 s at a time of light stationary cycling following each 30 s of weight lifting (155). In the exercising subjects, both the insulin and glucose areas under the oral glucose tolerance test curve decreased nonsignificantly, and there was no significant effect on HbA$_{1c}$. In a similar study, Maiorana et al. (156) randomized 16 subjects in a crossover design to nonexercise control, followed by 8 weeks of three times per week circuit training or vice versa. During each circuit training session, subjects alternated 45 s of aerobic exercise at a moderate-intensity stationary cycling station with 45 s of moderate-intensity weight lifting. Mean HbA$_{1c}$ was 8.5% following sedentary periods and 7.9% following exercise periods. This study and the 1998 Dunstan et al. study (155) shared two limitations. First, duration of the intervention was insufficient to significantly affect body composition through resistance training because 3–6 months of training are required for clinically significant muscle hypertrophy (157). Second, the mixed resistance and aerobic training design precluded distinguishing the independent effects of each modality.

In recent trial, Cuff et al. (158) randomized 28 well-controlled, obese, postmenopausal type 2 diabetic women to combined aerobic and resistance training, aerobic training alone, or a nonexercising control group. Subjects in the exercising groups participated in three 75-min gym sessions per week for 16 weeks. The aerobic exercise was at 60–75% of heart rate reserve, whereas the resistance training program included two sets of 12 repetitions of five exercises. The aerobic-only

group spent additional time on very-low-intensity warm-up and cool-down activity that was not expected to affect glucose metabolism. HbA$_{1c}$ was excellent in all groups before training (6.3–6.9%) and did not change with exercise training. However, insulin sensitivity assessed with glucose clamp was increased significantly more in the combined aerobic and resistance exercise group than in the aerobic exercise only or control groups. Body fat declined significantly and similarly in both exercise groups, but muscle mass increased significantly only in the combined aerobic and resistance exercise group.

Two clinical trials published in late 2002 (159,160) provided much stronger evidence for the value of resistance training in type 2 diabetes. Dunstan et al. (159) randomized 36 Australian sedentary, overweight, type 2 diabetic subjects aged 60–80 years to 6 months of moderate weight loss plus high-intensity resistance training (RT/WL group; progressing to three sets of 8–10 repetitions of 8–10 exercises three times per week at 75–80% of maximum) or moderate weight loss plus flexibility exercise (control/WL group). Absolute HbA$_{1c}$ declined 1.2% in the RT/WL group compared with just 0.4% in the control/WL group ($P < 0.05$ between groups). Mean weight loss and fat loss were similar in both groups, but mean lean body mass increased by 0.5 kg in RT/WL subjects while decreasing 0.4 kg in control/WL subjects ($P < 0.05$ between groups). Castaneda et al. (160) randomized 62 older sedentary Hispanic adults (40 women and 22 men; mean age 66 years) to 16 weeks of individually supervised high-intensity resistance exercise (RT group, progressing to three sets of eight repetitions of five exercises three times per week at 70–80% of maximum) or sedentary control. Mean HbA$_{1c}$ declined from 8.7 to 7.6% in RT but did not change in control subjects ($P = 0.01$ between groups), even though 72% of RT subjects (versus 3% of control subjects) had hypoglycemic medications reduced and 42% of control subjects (versus 7% of RT subjects) had hypoglycemic medications increased. Mean systolic blood pressure declined 9.7 mmHg in RT subjects and rose 7.7 mmHg in control subjects ($P = 0.05$ between groups). Free fatty acid concentrations declined significantly by 27% in the RT group compared with control subjects, in whom circulating free

fatty acids increased by 10% (161). There was a significant positive correlation between the changes in glycosylated hemoglobin and plasma free fatty acid concentrations in the groups combined. The interventions in these two studies involved higher exercise intensity (70–85% of one repetition maximum versus 40–60% of one repetition maximum) and more sets of each exercise (three sets vs. one to two sets) than the other studies described above. Both studies enrolled only older subjects, with mean age of ~66 years in both.

Resistance exercise improves bone density, muscle mass, strength, balance, and overall capacity for physical activity and therefore is potentially important for prevention of osteoporotic fractures in the elderly (162,163).

The ACSM recommends a resistance training regimen for type 2 diabetic individuals whenever possible. It recommends "a minimum of 8–10 exercises involving the major muscle groups. . . with a minimum of one set of 10–15 repetitions to near fatigue. Increased intensity of exercise, additional sets, or combinations of volume and intensity may produce greater benefits and may be appropriate for certain individuals." These recommendations were published in 2000, before the 2002 Dunstan et al. (159) and Castaneda et al. (160) results were known. Given the superiority of Castaneda et al. and Dunstan et al.'s results in programs requiring three sets of each exercise compared with the other trials evaluating programs requiring just one to two sets of each exercise, we advocate a resistance program similar to theirs: progressing to three sets of 8–10 repetitions of the heaviest weight that can be lifted 8–10 times to near fatigue. Although one set of each exercise may be sufficient to increase muscle strength (164), it appears that three sets of each exercise produce the greater metabolic benefit in type 2 diabetes.

A conservative approach is to begin with one set of 10–15 repetitions two to three times per week at moderate intensity for several weeks, then two sets of 10–15 repetitions two to three times per week for several weeks, and then progress to three sets of 8–10 repetitions at a weight that cannot be lifted more than 8–10 times (8–10 RM). In the studies by Dunstan et al. (159) and Castaneda et al. (160), intensity of resistance exercise was

increased more rapidly than this. Each workout should be preceded by 5 min of warm up and followed by 5 min of cool down, each consisting of light aerobic activity with or without flexibility exercises. Initial supervision and periodic reassessment by a qualified exercise specialist is recommended to optimize benefits while minimizing risk of injury; such supervision was included in all of the above published studies.

Safety of resistance training

Some medical practitioners have concerns about the safety of higher-intensity resistance exercise in middle-aged and older people who are at risk of CVD. The main concern is often that the acute rises in blood pressure associated with higher-intensity resistance exercise might be harmful, possibly provoking stroke, myocardial ischemia, or retinal hemorrhage. We have found no evidence that resistance training actually increases these risks. No serious adverse events have been reported in any research study of resistance training in patients with type 2 diabetes, although the total number of subjects enrolled in these studies (152–155,159,160) was small. A review of 12 resistance exercise studies in a total of 246 male cardiac rehabilitation patients (166) found no angina, ST depression, abnormal hemodynamics, ventricular dysrhythmias, or other cardiovascular complications. A study of 12 men with known coronary ischemia and ECG changes inducible by moderate aerobic exercise found that even maximal-intensity resistance exercise did not induce ECG changes (167). Therefore, moderate- to high-intensity resistance training was found to be safe even in men at significant risk of cardiac events. Lombardi et al. (168) analyzed data from the National Electronic Injury Surveillance System (NEISS, a nationwide representative sample of hospital emergency departments), the National Death Index, the U.S. Consumer Products Safety Commission, and two other databases in an effort to determine the morbidity and mortality associated with resistance training in the U.S. Between 1999 and 2001 there were 20 deaths in the U.S. associated with weight lifting. All of them were related to weights or barbells falling and causing injury. Fourteen of the deaths were due to asphyxia, primarily from dropping a barbell on the chest and neck. Most of these

occurred in subjects' homes. There were no cases of death from myocardial infarction or stroke associated with resistance exercise.

The reason why resistance exercise appears less likely to induce ischemia than aerobic exercise has not been clearly demonstrated. A number of reasons seem plausible. First, in resistance exercise at least as much time is spent resting between sets as is spent lifting, lifting generally does not last >60 s at a time. In contrast, with aerobic exercise, there is generally no rest during the exercise session. Second, during resistance exercise, systolic and diastolic blood pressure rise in parallel, possibly helping to maintain coronary perfusion, whereas in aerobic exercise systolic pressure rises significantly more than diastolic pressure (169). Third, the rise in cardiac output with high-intensity resistance exercise is significantly less than that associated with high-intensity aerobic exercise (170).

Although it is well known that blood pressure rises while lifting a heavy weight, it is often not appreciated that blood pressure can also rise considerably in healthy older people performing aerobic exercise. Benn et al. (171) studied the responses to aerobic and resistance exercise in 17 healthy men aged 64 ± 6 years. Subjects performed each of the following exercises with continuous monitoring of heart rate and intra-arterial blood pressure: one-arm military press, one-arm curl at 70% of 1-RM (moderate intensity), single- and double-leg press at 80% of 1-RM (high intensity), horizontal walking for 20 min at 2.5 mph carrying 20 lbs in minutes 4–6 then 30 lbs in minutes 8–10, 4-min treadmill walk at 3 mph up an 8% incline, and 192 steps on a Stairmaster in ~3 min. The highest peak systolic blood pressures occurred in stair climbing (271 mmHg) and military press (261 mmHg), whereas the lowest peaks were in the single-arm curl (224 mmHg) and carrying a 20-lb weight (220 mmHg). Peak diastolic pressures were 128–151 mmHg in the resistance exercises, 121 mmHg in stair climbing, and 101–118 mmHg in the various treadmill exercises. Rate-pressure product, which is significantly correlated with myocardial oxygen demand, was highest at 41,000 for stair climbing; it was 22,000–30,000 for resistance exercises and 23,000–28,000 for treadmill exercises. Therefore, the myocardial demands of high-intensity resistance exercise are

not out of line with those occasionally needed for activities of daily living, such as climbing stairs, walking up a hill, or carrying 20–30 lbs of groceries.

There is little or no evidence to guide practitioners in terms of whether stress testing before undertaking resistance training is necessary. One might ask whether such testing should use resistance exercise, rather than the usual aerobic exercise, during a stress test in such circumstances. Very few test centers would currently be equipped for such testing, and such tests have not been standardized. In contrast, aerobic exercise stress testing is widely available, standardized, and of proven prognostic value.

Recommendations: resistance exercise

In the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance exercise three times a week, including all major muscle groups, progressing to three sets of 8–10 repetitions at a weight that cannot be lifted >8–10 times (8–10 RM).

Level of evidence. A. In order to ensure resistance exercises are performed correctly, maximize health benefits, and minimize the risk of injury, we recommend initial supervision and periodic reassessments by a qualified exercise specialist, as was done in the clinical trials (159,160).

FLEXIBILITY EXERCISE

Flexibility exercise (stretching) has frequently been recommended as a means of increasing range of motion and hopefully reducing risk of injury. However, two systematic reviews (172,173) have found that flexibility exercise does not reduce risk of exercise-induced injury. It should be noted that most studies included in these systematic reviews evaluated younger subjects undertaking very vigorous activity programs, such as those in military basic training; these results may not be generalizable to older subjects. Flexibility exercise has been successfully used in clinical trials as a "placebo" exercise (159,174), since there is no evidence that flexibility exercise affects metabolic control or quality of life. We found two small studies providing indirect support for flexibility exercise in reducing risk of foot ulceration. In a case-control study (175), 25 diabetic patients with a history of neuropathic foot ulceration had higher

pressure on the plantar aspect of the foot and lower ankle joint flexibility than 50 control subjects without neuropathy or foot ulceration. In a small randomized trial, 19 diabetic subjects were randomized to unsupervised active and passive range of motion exercises of the joints in feet or an inactive control group. After 1 month, the nine who performed range of motion exercises had a 4.2% decrease in peak plantar pressures compared with a 4.4% increase in peak plantar pressures in the control group. We found no studies that directly evaluated whether flexibility training reduced the risk of ulceration or injury in people with diabetes. Therefore, we feel that there is insufficient evidence to recommend for or against flexibility exercise as a routine part of the exercise prescription.

EXERCISE IN THE PRESENCE OF NONOPTIMAL GLYCEMIC CONTROL

Hyperglycemia

When people with type 1 diabetes are deprived of insulin for 12–48 h and ketotic, exercise can worsen the hyperglycemia and ketosis (176). Previous ADA exercise position statements have suggested that physical activity be avoided if fasting glucose levels are >250 mg/dl and ketosis is present and performed with caution if glucose levels are >300 mg/dl even if no ketosis is present (93). We agree that vigorous activity should probably be avoided in the presence of ketosis. However, the recommendation to avoid physical activity if plasma glucose is >300 mg/dl, even in the absence of ketosis, is probably more cautious than necessary for a person with type 2 diabetes, especially in a postprandial state. In the absence of very severe insulin deficiency, light- or moderate-intensity exercise would tend to decrease plasma glucose. Therefore, provided the patient feels well and urine and/or blood ketones are negative, it is not necessary to postpone exercise based simply on hyperglycemia.

Hypoglycemia

In individuals taking insulin and/or insulin secretagogues, physical activity can cause hypoglycemia if medication dose or carbohydrate consumption is not altered. This is particularly so at times when exogenous insulin levels are at their peaks and if physical activity is prolonged. Hypoglycemia would be rare in diabetic in-

dividuals who are not treated with insulin or insulin secretagogues. Previous ADA guidelines suggest that added carbohydrate should be ingested if pre-exercise glucose levels are <100 mg/dl (93). We agree with this recommendation for individuals on insulin and/or an insulin secretagogue. However, the revised guidelines clarify that supplementary carbohydrate is generally not necessary for individuals treated only with diet, metformin, α-glucosidase inhibitors, and/or thiazolidinediones without insulin or a secretagogue.

Those who take insulin or secretagogues should check capillary blood glucose before, after, and several hours after completing a session of physical activity, at least until they know their usual glycemic responses to such activity. For those who show a tendency toward hypoglycemia during or after exercise, several strategies can be used. Doses of insulin or secretagogues can be reduced before sessions of physical activity, extra carbohydrate can be consumed before or during physical activity, or both. For a detailed discussion of medication adjustments to reduce risk of hypoglycemia, see Ref. 177.

Concomitant medications

Diabetic patients frequently take diuretics, β-blockers, ACE inhibitors, aspirin, and lipid-lowering agents. In most type 2 diabetic individuals, medications will not interfere with the physical activities they choose to perform, but patients and health care personnel should be aware of potential problems to minimize their impact. Diuretics, especially in higher doses, can interfere with fluid and electrolyte balance. β-Blockers can blunt the adrenergic symptoms of hypoglycemia, possibly increasing risk of hypoglycemia unawareness. They can reduce maximal exercise capacity to ~87% of what it would be without β-blockade (11) through their negative inotropic and chronotropic effects. However, most people with type 2 diabetes do not choose to exercise at very high intensity, so this reduction of maximum capacity is generally not problematic. In people with CAD, β-blockade actually increases exercise capacity by reducing coronary ischemia. ACE inhibitors may modestly increase insulin sensitivity, and both ACE inhibitors and aspirin (especially in high doses [4–6 g/day]) may increase risk of hypoglycemia in some individuals through unclear

mechanisms. In rare cases, statins, especially in combination with fibrates, can produce myositis. For additional discussion of the impact of concomitant medications on physical activity, see Ref. 92.

EXERCISE IN THE PRESENCE OF SPECIFIC LONG-TERM COMPLICATIONS OF DIABETES

There is a paucity of research on risks and benefits of exercise in the presence of diabetes complications. Therefore, recommendations in this section are based largely on "expert opinion."

Retinopathy
Exercise and physical activity are not known to have any adverse effects on vision or the progression of nonproliferative diabetic retinopathy or macular edema (178). This applies to resistance training as well as aerobic training. However, in the presence of proliferative or severe nonproliferative diabetic retinopathy, vigorous aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment (178). We found no research studies that would provide guidance as to an appropriate time interval between successful laser photocoagulation and initiation or resumption of resistance exercise. Opthalmologists with whom one of us (C.C.-S.) consulted suggested waiting 3–6 months after laser photocoagulation before initiating or resuming this type of exercise.

Peripheral neuropathy
We are unaware of research studies assessing the risk of exercise-induced injury in people with peripheral sensory neuropathy. Common sense, however, would indicate that decreased pain sensation in the extremities would result in increased risk of skin breakdown and infection and of Charcot joint destruction. Therefore, in the presence of severe peripheral neuropathy, it may be best to encourage non–weight-bearing activities such as swimming, bicycling, or arm exercises (179,180).

Autonomic neuropathy
Autonomic neuropathy can increase the risk of exercise-induced injury by decreasing cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation due to impaired skin blood flow and sweating, impaired night vision due to impaired papillary reaction, impaired thirst increasing risk of dehydration, and gastroparesis with unpredictable food delivery (179). Autonomic neuropathy is also strongly associated with CVD in people with diabetes (181). People with diabetic autonomic neuropathy should definitely undergo cardiac investigation before beginning physical activity more intense than that to which they are accustomed. Some experts advocate thallium scintigraphy as the preferred screening technique for CVD in this high-risk population (179).

Microalbuminuria and nephropathy
Physical activity can acutely increase urinary protein excretion. The magnitude of this increase is in proportion to the acute increase in blood pressure. This finding has led some experts to recommend (182) that people with diabetic kidney disease perform only light or moderate exercise, such that blood pressure during exercise would not rise to >200 mmHg. However, there is no evidence from clinical trials or cohort studies demonstrating that vigorous exercise increases the rate of progression of diabetic kidney disease. Several randomized trials in animals with diabetes and proteinuria showed that aerobic exercise training decreased urine protein excretion (183,184), possibly in part due to improved glycemic control, blood pressure, and insulin sensitivity. Resistance training also may be of benefit. In one clinical trial (185), 26 older people with renal disease treated with a low-protein diet, including 10 with diabetic nephropathy, were randomized to 12 weeks of high-intensity resistance training or an inactive control group. Those allocated to resistance training had significant improvements in muscle mass, nutritional status, functional capacity, and even glomerular filtration rate compared with control subjects. Because of these encouraging findings, we believe there may be no need for any specific exercise restrictions for people with diabetic kidney disease. However, because microalbuminuria and proteinuria are associated with increased risk for CVD, it is important to perform an exercise ECG stress test before beginning exercise significantly more intense than the demands of everyday living.

COMPARISON BETWEEN THE PROPOSED NEW ADA GUIDELINES AND THE 2000 ACSM POSITION STAND ON TYPE 2 DIABETES AND EXERCISE

There is substantial agreement between our recommendations and those of the 2000 ACSM Position Stand. Our position on the recommended frequency, duration, and intensity of aerobic exercise is similar to the ACSM recommendations. The ACSM document was written before the publication of most resistance exercise trials in type 2 diabetes, but nevertheless endorsed resistance training. Our new recommendations for three sets of 8–10 repetitions of a range of resistance exercises are based on trials published in 2002 (159,160) in which results were superior with this type of regimen compared with other trials evaluating less-intense regimens. The ACSM Position Stand is similar to ours in firmly recommending aerobic and resistance exercise, but explicitly recommending for or against flexibility exercise. See Table 2 for descriptions of the positions of other major professional associations on the recommended types and amounts of physical activity.

Our position on which individuals should undergo stress testing is based on a re-evaluation of the evidence rather than on new evidence. The ACSM Position Stand, similarly to the previous ADA position, advocates stress testing for all diabetic individuals aged ≥35 years before participating in most physical activity. Our position advocates stress testing for those age >30 years with additional risk factors, and age >40 years regardless of additional risk factors, who wish to undertake vigorous exercise. We see stress testing as less essential for detection of ischemia in younger individuals because of their relatively low absolute risks of CVD. However, we continue to recognize the potential value of maximal exercise testing for the purposes of setting appropriate exercise intensities and assessing physical capacity and prognosis.

References
1. American Diabetes Association: Introduction. *Diabetes Care* 27 (Suppl. 1):S1–S2, 2004
2. U.S. Department of Health and Human Services: *Physical Activity and Health: A*

Report of the Surgeon General. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996

3. Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud AC, Ward A: Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J* 103:363–373, 1982

4. Wasserman DH, Davis SN, Zinman B: Fuel metabolism during exercise in health and diabetes. In *Handbook of Exercise in Diabetes*. Ruderman N, Devlin JT, Schneider SH, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 63–99

5. Ivy JL: Exercise physiology and adaptations to training. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 23–62

6. Goodyear LJ, Horton ES: Signal transduction and glucose transport in muscle. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 101–124

7. Wasserman DH, Cherrington AD: Regulation of extramuscular fuel sources during exercise. In *Handbook of Physiology*. Rowell LB, Shepherd JT, Eds. Columbia, MD, Bermedica Production, 1996

8. Koyama Y, Coker RH, Denny JC, Lacy DB, Jabbour K, Williams PE, Wasserman DH: Role of carotid bodies in the neuroendocrine response to exercise. *Am J Physiol* 281:E742–E748, 2001

9. Krishna MG, Coker RH, Lacy DB, Zinker BA, Halseth AE, Wasserman DH: Glucagon response to exercise is critical for accelerated hepatic glutamine metabolism and nitrogen disposal. *Am J Physiol* 279:E638–E645, 2000

10. Marliss EB, Sigal RJ, Manzon A, Halter JB, Vranic M: Glucoregulation in intense exercise, and its implications for persons with diabetes mellitus. In *Proceedings of the IDF Satellite Symposium on Exercise, Fuel Homeostasis and Diabetes Mellitus, Nara, Japan, 12–13 November 1994*. London, Smith-Gordon, 1995

11. Sigal RJ, Purdon C, Bilinski D, Vranic M, Halter JB, Marliss EB: Glucoregulation during and after intense exercise: effects of beta-blockade. *J Clin Endocrinol Metab* 78:359–366, 1994

12. Sigal RJ, Fisher S, Halter JB, Vranic M, Marliss EB: The roles of catecholamines in glucoregulation in intense exercise as defined by the islet cell clamp technique. *Diabetes* 45:148–156, 1996

13. Kreisman SH, Mew NA, Halter JB, Vranic M, Marliss EB: Norepinephrine infusion during moderate-intensity exercise increases glucose production and uptake. *J Clin Endocrinol Metab* 86:2118–2124, 2001

14. Kreisman SH, Mew NA, Arsenault M, Nessim SJ, Halter JB, Vranic M, Marliss EB: Epinephrine infusion during moderate intensity exercise increases glucose production and uptake. *Am J Physiol* 278:E949–E957, 2000

15. Kreisman SH, Halter JB, Vranic M, Marliss EB: Combined infusion of epinephrine and norepinephrine during moderate exercise reproduces the glucoregulatory response of intense exercise. *Diabetes* 52:1347–1354, 2003

16. Sigal RJ, Fisher SJ, Halter JB, Vranic M, Marliss EB: Glucoregulation during and after intense exercise: effects of beta-adrenergic blockade in subjects with type 1 diabetes mellitus. *J Clin Endocrinol Metab* 84:3961–3971, 1999

17. Sigal RJ, Fisher SJ, Manzon A, Morais JA, Halter JB, Vranic M, Marliss EB: Glucoregulation during and after intense exercise: effects of alpha-adrenergic blockade. *Metabolism* 49:386–394, 2000

18. Coker RH, Krishna MG, Lacy DB, Allen EJ, Wasserman DH: Sympathetic drive to liver and nonhepatic splanchnic tissue during heavy exercise. *J Appl Physiol* 82:1244–1249, 1997

19. Sigal RJ, Purdon C, Fisher SJ, Halter JB, Vranic M, Marliss EB: Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 79:1049–1057, 1994

20. Purdon C, Brusson M, Nyreen SL, Miles PDG, Halter J, Vranic M, Marliss EB: The roles of insulin and catecholamines in the glucoregulatory response during intense exercise and early recovery in insulin-dependent diabetic and control subjects. *J Clin Endocrinol Metab* 76:566–573, 1993

21. Minuk HL, Vranic M, Hanna AK, Albisser AM, Zinman B: Glucoregulatory and metabolic response to exercise in obese noninsulin-dependent diabetes. *Am J Physiol* 240:E458–E464, 1981

22. Larsen JJ, Dela F, Kjaer M, Galbo H: The effect of moderate exercise on postprandial glucose homeostasis in NIDDM patients. *Diabetologia* 40:447–453, 1997

23. Wolfe RR, Klein S, Carraro F, Weber JM: Role of triglyceride-fatty acid cycle in controlling fat metabolism in humans during and after exercise. *Am J Physiol* 258:E382–E389, 1990

24. Harant I, Marion-Latard F, Crampes F, deGlisezinski I, Berlan M, Stich V, Riviere D: Effect of a long-duration physical exercise on fat cell lypolytic responsiveness to adrenergic agents and insulin in obese men. *Int J Obes* 26:1373–1378, 2002

25. Sacchetti M, Saltin B, Osada T, Hall Gv: Intramuscular fatty acid metabolism in contracting and non-contracting human skeletal muscle. *J Physiol* 540:387–395, 2002

26. Horowitz JF, Klein S: Lipid metabolism during endurance exercise. *Am J Clin Nutr* 72 (Suppl.):558S–563S, 2000

27. Blaak EE, van Aggel-Leijssen DP, Wagenmakers AJ, Saris WH, van Baak MA: Impaired oxidation of plasma-derived fatty acids in type 2 diabetic subjects during moderate-intensity exercise. *Diabetes* 49:2102–2107, 2000

28. Borghouts LB, Wagenmakers AJ, Goyens PL, Keizer HA: Substrate utilization in non-obese type II diabetic patients at rest and during exercise. *Clin Sci (Lond)* 103:559–566, 2002

29. Howlett RA, Parolin ML, Dyck DJ, Hultman E, Jones NL, Heigenhauser GF, Spriet LL: Regulation of skeletal muscle glycogen phosphorylase and PDH at varying exercise power outputs. *Am J Physiol* 275:R418–R425, 1998

30. Rush JW, Spriet LL: Skeletal muscle glycogen phosphorylase a kinetics: effects of adenine nucleotides and caffeine. *J Appl Physiol* 91:2071–2278, 2001

31. Hargreaves M, Kiens B, Richter EA: Effect of increased plasma free fatty acid concentrations on muscle metabolism in exercising men. *J Appl Physiol* 70:194–201, 1991

32. Richter EA: Glucose utilization. In *Handbook of Physiology*. Rowell LB, Shepherd JT, Eds. New York, Oxford University Press, 1996, p. 912–951

33. Hespel P, Vergauwen L, Vandenberghe K, Richter EA: Important role of insulin and flow in stimulating glucose uptake in contracting skeletal muscle. *Diabetes* 44:210–215, 1995

34. Lund S, Holman GD, Schmitz O, Pedersen O: Contraction stimulates translocation of glucose transporter GLUT4 in skeletal muscle through a mechanism distinct from that of insulin. *Proc Natl Acad Sci U S A* 92:5817–5821, 1995

35. Kemp BE, Mitchelhill KI, Stapleton D, Michell BJ, Chen ZP, Witters LA: Dealing with energy demand: the AMP-activated protein kinase. *Trends Biochem Sci* 24:22–25, 1999

36. Chen ZP, McConnell GK, Michell BJ, Snow RJ, Canny BJ, Kemp BE: AMPK signaling in contracting human skeletal muscle: acetyl-CoA carboxylase and NO synthase phosphorylation. *Am J Physiol* 279:E1202–E1206, 2000

37. Stephens TJ, Chen ZP, Canny BJ, Michell BJ, Kemp BE, McConnell GK: Progressive increase in human skeletal muscle

AMPKα2 activity and ACC phosphorylation during exercise. *Am J Physiol* 282: E688–E694, 2002

38. Kurth-Kraczek EJ, Hirshman MF, Goodyear LJ, Winder WW: 5′AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. *Diabetes* 48:1667–1671, 1999

39. Ai H, Ihlemann J, Hellsten Y, Lauritzen HPMM, Hardie DG, Galbo H, Ploug T: Effect of fiber type and nutritional state on AICAR- and contraction-stimulated glucose transport in rat muscle. *Am J Physiol* 282:E1291–E1300, 2001

40. Mu J, Brozinick JT, Valladares O, Bucan M, Birnbaum MJ: A role of AMP-activated protein kinase in contraction- and hypoxia-regulated glucose transport in skeletal muscle. *Mol Cell* 7:1085–1094, 2001

41. Saha AK, Schwarsin AJ, Roduit R, Masse F, Kaushik V, Tornheim K, Prentki M, Ruderman NB: Activation of malonyl-CoA decarboxylase in rat skeletal muscle by contraction and the AMP-activated protein kinase activator 5-aminoimidazaole-4-carboxamide-1-B-D-furanoside. *J Biol Chem* 275:24279–24283, 2000

42. Stoppani J, Hildebrandt AL, Sakamoto K, Cameron-Smith D, Goodyear LJ, Neufer PD: AMP-activated protein kinase activates transcription of the UCP3 and HKII genes in rat skeletal muscle. *Am J Physiol* 283:E1239–E1248, 2002

43. Zheng D, MacLean PS, Pohnert SC, Knight JB, Olson AL, Winder WW, Dohm GL: Regulation of muscle GLUT-4 transcription by AMP-activated protein kinase. *J Appl Physiol* 91:1073–1083, 2001

44. Balon TW, Nadler JL: Nitric oxide release is present from incubated skeletal muscle preparations. *J Appl Physiol* 77: 2519–2521, 1994

45. Bradley SJ, Kingwell BA, McConnell GK: Nitric oxide synthase inhibition reduces leg glucose uptake but not blood flow during dynamic exercise. *Diabetes* 48: 1815–1821, 1999

46. Fryer LG, Hajduch E, Rencurel R, Salt IP, Hundal HS, Hardie DG, Carling D: Activation of glucose transport by AMP-activated protein kinase via stimulation of nitric oxide synthase. *Diabetes* 49:1978–1985, 2000

47. Wasserman DH, Halseth AE: An overview of muscle glucose uptake during exercise: sites of regulation. In *Advances in Experimental Medicine and Biology*. Richter EA, Kiens B, Galbo H, Saltin B, Eds. New York, Plenum Press, 1998, p. 1–16

48. Halseth A, Bracy D, Wasserman D: Overexpression of hexokinase II increases insulin- and exercise-stimulated muscle glucose uptake in vivo. *Am J Physiol* 276:

E70–E77, 1999

49. Cusi K, Pratipanawatr T, Koval J, Printz R, Ardehali H, Granner DK, Defronzo RA, Mandarino LJ: Exercise increases hexokinase II mRNA, but not activity in obesity and type 2 diabetes. *Metabolism* 50:602–606, 2001

50. Koval JA, DeFronzo RA, O'Doherty RM, Printz RL, Ardehali H, Granner DK, Mandarino LJ: Regulation of hexokinase II activity and expression in human muscle by moderate exercise. *Am J Physiol* 274:E304–E308, 1998

51. O'Doherty RM, Bracy DP, Osawa H, Wasserman DH, Granner DK: Rat skeletal muscle hexokinase II mRNA and activity are increased by a single bout of acute exercise. *Am J Physiol* 266:E171–E178, 1994

52. Wojtaszewski JF, Nielsen JN, Richter EA: Effect of acute exercise on insulin signaling and action in humans. *J Appl Physiol* 93:384–392, 2002

53. Sakamoto K, Goodyear LJ: Intracellular signaling in contracting skeletal muscle. *J Appl Physiol* 93:369–383, 2002

54. Coderre L, Kandror KV, Vallega G, Pilch PF: Identification and characterization of an exercise-sensitive pool of glucose transporters in skeletal muscle. *J Biol Chem* 270:27584–27588, 1995

55. Goodyear LJ, Giorgino F, Balon TW, Condorelli G, Smith RJ: Effects of contractile activity on tyrosine phosphoproteins and PI 3-kinase activity in rat skeletal muscle. *Am J Physiol* 268:E987–E995, 1995

56. Kennedy JW, Hirshman MF, Gervino EV, Ocel JV, Forse RA, Hoenig SJ, Aronson D, Goodyear LJ, Horton ES: Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects and subjects with type 2 diabetes. *Diabetes* 48:1192–1197, 1999

57. Ivy JL, Zderic TW, Fogt DL: Prevention and treatment of non-insulin-dependent diabetes mellitus. *Exerc Sport Sci Rev* 27: 1–35, 1999

58. Mandarino LJ, Bonadonna RC, McGuinness OP, Halseth AE, Wasserman DH: Regulation of muscle glucose uptake in vivo. In *The American Physiological Society Handbook of Physiology-Endocrine Pancreas*. Jefferson LS, Cherrington AD, Eds. Rockville, MD, Waverly Press, 2001, p. 803–848

59. Coyle EF, Coggin AR, Hemmert MK, Ivy JL: Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. *J Appl Physiol* 61:165–172, 1986

60. Adopo E, Peronnet F, Massicotte D, Brisson GR, Hillaire-Marcel C: Respective of oxidation of exogenous glucose and fructose given in the same drink during exercise. *J Appl Physiol* 76:1014–1019,

1994

61. Pirnay F, Crielaard JM, Pallikarakis N, Lacroix M, Mosora F, Luyckx A, Lefebvre PJ: Fate of exogenous glucose during exercise of different intensities in humans. *J Appl Physiol* 43:258–261, 1982

62. Duchman SM, Ryan AJ, Schedl HP, Summers RW, Bleiler TL, Gisolfi CV: Upper limit for intestinal absorption of a dilute glucose solution in men at rest. *Med Sci Sports Exerc* 29:482–488, 1997

63. Howlett KF, Sakamoto K, Hirshman MF, Aschenbach WG, Dow M, White MF, Goodyear LJ: Insulin signaling after exercise in insulin receptor substrate-2–deficient mice. *Diabetes* 51:479–483, 2002

64. Sherwood DJ, Dufresne SD, Markus JF, Cheatham B, Moller DE, Aronson D, Goodyear LJ: Differential regulation of MAP kinase, p709(s6k) and akt by contraction and insulin in rat skeletal muscles. *Am J Physiol* 276:E870–E878, 1999

65. Wojtaszewski JF, Hansen BF, Urso B, Richter EA: Wortmannin inhibits both insulin-stimulated and contraction-stimulated glucose uptake and transport in rat skeletal muscle. *J Appl Physiol* 81: 1501–1509, 1996

66. Wojtaszewski JF, Higaki Y, Hirshman MF, Michael MD, Dufresne SD, Kahn CR, Goodyear LJ: Exercise modulates postreceptor insulin signaling and glucose transport in muscle-insulin receptor knockout mice. *J Clin Invest* 104:1257–1264, 1999

67. Ren JM, Semenkovich CF, Gulve EA, Gao JG, Holloszy JO: Exercise induces rapid increases in GLUT4 expression, glucose transport capacity, and insulin-stimulated glycogen storage in muscle. *J Biol Chem* 269:14396–14401, 1994

68. Kraniou Y, Cameron-Smith D, Misso M, Collier G, Hargreaves M: Effects of exercise on GLUT-4 and glycogenin gene expression in human skeletal muscle. *J Appl Physiol* 88:794–796, 2000

69. Iglesias MA, Ye JM, Frangioudakis G, Saha AK, Tomas E, Ruderman NB, Cooney GJ, Kraegen EW: AICAR administration causes an apparent enhancement of muscle and liver insulin action in insulin-resistant high-fat-fed rats. *Diabetes* 51:2886–2894, 2002

70. Nader G, Nader KA: Intracellular signaling specificity in skeletal muscle in response to different modes of exercise. *J Appl Physiol* 90:1936–1942, 2001

71. Sakamoto K, Hirshman MF, Aschenbach WG, Goodyear LJ: Contraction regulation of Akt in rat skeletal muscle. *J Biol Chem* 277:11910–11917, 2002

72. Osman AA, Pendergrass M, Koval J, Maezono K, Cusi K, Pratipanawatr T, Mandarino LJ: Regulation of MAP kinase pathway activity in vivo in human skel-

etal muscle. *Am J Physiol* 278:E992–E999, 2000

73. Markuns JF, Wojtaszewski JFP, Goodyear LJ: Insulin and exercise decrease glycogen synthase kinase-3 activity by different mechanisms in rat skeletal muscle. *J Biol Chem* 274:24896–24900, 1999

74. Galassetti P, Coker RH, Lacy DB, Cherrington AD, Wasserman DH: Prior exercise increases net hepatic glucose uptake during a glucose load. *Am J Physiol* 276:E1022–E1029, 1999

75. Casey A, Mann R, Banister K, Fox J, Morris PG, MacDonald IA, Greenhaff PL: Effect of carbohydrate ingestion on glycogen resynthesis in human liver and skeletal muscle, measured by 13C MRS. *Am J Physiol* 278:E65–E75, 2000

76. Pencek RR, James FD, Lacy DB, Jabbour K, Williams PE, Fueger PT, Wasserman DH: Interaction of insulin and prior exercise in control of hepatic metabolism of a glucose load. *Diabetes* 52:1897–1903, 2003

77. Hamilton KS, Gibbons FK, Bracy DP, Lacy DB, Cherrington AD, Wasserman DH: Effect of prior exercise on the partitioning of an intestinal glucose load between splanchnic bed and skeletal muscle. *J Clin Invest* 98:125–135, 1996

78. Koranyi LI, Bourey RE, Slentz CA, Holloszy JO: Coordinate reduction of rat pancreatic islet glucokinase and proinsulin mRNA by exercise training. *Diabetes* 40:401–404, 1991

79. Lee JS, Bruce CR, Tunstall RJ, Cameron-Smith D, Hugel H, Hawley JA: Interaction of exercise and diet on GLUT-4 protein and gene expression in type I and type II rat skeletal muscle. *Acta Physiol Scand* 175:37–44, 2002

80. Terada S, Yokozeki T, Kawanaka K, Ogawa K, Higuchi M, Ezaki O, Tabata I: Effects of high-intensity swimming training on GLUT-4 and glucose transport activity in rat skeletal muscle. *J Appl Physiol* 90:2019–2024, 2001

81. Kirwin JP, Aguila LFD, Hernandez JM, Williamson DL, O'Gorman DJ, Lewis R, Krishnan RK: Regular exercise enhances activation of IRS-1-associated PI3-kinase in human skeletal muscle. *J Appl Physiol* 88:797–803, 2000

82. Houmard JA, Shaw CD, Hickey MS, Tanner CJ: Effect of short-term exercise training on insulin-stimulated PI3-kinase activity in human skeletal muscle. *Am J Physiol* 277:E1055–E1060, 1999

83. Chibalin AV, Yu M, Ryder JW, Song XM, Galuska D, Krook A, Wallberg-Henricksson H, Zierath JR: Exercise-induced changes in expression and activity of proteins involved in insulin signal transduction in skeletal muscle: differential effects on insulin receptor substrates 1

and 2. *Proc Natl Acad Sci U S A* 97:38–43, 2000

84. Osman A, Hancock J, Hunt DG, Ivy JL, Mandarino LJ: Exercise training increases ERK3 activity in skeletal muscle of obese Zucker rats. *J Appl Physiol* 90:454–460, 2001

85. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JF, Dela F: Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. *Diabetes* 53:294–305, 2004

86. Romijn JA, Klein S, Coyle EF, Sidossis LS, Wolfe RR: Strenuous endurance training increases lipolysis and triglyceride-fatty acid cycling at rest. *J Appl Physiol* 75:108–113, 1993

87. Izawa T, Komabayashi T, Mochizuki T, Suda K, Tsuboi M: Enhanced coupling of adenylate cyclase to lipolysis in permeabilized adipocytes from trained rats. *J Appl Physiol* 71:23–29, 1991

88. Schrauwen P, Aggel-Leijssen DPv, Hul G, Wagenmakers AJ, Vidal H, Saris WH, Baak MAv: The effect of a 3-month low-intensity endurance training program on fat oxidation and acetyl-CoA carboxylase-2 expression. *Diabetes* 51:2220–2226, 2002

89. Tunstall RJ, Mehan KA, Wadley GD, Collier GR, Bonen A, Hargreaves M, Cameron-Smith D: Exercise training increases lipid metabolism gene expression in human skeletal muscle. *Am J Physiol* 283:E66–E72, 2002

90. Kiens B, Kristiansen S, Richter EA, Turcotte LP: Membrane associated FABP in human skeletal muscle is increased by endurance training. *Biochem Biophys Res Com* 231:463–465, 1997

91. Goodpaster BH, He J, Watkins S, Kelley DE: Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. *J Clin Endocrinol Metab* 86:5755–5761, 2001

92. Ganda OP: Patients on various drug therapies. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 587–599

93. Zinman B, Ruderman N, Campaigne BN, Devlin JT, Schneider SH: Physical activity/exercise and diabetes mellitus (Position Statement). *Diabetes Care* 26 (Suppl 1):S73–S77, 2003

94. Stevens RJ, Kothari V, Adler AI, Stratton IM: The UKPDS Risk Engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)* 101:671–679, 2001

95. Fowler-Brown A, Pignone M, Pletcher M, Tice JA, Sutton SF, Lohr KN: Exercise tolerance testing to screen for coronary

heart disease: a systematic review for the technical support for the U.S. Preventive Services Task Force. *Ann Intern Med* 140:W9–W24, 2004

96. US Preventive Services Task Force: Screening for coronary heart disease: recommendation statement. *Ann Intern Med* 140:569–572, 2004

97. Borg GA: Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14:377–381, 1982

98. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS Jr: Relative intensity of physical activity and risk of coronary heart disease. *Circulation* 107:1110–1116, 2003

99. Whaley MH, Brubaker PH, Kaminsky LA, Miller CR: Validity of rating of perceived exertion during graded exercise testing in apparently healthy adults and cardiac patients. *J Cardiopulm Rehabil* 17:261–267, 1997

100. Whaley MH, Woodall T, Kaminsky LA, Emmett JD: Reliability of perceived exertion during graded exercise testing in apparently healthy adults. *J Cardiopulm Rehabil* 17:37–42, 1997

101. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC Jr: ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 106:1883–1892, 2002

102. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL Jr, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ: ACC/AHA guidelines for exercise testing: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Circulation* 96:345–354, 1997

103. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997

104. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka

P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001

105. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J: The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26: 3230–3236, 2003

106. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346: 393–403, 2002

107. Diabetes Prevention Program Research Group: The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care* 25:2165–2171, 2002

108. Eriksson KF, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmo feasibility study. *Diabetologia* 34:891–898, 1991

109. Eriksson KF, Lindgarde F: No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmo Preventive Trial with diet and exercise. *Diabetologia* 41:1010–1016, 1998

110. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991

111. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 268:63–67, 1992

112. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991

113. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Lee CD, Blair SN: The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. *Ann Intern Med* 130:89–96, 1999

114. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE: Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA* 282:1433–1439, 1999

115. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB: Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med* 161:1542–1548, 2001

116. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345: 790–797, 2001

117. Burchfiel CM, Sharp DS, Curb JD, Rodriguez BL, Hwang LJ, Marcus EB, Yano K: Physical activity and incidence of diabetes: the Honolulu Heart Program. *Am J Epidemiol* 141:360–368, 1995

118. Lynch J, Helmrich SP, Kakha TA, Kaplan GA, Cohen RD, Salonen R, Salonen JT: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med* 156:1307–1314, 1996

119. Boulé NG, Haddad E, Kenny GP, Wells GA, Sigal RJ: Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 286: 1218–1227, 2001

119a. Holloszy JO, Constable SH, Young DA: Activation of glucose transport in muscle by exercise. *Diabetes Metab Rev* 1:409–423, 1986

120. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ: Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia* 46:1071–1081, 2003

121. Mourier A, Gautier JF, De Kerviler E, Bigard AX, Villette JM, Garnier JP, Duvallet A, Guezennec CY, Cathelineau G: Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM: effects of branched-chain amino acid supplements. *Diabetes Care* 20:385–391, 1997

122. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN: Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med* 132: 605–611, 2000

123. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, Blair SN: Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 27:83–88, 2004

124. U.S. Department of Health and Human Services: *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996

125. American College of Sports Medicine: American College of Sports Medicine Position Stand: the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc* 30: 975–991, 1998

126. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner D, Ettinger W, Heath GW, King AC, et al.: Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 273:402–407, 1995

127. Albright A, Franz M, Hornsby G, Kriska A, Marrero D, Ullrich I, Verity LS: American College of Sports Medicine Position Stand: exercise and type 2 diabetes. *Med Sci Sports Exerc* 32:1345–1360, 2000

128. Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, Manson JE: Physical activity and risk for cardiovascular events in diabetic women. *Ann Intern Med* 134:96–105, 2001

129. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE: Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 346:793–801, 2002

130. Whelton SP, Chin A, Xin X, He J: Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 136:493–503, 2002

131. Leon AS, Sanchez OA: Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc* 33:S502–S515, 2001 [discussion in *Med Sci Sports Exerc* 33:S528–S509, 2001]

132. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA: Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med* 347: 1483–1492, 2002

133. Despres JP: Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. *Exerc Sport Sci Rev* 25:271–300, 1997

134. Despres JP, Lamarche B: Low-intensity endurance exercise training, plasma lipoproteins and the risk of coronary heart disease. *J Intern Med* 236:7–22, 1994

135. Despres JP, Lamarche B, Bouchard C, Tremblay A, Prud'homme D: Exercise and the prevention of dyslipidemia and coronary heart disease. *Int J Obes Relat Metab Disord* 19 (Suppl. 4):S45–S51, 1995

136. Després JP, Couillard C, Bergeron J, Lamarche B: Regional body fat distribution, the insulin resistance-dyslipidemic syndrome, and the risk of type 2 diabetes and coronary heart disease. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 197–234

137. Stewart KJ: Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. *JAMA* 288:1622–1631, 2002

138. Wallberg-Henriksson H, Rincon J, Zierath JR: Exercise in the management of non-insulin-dependent diabetes mellitus. *Sports Med* 25:25–35, 1998

139. Zachwieja JJ, Toffolo G, Cobelli C, Bier DM, Yarasheski KE: Resistance exercise and growth hormone administration in older men: effects on insulin sensitivity and secretion during a stable-label intravenous glucose tolerance test. *Metabolism* 45:254–260, 1996

140. Wing RR: Exercise and weight control. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 355–364

141. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I: Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. *Ann Intern Med* 133:92–103, 2000

142. Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO: A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr* 66:239–246, 1997

143. Pavlou KN, Krey S, Steffee WP: Exercise as an adjunct to weight loss and maintenance in moderately obese subjects. *Am J Clin Nutr* 49:1115–1123, 1989

144. Schoeller DA, Shay K, Kushner RF: How much physical activity is needed to minimize weight gain in previously obese women? *Am J Clin Nutr* 66:551–556, 1997

145. Weinsier RL, Hunter GR, Desmond RA, Byrne NM, Zuckerman PA, Darnell BE: Free-living activity energy expenditure in women successful and unsuccessful at maintaining a normal body weight. *Am J Clin Nutr* 75:499–504, 2002

146. Saris WH, Blair SN, van Baak MA, Eaton SB, Davies PS, Di Pietro L, Fogelholm M, Rissanen A, Schoeller D, Swinburn B, Tremblay A, Westerterp KR, Wyatt H: How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st Stock Conference and consensus statement. *Obes Rev* 4:101–114, 2003

147. Reference deleted.

148. Willey KA, Fiatarone-Singh MA: Battling insulin resistance in elderly obese people with type 2 diabetes: bring on the heavy weights. *Diabetes Care* 26:1580–1588, 2003

149. Hornsby WG, Chetlin RD: Resistance training. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 311–319

150. Ivy JL: Role of exercise training in the prevention and treatment of insulin resistance and non-insulin-dependent diabetes mellitus. *Sports Med* 24:321–336, 1997

151. American College of Sports Medicine: American College of Sports Medicine Position Stand: exercise and physical activity for older adults. *Med Sci Sports Exerc* 30:992–1008, 1998

152. Eriksson J, Taimela S, Eriksson K, Parviainen S, Peltonen J, Kujala U: Resistance training in the treatment of non-insulin-dependent diabetes mellitus. *Int J Sports Med* 18:242–246, 1997

153. Ishii T, Yamakita T, Sato T, Tanaka S, Fujii S: Resistance training improves insulin sensitivity in NIDDM subjects without altering maximal oxygen uptake. *Diabetes Care* 21:1353–1355, 1998

154. Honkola A, Forsen T, Eriksson J: Resistance training improves the metabolic profile in individuals with type 2 diabetes. *Acta Diabetol* 34:245–248, 1997

155. Dunstan DW, Puddey IB, Beilin LJ, Burke V, Morton AR, Stanton KG: Effects of a short-term circuit weight training program on glycaemic control in NIDDM. *Diabetes Res Clin Pract* 40:53–61, 1998

156. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D: Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. *Diabetes Res Clin Pract* 56:115–123, 2002

157. Baechle TR, Earle RW: *Essentials of Strength Training and Conditioning.* Champaigne, IL, Human Kinetics, 2000

158. Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ: Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care* 26:2977–2982, 2003

159. Dunstan DW, Daly RM, Owen N, Jolley D, de Courten M, Shaw J, Zimett P: High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care* 25:1729–1736, 2002

160. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, Roubenoff R, Tucker KL, Nelson ME: A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care* 25:2335–2341, 2002

161. Castaneda C, Layne JE, Gordon PL, Huyng T, Foldari M, Walsmith J, Munoz-Orians L, Roubenoff R, Nelson ME: Skeletal muscle hypertrophy in poorly controlled Hispanic older adults with type 2 diabetes in response to progressive resistance exercise training, *FASEB J* 24:A24, 2002

162. Evans WJ: Exercise and aging. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 567–585

163. Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ: Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures: a randomized controlled trial. *JAMA* 272:1909–1914, 1994

164. Carpinelli RN, Otto RM: Strength training: single versus multiple sets. *Sports Med* 26:73–84, 1998

165. Reference deleted

166. Wenger NK, Froelicher ES, Smith LK, Ades PA, Berra K, Blumenthal JA, Certo CM, Dattilo AM, Davis D, DeBusk RF, et al.: Cardiac rehabilitation as secondary prevention: Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute. *Clin Pract Guidel Quick Ref Guide Clin* 17:1–23, 1995

167. Featherstone JF, Holly RG, Amsterdam EA: Physiologic responses to weight lifting in coronary artery disease. *Am J Cardiol* 71:287–292, 1993

168. Lombardi VP, Troxel RA: US deaths and injuries associated with weight training (Abstract). *Med Sci Sports Exerc* 35:S203, 2003

169. McCartney N: Role of resistance training in heart disease. *Med Sci Sports Exerc* 30: S396–S402, 1998

170. Gordon NF, Kohl HW 3rd, Pollock ML, Vaandrager H, Gibbons LW, Blair SN: Cardiovascular safety of maximal strength testing in healthy adults. *Am J Cardiol* 76:851–853, 1995

171. Benn SJ, McCartney N, McKelvie RS: Circulatory responses to weight lifting, walking, and stair climbing in older males. *J Am Geriatr Soc* 44:121–125, 1996

172. Shrier I: Stretching before exercise does not reduce the risk of local muscle injury: a critical review of the clinical and basic science literature. *Clin J Sport Med* 9:221–227, 1999

173. Yeung EW, Yeung SS: Interventions for preventing lower limb soft-tissue inju-

ries in runners. *Cochrane Database Syst Rev* 3:CD001256, 2001

174. Beniamini Y, Rubenstein JJ, Zaichkowsky LD, Crim MC: Effects of high-intensity strength training on quality-of-life parameters in cardiac rehabilitation patients. *Am J Cardiol* 80:841–846, 1997

175. Bennett PJ, Stocks AE, Whittam DJ: Analysis of risk factors for neuropathic foot ulceration in diabetes mellitus. *J Am Podiatr Med Assoc* 86:112–116, 1996

176. Berger M, Berchtold P, Cuppers HJ, Drost H, Kley HK, Muller WA, Wiegelmann W, Zimmerman-Telschow H, Gries FA, Kruskemper HL, Zimmermann H: Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. *Diabetologia* 13:355–365, 1977

177. Berger M: Adjustment of insulin and oral agent therapy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 365–376

178. Aiello LP, Wong J, Cavallerano JD, Bursell S-E, Aiello LM: Retinopathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 401–413

179. Vinik AI, Erbas T: Neuropathy. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 463–496

180. Levin ME: The diabetic foot. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 385–399

181. Valensi P, Sachs RN, Harfouche B, Lormeau B, Paries J, Cosson E, Paycha F, Leutenegger M, Attali JR: Predictive value of cardiac autonomic neuropathy in diabetic patients with or without silent myocardial ischemia. *Diabetes Care* 24:339–343, 2001

182. Mogensen CE: Nephropathy: early. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin JT, Schneider SH, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 433–449

183. Ward KM, Mahan JD, Sherman WM: Aerobic training and diabetic nephropathy in the obese Zucker rat. *Ann Clin Lab Sci* 24:266–277, 1994

184. Albright AL, Mahan JD, Ward KM, Sherman WM, Roehrig KL, Kirby TE: Diabetic nephropathy in an aerobically trained rat model of diabetes. *Med Sci Sports Exerc* 27:1270–1277, 1995

185. Castaneda C, Gordon PL, Uhlin KL, Levey AS, Kehayias JJ, Dwyer JT, Fielding RA, Roubenoff R, Singh MF: Resistance training to counteract the catabolism of a low-protein diet in patients with chronic renal insufficiency: a randomized, controlled trial. *Ann Intern Med* 135:965–976, 2001

186. Health Canada: *Canada's Physical Activity Guide to Healthy Active Living.* Ottawa, Government of Canada, 1998

187. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML: Exercise standards: a statement for healthcare professionals from the American Heart Association Writing Group. *Circulation* 91:580–615, 1995

188. American Association of Cardiovascular and Pulmonary Rehabilitation: *Guidelines for Cardiac Rehabilitation Programs.* Champaign, IL, Human Kinetics Publishers, 1999

189. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee: Physical activity and diabetes. *Can J Diabetes* 27:S24–S26, 2003

190. American Diabetes Association: Diabetes mellitus and exercise (Position Statement). *Diabetes Care* 25 (Suppl. 1):S64, 2002