Role of exercise training on cardiovascular disease in persons who have type 2 diabetes and hypertension

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Regular exercise is an important modality in the treatment of type 2 diabetes. Most studies of exercise training in patients who had diabetes were concerned with glycemic and weight control and less on its affect on cardiovascular health. Hypertension is a common comorbid condition in patients who have type 2 diabetes. Although it is well-established that exercise reduces blood pressure in persons who do not have diabetes, the effects of exercise on blood pressure and parameters of cardiovascular structure and function in patients who have type 2 diabetes and hypertension has not been examined fully. This article identifies the cardiovascular consequences of these conditions, discusses the potential mechanisms by which exercise training may improve cardiovascular health, and provides practical guidelines for exercise prescription.

Type 2 diabetes and cardiovascular health

Type 2 diabetes is associated with dysfunction and failure of various organs, especially the heart and peripheral blood vessels. The molecular basis for type 2 diabetes is poorly understood but insulin resistance and β-cell dysfunction are well-documented [1,2]. Environmental influences and genetic factors [3,4], and in particular, the increasing prevalence of obesity [5] and a sedentary lifestyle [6] are likely contributors to the increasing prevalence of type 2 diabetes.

Two other metabolic conditions that precede the development of overt diabetes also have adverse effects on cardiovascular health. Prediabetes is a metabolic condition that is between normal glucose homeostasis and diabetes [7]; its prevalence in 2000 was estimated at nearly 12 million adults in the United States [8]. The risk of progressing from prediabetes to overt diabetes is about 10% over 6.5 years [9]. There also is a 40% increased risk of mortality, independent of other risk factors, in persons who have impaired glucose tolerance [10]. The metabolic syndrome also stems from an underlying abnormality in insulin resistance [11–13]. The Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III) [14] included clinical criteria for diagnosis of the metabolic syndrome. Its estimated prevalence is greater than 20% of the United States adult population [15] and approaches 50% in older groups [16].

Although type 2 diabetes increases the risk of microvascular complications, such as retinopathy and nephropathy [17,18], most diabetic patients die of macrovascular complications, including coronary artery disease and stroke. Type 2 diabetes increases the risk of cardiovascular disease by 200% to 400% [19]. The burden of cardiovascular disease is pronounced, especially in women who have diabetes [20]. The risk of macrovascular disease is increased before glucose levels reach the diagnostic threshold for diabetes; 25% of newly diagnosed patients already have overt cardiovascular disease [21].

The coexistence of type 2 diabetes and hypertension

Hypertension is associated with diabetes, largely independent of age and obesity [22], although abdominal visceral obesity is an especially strong risk factor for the development of both conditions [23]. Hypertension is part of the metabolic
syndrome [24], with a prevalence as high as 60% in patients who have type 2 diabetes [25]. According to The Seventh Report Of The Joint National Committee On Prevention, Detection, Evaluation, and Treatment Of High Blood Pressure [26], diabetes is a compelling indication for treating hypertension aggressively in affected patients. There is an estimated doubling of cardiovascular events when hypertension and diabetes coexist [27]. These patients have abnormalities in central and peripheral parameters of cardiovascular structure and function that precede the clinical manifestation of cardiovascular disease, including increased left ventricular mass and wall thickness, left ventricular diastolic filling abnormalities, impaired endothelial function, increased arterial stiffness, and systemic inflammation. In the Strong Heart study [28], clinically-relevant findings were that left ventricular mass was 6% to 14% greater, left ventricular function was 5% less, and arterial stiffness was 12% greater among patients with diabetes. Although glycemic control is essential for preventing microvascular disease [29], intensive blood pressure control is required for reducing cardiovascular events in diabetic patients who have hypertension [27,29]. Low-dosage diuretics, β-blockers, angiotensin-converting enzyme inhibitors, or calcium antagonists are used as first-line therapy [30]. In the Hypertension Optimal Treatment Study [31], intensive diastolic blood pressure lowering was associated with a 49% reduction in cardiovascular events in diabetic patients who had hypertension [27,29]. A meta-analysis of 14 trials reported that exercise training reduced hemoglobin A1c (HbA1c) by 0.66%—a clinically important reduction [35]. An evidence-based review found that the effect of aerobic or resistance training on glycemic control in type 2 diabetes is positive, although evidence for a dose-response relationship is lacking [36].

Increased participation in exercise also plays a role in the prevention of type 2 diabetes and related metabolic conditions. Laaksonen and colleagues [37] found that men who engaged in more than 3 hours per week of moderate or vigorous leisure time physical activity were half as likely as their sedentary counterparts to develop the metabolic syndrome over a follow-up period of 4 years. In the multicultural Insulin Resistance Atherosclerosis Study [38], increased levels of nonvigorous and vigorous physical activity were associated with higher insulin sensitivity. Among women in the Nurse’s Health Study [39], sedentary behaviors, especially television watching, were associated with an elevated risk of obesity and type 2 diabetes, whereas even light to moderate activity was associated with a decreased risk of developing these conditions. In the Diabetes Prevention Program Research Group Study [40], which enrolled subjects who had impaired glucose tolerance, the intensive lifestyle intervention reduced the incidence of developing type 2 diabetes by 58%, whereas pharmacologic therapy with metformin reduced the incidence by 31% as compared with placebo. The lifestyle intervention, which included at least 30 minutes of moderate physical activity every day, was significantly more effective than metformin. The risk of developing diabetes after 4 years also was reduced by 58% after participation in a diet and exercise program in older, obese Finnish men and women [41].

The efficacy of exercise training to lower blood pressure is well-established in patients who do not have diabetes [42]. A meta-analysis of 54 randomized trials found that aerobic exercise was associated with an average reduction in blood pressure of 3.9/2.6 mm Hg across all initial blood pressure levels and was independent of body weight and race. Subgroup analysis showed an average
reduction of 4.9/3.7 mm Hg in hypertensive persons [43]. The degree of blood pressure reduction did not differ by frequency or intensity of exercise; this suggests that all forms are effective. This notion is supported by a recent study [44] that reported a decrease in blood pressure of about 6/6 mm Hg with 30 to 60 minutes of physical activity per week in previously sedentary hypertensive subjects. The magnitude of reduction in systolic blood pressure was about 11 mm Hg with 61 to 90 minutes of activity; however, there were no further reductions in blood pressure with further increases in amount of time spent in exercise. There did not seem to be any dose-response relation for diastolic blood pressure. These results suggest that the volume of exercise that is required to reduce blood pressure may be modest and should be attainable by a sedentary hypertensive population. Another meta-analysis of 47 trials [45] estimated decreases in blood pressure of 6/5 mm Hg (about 4/5%) in hypertensive patients and decreases of 2/3 mm Hg (about 2/1%) in normotensive persons [47]. In another meta-analysis of 16 studies with walking as the intervention, normotensive and hypertensive patients decreased their blood pressure by 3/2 mm Hg (about 2%) after an average of 25 weeks [46]. In older persons who had mild or moderate hypertension who performed endurance exercise for 7 months, the reduction in systolic blood pressure was accompanied by regression of left ventricular mass and concentric left ventricular remodeling [47]. Because of differences among studies in the type, intensity, and duration of exercise; baseline blood pressure; and concomitant use of antihypertensive medications, there is wide variation in the magnitude of blood pressure reduction across studies and meta-analyses. Nonetheless, exercise training seems to reduce blood pressure to some degree.

Exercise can play an important role in glycemic and blood pressure control; however, few studies have investigated the effect of physical activity on cardiovascular disease outcomes among patients who had type 2 diabetes. In the Health Professionals’ Follow-up Study [48], a large-scale epidemiologic trial, physical activity was associated with reduced risk of cardiovascular disease, cardiovascular death, and total mortality in men who had type 2 diabetes after 14 years of follow-up. Although no randomized exercise trials have examined the efficacy of exercise on the cardiovascular consequences of diabetes and hypertension, studies in patients who had diabetes, hypertension, cardiovascular disease, or related conditions, and animal data suggest that exercise training also is a potentially efficacious treatment for improving cardiovascular health in patients who have these conditions.

Left ventricular diastolic dysfunction: a precursor to heart failure

Heart failure is a frequent consequence of type 2 diabetes, independent of coronary artery disease [49,50]. The most common feature of the diabetic heart is abnormal early left ventricular diastolic filling which suggests reduced compliance or prolonged relaxation [51]. Several mechanisms for diabetic cardiomyopathy have been proposed, including small and microvascular disease, autonomic dysfunction, metabolic derangements, and interstitial fibrosis [50]. Hypertension also is associated with impaired diastolic filling. [52] Several studies have demonstrated left ventricular diastolic dysfunction (LVDD) in patients who had well-controlled type 2 diabetes without cardiovascular complications [53–56]. Two similar studies evaluated patients who had type 2 diabetes who did not have clinical heart disease or hypertension [57,58]. Each used the Valsalva maneuver and pulmonary venous echocardiographic recordings to reveal a pseudonormal mitral flow pattern of left ventricular diastolic filling. Pseudonormalization refers to the masking of impaired left ventricular filling that is caused by a compensatory increase in left atrial pressure. Poirier et al [57] found LVDD in 28 subjects (60%), 13 of whom (28%) had a pseudonormal pattern of diastolic filling and 15 (32%) had impaired relaxation. Zabalgoitia et al [58] found LVDD in 41 subjects (47%), of which 15 (17%) had a pseudonormal-filling pattern and 26 (30%) had impaired relaxation. Thus, LVDD in patients who have type 2 diabetes may be more prevalent than the previously reported estimate of 32% [53]. Although the clinical relevance of pseudonormalization remains uncertain, this pattern denotes an advanced stage of LVDD which is a robust prognostic marker for heart failure [59]. A recent study reported an association of LVDD with cardiac autonomic neuropathy in patients who had type 2 diabetes who were free of clinically overt heart disease [60]. This association was seen with the impaired relaxation or pseudonormal-filling pattern of LVDD and was independent of metabolic control.

LVDD is associated with reduced exercise performance in patients who have type 2 diabetes
and normal systolic function [61,62]. The left ventricular ejection fraction response to exercise may also be impaired although resting systolic function is normal [56]. Possible causes of left ventricular dysfunction are latent global myocardial ischemia [63,64] or metabolic myocardial disturbances [51,65]. Animal data suggest that impaired myocyte handling of calcium contributes to LVDD [66]. Scheuermann-Freestone et al [67] reported that patients who have type 2 diabetes and apparently normal cardiac function at rest have impaired myocardial and skeletal muscle energy metabolism during exercise. The abnormalities in circulating metabolic substrates correlated negatively with exercise tolerance. Some studies showed a correlation of glycemic control and LVDD with treatment [68,69], whereas others did not [53,70,71]. Differences in medications, treatment duration, duration of diabetes, techniques for measuring left ventricular diastolic function, and small sample sizes contribute to the lack of agreement among studies on the efficacy of glycemic control on cardiac function.

Generally, it is accepted that diabetes affects diastolic function before systolic function. Fang et al [72] used newer tissue Doppler imaging techniques to demonstrate subtle abnormalities in systolic function, in addition to diastolic function, in patients who had diabetes but not coronary disease. The same investigators also examined myocardial reflectivity—an echocardiographic finding that is indicative of collagen accumulation—and reduced myocardial strain rate—a fundamental quality of tissue that reflects its ability to shorten [73]. Patients who had diabetes but did not have left ventricular hypertrophy demonstrated evidence of abnormalities in these indices of systolic structure and function that were similar to those that were attributed to left ventricular hypertrophy alone; these were incrementally worse in patients who had both conditions.

Exercise and left ventricular diastolic dysfunction

The age-related decline in early diastolic filling is less pronounced in healthy, older persons who have a long history of endurance exercise compared with their sedentary peers [74,75]. Moderate-intensity aerobic and resistance exercise for 10 weeks improved LVDD in men who had mild hypertension [76]. In healthy normotensive men, 60 to 82 years of age and 24 to 32 years of age [77], aerobic training for 6 months increased early diastolic filling at rest and during acute exercise by 14%, increased left ventricular mass by 8%, and increased maximal oxygen uptake by 19%. Training also reduced elevated resting atrial filling rate in the older men by 27%. The increased left ventricular mass and improved diastolic filling represent a desirable physiologic, rather than a pathologic, hypertrophy.

The mechanisms by which exercise training enhance early diastolic filling have not been elucidated fully. Twelve weeks of treadmill running reversed the age-associated decline in early diastolic filling in older rats, whereas controls did not improve [78]. Relevant to patients who have type 2 diabetes and hypertension who are at a high risk for atherosclerotic disease, the increased degree of diastolic stiffening that is due to ischemia in isolated rat hearts was not seen in the exercise-trained group. Abete et al [79] found that exercise training may restore ischemia preconditioning, a powerful endogenous cardioprotective mechanism, in the senescent rat heart through an increase of norepinephrine release. Exercise training in these animals was performed at an intensity of 70% to 85% of maximal oxygen uptake, whereas the recommended starting intensity is 40% to 70% for most patients who have type 2 diabetes [25]. Although some patients may perform a higher intensity of exercise gradually [80], it is unknown if less intensive exercise produces comparable enhancements in diastolic filling in humans.

Impairment of endothelial vasodilator function

Impaired endothelium-dependent vasodilator function in the micro- and macrocirculation, which is mediated primarily by nitric oxide, is well-established in type 2 diabetes [81–87]. An attenuation of leg blood flow secondary to impaired endothelium-dependent vasodilation was demonstrated in patients who had type 2 diabetes [88]. This mechanism may be of importance in determining the leg ischemic threshold in diabetic individuals who have peripheral arterial disease. Impairment of endothelial function also is found in patients who have hypertension [89] and was related independently to left ventricular mass in patients who had mild hypertension but who did not have left ventricular hypertrophy [90]. Endothelial dysfunction seems to be part of the metabolic syndrome, independent of hyperglycemia [91]. Some data suggest that sustained
hyperinsulinemia impairs nitric oxide synthesis, which may contribute to the development of insulin resistance and hypertension [92,93].

Exercise and endothelial vasodilator function

Exercise increases blood flow to active muscles; the elevated shear stress on the vessel walls could be a mechanism for the increased production of endothelium-derived nitric oxide that leads to smooth muscle relaxation and vasodilation [94]. In a rat model of noninsulin-dependent diabetes [95], 16 weeks of running, but not food restriction or a sedentary condition, improved endothelial vasodilator function in the aorta—presumably because of an increase in nitric oxide—as suggested by increased urinary nitrite excretion. Regular physical activity improved endothelium-dependent vasodilation in patients who had type 1 diabetes [96], coronary artery disease [97], heart failure [98], and peripheral arterial disease [99]. In a randomized, crossover study, patients who had type 2 diabetes who performed 8 weeks of aerobic and resistance training had improved reactive hyperemic brachial artery vasodilation and forearm blood flow [100]. Because the exercise regimen avoided hand and forearm exercises, the improvements in endothelial vasodilator function can be attributed to systemic effects of exercise, rather than a local response in the exercise-trained arm. In contrast, nondiabetic subjects who also exercised had no improvement in endothelial function, despite increases in fitness [101]. In a randomized, controlled trial, exercise training improved brachial artery endothelial vasodilator function in patients who had the metabolic syndrome [102]. The 12-week program, which consisted of three weekly sessions of stationary cycling at 80% of maximal heart rate for 30 minutes, induced an increase of 18% in fitness, but no change in the baseline blood pressure of 148/95 mm Hg, BMI, insulin resistance, lipids, and big endothelin-1. The improved vasodilator function was not explained by any known atherosclerosis risk factors; this suggests that chronic exercise hyperemia may upregulate endothelial release of nitric oxide directly. In other studies, 12 weeks of brisk walking in patients who had mild to moderate hypertension improved endothelial vasodilator function through increased nitric oxide release [103,104]. Blood pressure decreased by a mean 8/4 mm Hg but the improvements in endothelial function did not correlate with blood pressure changes.

Besides vasomotor tone, the endothelium also regulates fibrinolysis and thrombosis, the inflammatory response, and growth of vascular smooth muscle [105]. Exercise training seems to improve endothelial function; it may be through this mechanism that exercise may improve the cardiovascular health of patients who have type 2 diabetes and hypertension.

Increased arterial stiffness

With aging and hypertension, the arteries stiffen from progressive degeneration of the arterial media, increased collagen and calcium content, and large artery dilation and hypertrophy [106]. Aortic stiffening is a stronger predictor of cardiovascular events and recently was shown to be an independent predictor of fatal stroke in patients who had essential hypertension [107]. The process of artery stiffening is accelerated by diabetes [28,108] and insulin resistance [109]. The Atherosclerosis Risk in Communities Study [110], a large sample of middle-aged men and women, found that several indices of common carotid artery stiffness were greater in patients who had type 2 diabetes or impaired glucose tolerance compared with persons who had normal glucose tolerance. Elevated glucose, insulin, and triglycerides levels contributed to increased artery stiffness. Glycation-induced cross-linking formation in interstitial collagen seemed to contribute to arterial stiffness in aging and diabetes [111]. Structural changes, like medial degeneration, reduce arterial compliance and cause more stiffening. These factors increase the systolic blood pressure and the risk of atherosclerosis and adverse cardiovascular events.

Exercise and arterial stiffness

It was suggested that growth factors that are released during repeated bouts of exercise may mediate stiffness or that increases in heart rate and blood pressure during exercise condition artery walls [112]. In rats that ran on exercise wheels for 16 weeks, aortic cross-sectional compliance was higher than in sedentary animals; this indicated favorable structural adaptations to exercise [113,114]. In the Baltimore Longitudinal Study of Aging [115], higher maximal oxygen uptake was associated with less arterial stiffness at any age and in both genders. Moreover, pulse wave velocity was decreased by 26% and carotid arterial pressure...
pulse augmentation index was decreased by 36% in men, ages 54 to 75 years who had a history of endurance training, when compared with their sedentary peers. In a similar cross-sectional study of men with a mean age of 75 years, a history of lifelong regular strenuous exercise was associated with less stiffness by the carotid arterial pressure pulse augmentation index [116].

These cross-sectional data suggest, but do not establish, cause and effect between increased fitness and reduced arterial stiffening. Conversely, in a small, randomized, crossover study of 10 patients who had isolated systolic hypertension who were aged 64 ± 7 years, 8 weeks of cycling at 65% of maximal heart rate had no effect on large artery stiffness [117]. Although aerobic capacity and workload increased, the baseline systolic blood pressure of 154 ± 7 mm Hg did not decrease with training. It is unknown whether established isolated systolic hypertension, a clinical manifestation of larger artery stiffening, is particularly resistant to exercise training compared with essential hypertension or whether exercise of longer than 8 weeks or of greater intensity is needed to reduce arterial stiffness. Longer-term exercise training in older men has been associated with reduced arterial stiffness [115,116]. Thus, although exercise-induced mechanisms that reduce arterial stiffness may be a potential benefit of the training response, randomized studies are needed to establish this benefit definitively.

Systemic inflammation: does it underlie the development of diabetes and hypertension?

In The Women’s Health Study [118], elevated C-reactive protein and interleukin-6 levels predicted the development of type 2 diabetes. This association was independent of BMI, family history of diabetes, smoking, exercise, alcohol use, and hormone replacement therapy. The Atherosclerosis Risk in Communities Study [119] reported that inflammation markers and endothelial dysfunction predicted the development of diabetes and obesity. In the Monitoring of Trends and Determinants in Cardiovascular Disease study [120], men who had C-reactive protein levels that were in the highest quartile (≥2.91 mg/L) had a 2.7 times higher risk of developing diabetes. This association was not statistically significant after adjustment for BMI, smoking, and systolic blood pressure; this suggested that inflammation could be a mechanism by which known risk factors, such as obesity, smoking, and hypertension promote the development of diabetes mellitus. C-reactive protein levels also are associated with many components of the metabolic syndrome [121]. In a cross-sectional study that involved 508 healthy men, elevated blood pressure was associated with inflammation markers [122]. Data from the Third National Health and Nutrition Examination Survey [123] suggest that increases in pulse pressure are associated with elevated C-reactive protein levels among healthy adults, independent of blood pressure. Thus, the chronic activation of the immune system may be a common adverse mechanism among cardiovascular and metabolic disease.

Exercise and inflammation

In the Cardiovascular Health Study [124], higher self-reported physical activity was associated with lower concentrations of several inflammation markers, independent of gender, cardiovascular disease, age, race, smoking, BMI, diabetes, and hypertension. In recent data from the National Health and Nutrition Examination Survey III [125], regular participants in jogging and aerobic dancing were less likely to have elevated cardiovascular markers, independent of age, race, sex, BMI, smoking, and health status. C-reactive protein levels were reduced after 9 months in distance runners but not in sedentary controls, which suggested that exercise has a systemic anti-inflammatory effect [126]. In patients who had chronic heart failure, 12 weeks of moderate-intensity cycling for 30 minutes, 5 days per week, improved exercise tolerance and attenuated peripheral inflammatory markers reflecting monocyte/macrophage–endothelial cell interactions [127]. In a recent study, exercise training significantly reduced the local expression of tumor necrosis factor-α, interleukin-1β, and interleukin-6 in the skeletal muscle of patients who had chronic heart failure who exercised for 6 months; measurements in controls did not change [128]. There also was a reduction in the inducible isoform of nitric oxide synthase and intracellular accumulation of nitric oxide which was suggestive of less oxidative stress. Inflammatory markers also were reduced in patients who had peripheral arterial disease after 6 months of walking; this also improved claudication symptoms [129]. In a randomized, controlled trial program that
aimed to reduce body weight in premenopausal obese women, the intervention, which consisted of a low calorie diet and increased physical activity, was associated with a reduction in markers of vascular inflammation and insulin resistance [130]. Although direct data about the effects of exercise training on the inflammatory process in patients who have diabetes and hypertension are lacking, the available evidence suggests that a reduction in systemic inflammation is an important feature of the training response.

Exercise and lipoproteins

Patients who have type 2 diabetes have a dyslipidemia that is characterized by increases in atherogenic small, dense, low-density lipoprotein (LDL) subfractions and serum triglycerides and decreases in high-density lipoprotein (HDL)-2 cholesterol [131]. After a 4-week program of exercise training and reduced calorie diet in patients who had type 2 diabetes, reductions in body weight and improvements in glycemic control were associated with reductions in serum cholesterol and apolipoprotein B concentrations in very low-density lipoprotein, intermediate-density lipoprotein, and small, dense (>1.040 g/mL) LDL particles [132]. Thus, lifestyle interventions, including exercise, seem to improve the LDL subfraction profile with a decrease in small, dense LDL particles and may protect against cardiovascular disease, despite a lack of reduction of total or LDL cholesterol. Because the amount of exercise training, rather than the intensity of exercise, may be a more important determinant of lipoprotein particle size, it is important for patients to engage in frequent and regular exercise [133].

The role of body composition and fat distribution

The increasing prevalence of type 2 diabetes is correlated highly with the prevalence of obesity [134]. Based on data from Behavioral Risk Factor Surveillance System [135], the prevalence of obesity (BMI ≥30) 19.8% in 2000 and was 20.9% in 2001 (an increase of 5.6%), whereas the prevalence of diabetes increased to 7.9% from 7.3% (an increase of 8.2%). The prevalence of BMI of 40 or higher in 2001 was 2.3%. Overweight and obesity were associated significantly with diabetes, high blood pressure, high cholesterol, asthma, arthritis, and poor health status. In the Nurse’s Health Study [39], during 6 years of follow-up, sedentary behaviors, especially TV watching, were associated with significantly elevated risk of obesity and type 2 diabetes, whereas even light to moderate activity was associated with substantially lower risk. Besides total fat, abdominal obesity is an independent predictor of diabetes and hypertension [136–139] and may play a role in the development of cardiovascular abnormalities. A recent study found that intra-abdominal adiposity predicted coronary artery calcium scores in persons who had insulin resistance, independent of blood pressure, HDL, triglycerides, glucose, insulin, insulin resistance, or β-cell function [140]. In another study, impaired endothelial vasodilator function was predicted by abdominal obesity, independent of total body weight, blood pressure, and metabolic parameters [141]. Because visceral and subcutaneous adipose tissues are the major sources of cytokines (adipokines), increased adipose tissue is associated with alteration in adipokine production, such as overexpression of tumor necrosis factor-α, interleukin-6, plasminogen activator inhibitor-1, and underexpression of adiponectin in adipose tissue [87]. The proinflammatory status that is associated with these changes also provides a potential link between insulin resistance, endothelial dysfunction, and type 2 diabetes.

Exercise and body composition

The exercise training–induced improvements in glycemic control can occur independent of changes in total body weight. Because few studies report body mass in terms of lean and fat mass, or visceral fat, it is uncertain if glycemic changes are independent of reductions in fat mass or increases in lean tissue. Studies in persons who did not have diabetes showed that increased fitness and activity may reduce abdominal fat [137,142,143]; limited data suggest a preferential loss of abdominal visceral fat with exercise training [143,144]. A recent randomized trial in sedentary, overweight, postmenopausal women, a group who is at high risk for diabetes, showed that exercise training without diet for 12 months resulted in a 4.2% loss in total body fat and a 6.9% loss of intra-abdominal visceral fat [145]. A significant dose response for greater body fat loss was observed with increasing duration of exercise. Walking was the activity that was reported most frequently. In a randomized trial of patients who had type 2 diabetes, patients who performed high-intensity aerobic exercise three times per week for 2 months increased aerobic capacity by 41% and
insulin sensitivity by 46% [80]. Although there was no change in total body weight with exercise training, there was a 48% loss of abdominal visceral fat and an 18% loss of abdominal subcutaneous fat. The change in visceral fat correlated highly with improved insulin sensitivity. Obese women who did not have diabetes who performed moderate-intensity aerobic exercise four to five times a week for 14 months increased fitness and decreased body fat mass, with a greater loss of abdominal fat compared with midthigh fat [146]. A key finding was that the reduction in the insulinogenic index correlated with reductions in total fat mass and deep abdominal fat, but not with changes in fitness.

Thus, the reduction of abdominal obesity, either independently or in combination with changes in total fat, is an important benefit of exercise training. These changes in body composition and fat distribution are associated with decreases in blood pressure and improvements in glycemic control and they may play a role in improving the cardiovascular consequences of type 2 diabetes and hypertension.

Guidelines for exercise training

Generally, exercise is considered to be a standard of care for glycemic control and blood pressure reduction. Based on scientific evidence and expert opinion, exercise guidelines have been published by the American College of Sports Medicine for type 2 diabetes [25] and for hypertension [147]. Guidelines from the American Diabetes Association can be found in their *Handbook of Exercise in Diabetes* [148]. The key recommendations that are applicable to patients without significant health complications or limitations are summarized in Box 1.

Because patients who have diabetes and hypertension often have concomitant clinical or occult coronary artery disease, adverse cardiovascular and physiologic responses during exercise training are possible. The American Diabetes Association [149] and ATP III guidelines [150] consider diabetes as a coronary artery disease risk equivalent. The prevalence of silent myocardial ischemia in patients who have type 2 diabetes can be as high as 20% to 25%, especially in patients who are older than 60 years [151] or when the duration of diabetes is more than 10 years and there is the presence of other cardiovascular risk factors [152]. Thus, patients should undergo exercise stress testing before initiating a moderate-intensity exercise program or greater to identify ischemia, arrhythmias, anginal thresholds, and patients who have asymptomatic ischemia [153–155]. Exercise testing also provides data about heart rate and blood pressure responses for establishing an appropriate exercise prescription.

Patients should expend a minimum cumulative 1000 Kcal per week in aerobic exercise and participate in resistance training for improving fitness and body composition, reducing blood pressure, and controlling blood glucose levels [156,157]. Most patients can meet this level by exercising 3 days per week, whereas more frequent sessions are recommended when weight loss is a goal. Each exercise session should include 5 to 10 minutes of warm-up and 5 to 10 minutes of cool-down activities. Appropriate activities for these phases are calisthenics, range of motion, and low intensity aerobic exercise that allow for gradual transition to and from the higher metabolic demands of the main aerobic phase of the exercise session. Walking, cycling, and swimming are examples of aerobic activity; they should be increased gradually in duration to last for 30 to 45 minutes to reach energy expenditure recommendations [155].

Heart rate is the primary guide for aerobic exercise intensity and can be monitored by manually counting the pulse or with a heart rate monitor. The target heart rate for exercise is typically set at 60% to 90% of the maximum heart rate for healthy adults [155]. For patients who have diabetes and hypertension and other risk factors, such as smoking, hyperlipidemia, and obesity that further increase their cardiovascular disease risk, a target heart rate that corresponds to 55% to 79% of maximum heart rate is used instead [155]. The maximal heart rate can be obtained from exercise testing [153]. In the absence of exercise testing and for patients whose heart rate response is not limited by medications or autonomic neuropathy [154] or a cardiac pacemaker, the maximal heart rate can be estimated from age using the formula:

$$220 - \text{age} = \text{maximum heart beats per minute (bpm)}$$

For example, the age-predicted maximal heart rate for a 60-year old is calculated as $220 - 60 = 160$ bpm. If the individual has uncomplicated diabetes, the target heart rate range would be 55% to 79% of 160 bpm, or 88 to 126 bpm.

In patients who have a low initial level of fitness, the target heart rate can be set at 50% to 60% of maximum and increased as tolerated. A lower heart
rate range also may be necessary for patients who have autonomic neuropathy, which limits the heart rate response during exercise. The use of β-blockers and abnormal exercise stress test findings, such as ischemic ECG changes, require individualized adjustment of the target heart rate because the general guidelines do not apply. Although β-blockers attenuated the heart rate response during exercise, they did not generally preclude an improvement in aerobic and muscle fitness [158].

The American College of Sports Medicine [25] and the American Heart Association, in its Scientific Advisory on Resistance Training in Individuals With and Without Cardiovascular Disease [159], recommend resistance training, when appropriately prescribed and supervised. Resistance training produces beneficial effects on muscular strength and endurance, cardiovascular function, metabolism, coronary risk factors, and psychosocial well-being. The American Diabetes Association advises the use of light to moderate weights and high repetitions for maintaining or enhancing upper body strength in nearly all patients who have diabetes [160]. For the elderly patient who has diabetes, light-intensity resistance training has positive effects on bone density, osteoarthritic symptoms, mobility impairment, and self-efficacy [161]. It also alleviates symptoms of anxiety, depression, and insomnia in individuals who have clinical depression [161]. Resistance training should be performed at least twice per week, with a typical workout consisting of a minimum of 1 set of 8 to 10 exercises to cover the large muscle groups of the upper and lower body [162]. If maximal muscle strength testing is available, 1-repetition maximum evaluation can be performed to determine the patient’s initial level of strength [163]. The weight intensity for subsequent workouts are set at a moderate level, which corresponds to a load of 30% to 50% of maximum strength. At a moderate intensity, the patient should be able to perform 12 to 15 repetitions. For example, if the 1-repetition maximum for a given exercise is 100 pounds, the weight lifted during the workout is 30 pounds to 50 pounds and it should be lifted 12 to 15 times.
When 15 repetitions of an exercise can be completed without difficulty, the weight should be increased by 5 pounds to 10 pounds to assure a progressive muscle overload [162]. If muscle strength testing is not done, the individual can select an initial weight that can be lifted with moderate difficulty approximately 10 to 15 times [159,164]. Weight machines are recommended for their ease of use and safety. Alternatively, if the initial load on a particular machine is too heavy or machines are not available, hand weights, barbells, or elastic bands can be used instead. Studies in patients who have type 2 diabetes are needed to determine if they should be performing more intense or frequent resistance training than the current recommendations because of the potential benefit of resistance training for increasing muscle mass and reducing fat mass [35].

Exercise precautions

The risk-benefit of exercise is highly favorable for most patients who have diabetes and hypertension; however, some precautions are warranted (Table 1). Moderate or severe hypertension (systolic blood pressure \( \geq 160 \text{ mm Hg} \) or diastolic blood pressure \( \geq 100 \text{ mm Hg} \)) should be controlled to lower levels before starting an exercise program [165]. An exercise stress test should be performed to rule out ischemia, complex arrhythmias, and symptoms. Although contraindications to exercise based on glycemic control have been established for type 1 diabetes [148], guidelines for type 2 diabetes are less definitive. Badenhop et al [166] evaluated exercising patients who had type 2 diabetes and baseline glucose levels that ranged from 60 mg/dL to 400 mg/dL. Patients who used insulin were excluded. In more than 550 cases, there was no episode of ketosis or hypoglycemia in the 24 hours after exercise and the occurrence of hypoglycemia (blood glucose \( < 60 \text{ mg/dL} \)) during exercise was 2%. Thus, patients who have type 2 diabetes who do not use insulin may not need to have their blood glucose checked routinely when exercising. Supplementary food should be available, but it usually is not required unless the exercise session is exceptionally vigorous and of long duration [25]. Patients who use insulin should be encouraged to exercise and be given

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<td>Retinal hemorrhage</td>
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<td>Avoid high-intensity exercises, rapid head movements, head down maneuvers, and Valsalva maneuvers, especially during resistance training</td>
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<tr>
<td>Foot injury</td>
<td>Neuropathy and peripheral artery disease</td>
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<td>Wear proper footwear, engage in low-impact exercise, perform daily examination of feet</td>
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<td>Nephropathy</td>
<td>Vascular disease, glomerulosclerosis</td>
<td>Proteinuria, hypertension</td>
<td>Avoid increasing systolic blood pressure ( &gt; 180 \text{ mm Hg} ) during exercise</td>
</tr>
</tbody>
</table>
instructions about blood glucose monitoring, insulin dosing, and supplementary foods. Guidelines for exercise training in patients who use insulin can be found elsewhere [167]. To minimize excessive blood pressure responses, patients should be told to maintain normal controlled breathing while performing resistance training. Although short periods of breath holding are unavoidable at higher exercise intensities, extended breath holding should be avoided. Precautions for patients who have diabetic peripheral and autonomic neuropathy [25,148] and peripheral arterial disease [168] are discussed elsewhere. There is no evidence that properly prescribed exercise worsens diabetic retinopathy and it may reduce or delay the risk of eye complications by reducing blood pressure, increasing HDL cholesterol [169], and increasing fitness [170]. Because of a concern for vitreous hemorrhage or traction retinal detachment retinopathy, exercise that involves straining, such as heavy resistance training, should be avoided in patients who have active proliferative diabetic retinopathy or moderate or worse non-proliferative diabetic retinopathy. The exact threshold for this risk is unknown [169]. Whether patients who have had laser or surgical procedures for diabetic retinopathy can undertake more vigorous resistive exercise is unknown.

Summary

Exercise training is an essential component in the medical management of patients who have type 2 diabetes and hypertension. Regular exercise improves the cardiovascular health of individuals who have these conditions through multiple

![Fig. 1. Overview of the potential beneficial effects of exercise training in diabetes and hypertension. In addition to the well-established improvements in glycemic control, blood pressure levels, and fitness, exercise training also contributes to improvements in the cardiovascular consequences of type 2 diabetes and hypertension.](image-url)
mechanisms (Fig. 1). These mechanisms include improvements in endothelial vasodilator function, left ventricular diastolic function, arterial stiffness, systematic inflammation, and reducing left ventricular mass. Exercise training also reduces total and abdominal fat, which mediate improvements in insulin sensitivity and blood pressure, and possibly, endothelial function.

Persons who are in a prediabetic stage or those who have the metabolic syndrome may be able to prevent or delay the progression to overt diabetes by adopting a healthier lifestyle, of which increasing habitual levels of physical activity is a vital component. Most persons who have diabetes and hypertension or are at risk for these conditions should be able to initiate an exercise program safely after appropriate medical screening and the establishment of an individualized exercise prescription.

Despite the increasing amount of evidence that shows the benefits of exercise training, this modality of prevention and treatment continues to be underused. Although patients’ lack of knowledge of the benefits of exercise or lack of motivation contributes to this underuse, a lack of clear and specific guidelines from health care professionals also is an important factor. Clinicians need to educate patients about the benefits of exercise for managing their type 2 diabetes and assist in formulating specific advice for increasing physical activity. Specific instructions should be given to patients, rather than general advice, such as “you should exercise more often.” Many cardiac rehabilitation and clinical exercise programs can accommodate patients who have type 2 diabetes and hypertension. Such programs can establish individualized exercise prescriptions and provide an environment that is conducive for “lifestyle change” that underlies long-term compliance to exercise and risk factor modification.

References


[47] Turner MJ, Spina RJ, Kohrt WM, Ehsani AA. Effect of endurance exercise training on left ventricular size and remodeling in older adults with


