REVIEW ARTICLE

How can exercise reduce cardiovascular disease risk? A primer for the clinician

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KEY WORDS

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ABSTRACT

Despite advances in drug development and medical treatments, cardiovascular diseases (CVDs) remain a leading cause of mortality across the globe. Fortunately, CVD can be delayed by engaging in appropriate lifestyle behaviors. An abundance of epidemiological evidence supports a direct association between increased levels of physical activity or cardiovascular fitness and reduced premature CVD morbidity and mortality. These data have been used as the basis for many medical organizations to issue physical activity guidelines to citizens to improve physical activity participation and, ultimately, reduce the risk of CVDs and other chronic diseases. Despite these efforts, physical activity participation around the globe remains low. The medical professional is well suited to promote exercise as a preventative treatment for CVD, although promotion efforts may be less effective without a clear understanding of the mechanisms through which exercise confers cardioprotection. Thus, the purpose of this review is to highlight the cardioprotective effects of exercise training and to explore the underlying mechanistic pathways that might explain these benefits. The review will focus on those physiological pathways that are directly involved in atherosclerotic disease development. They include hypercholesterolemia, hypertension, chronic inflammation, and insulin resistance.

Introduction Advancements in drug development, medical devices, and imaging technologies have contributed to a significant decline in age-adjusted death rates from cardiovascular diseases (CVDs) over the last half century.[1] Yet, according to the World Health Organization, CVD remains the leading cause of death across the globe, accounting for 32% of all global deaths in 2019. Moreover, out of the 17 million deaths that occurred before the age of 70 years due to noncommunicable diseases, 38% were caused by CVD. Fortunately, the clinical threshold at which most CVDs compromise the health of individuals can be prevented or delayed by addressing lifestyle risk factors. Apart from eating a "healthy" diet and avoiding tobacco products, increasing levels of physical activity and exercise offers the most promising preventative treatment of CVDs.[2]

In 1953, Morris et al[3] reported that myocardial infarction among double-decker bus conductors in London was about half the rate as among the sedentary bus drivers. Shortly thereafter, in an 18-year follow-up prospective study of over 3000 San Francisco longshoremen, Paffenbarger et al[4] demonstrated that cargo handlers sustained mortality from coronary artery disease (CAD) at a 27% lower rate than their less active counterparts. At the same time, Slattery et al[5] were measuring cardiorespiratory fitness in a group of American railroad workers. The advantage of objectively measured cardiorespiratory fitness over classifying individuals according to job status is that it more accurately reflects physical activity habits at the time of assessment.[6] The researchers[5] followed the railroad workers for an average of 20 years and found that among the 2578 men who were free from diagnosed CVD when first examined, the least fit had the greatest risk of dying of coronary heart disease. Blair et al[7] extended these findings by demonstrating in a cohort of nearly 10 000 men that those who improved their fitness at subsequent medical examinations had an approximate 50% reduction in the risk of CVD mortality compared with those who were unfit at both examinations.

Since the publication of these landmark epidemiological papers, further evidence has accumulated that supports an independent and graded

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relationship between higher levels of physical activity and cardiorespiratory fitness and lower incidence of CVD outcomes.[8-11] Importantly, the protective benefits extend to women as well. For instance, among 73 743 postmenopausal, ethnically diverse women, those who reported a weekly energy expenditure score of over 10 metabolic equivalent (MET) hours per week and at least 100 minutes of vigorous exercise per week were about 60% less likely to develop CVD[12] compared with women who reported less than 2 MET hours per week and no vigorous exercise. Moreover, data derived from the Women's Health Study[13] show a linear reduction in CVD with a higher level of physical activity. Specifically, compared with a reference group of women who reported less than 200 kcal per week burned during physical activity at the baseline visit, those who achieved an activity level of 200 to 599 kcal, 600 to 1499 kcal, and more than 1500 kcal burned per week had relative risk reductions of CVD of 27%, 32%, and 41%, respectively.[13] Finally, in a representative cohort study[14] of 4840 American men and women over the age of 40 years, those who took 8000 steps per day, compared with those taking 4000 steps per day, had lower CVD morality (ie, 2.1 vs 4.6 deaths per 1000 adults per year) after adjustment for age, diet quality, body mass index, smoking status, and other CVD risk factors.

Given the strong evidence demonstrating that an "active" lifestyle is cardioprotective, (and, similarly, that a sedentary lifestyle is inherently dangerous),[15] several nations have issued guidelines for physical activity participation. The first of these documents was issued by the Center for Disease Control and Prevention and the American College of Sports Medicine (ACSM) in 1995.[16] The objectives of these evidence-based position statements are to encourage Americans of all ages to increase participation in physical activity and to provide guidance on the types and amount of exercise needed to promote good health and avoid chronic disease. Most recently, the American Heart Association and American College of Cardiology[17] and the European Society of Cardiology and European Atherosclerosis Society[18] have published nutrition and physical activity guidelines specific for the primary prevention of cardiovascular disease. With respect to general physical activity recommendations, both reports suggest that citizens achieve 150 minutes per week of moderate-intensity (3–5.9 METs) physical activity or 75 minutes per week of vigorous-intensity (>6 METs) physical activity, while emphasizing that individuals who cannot meet these thresholds may accrue cardioprotective benefits simply by increasing the physical activity levels above the baseline. A separate report, issued by the United States Preventative Services Task Force,[19] advises that patients with known hypertension, dyslipidemia, or metabolic syndrome achieve 90 to 180 minutes per week of moderate to vigorous physical activity. Furthermore, in 2007, the ACSM, in collaboration with the American Medical Association, launched the Exercise is Medicine (EIM) nonprofit initiative designed to urge healthcare providers to assess physical activity levels of their patients, provide physically inactive patients with counseling, and prescribe exercise or referrals to physical activity resources.

Despite the publication of physical activity guidelines and EIM growing into a global health initiative with a presence in 40 countries, data from the United States indicate that levels of physical activity remain relatively low.[20,21] This trend may, in part, reflect a reluctance by practitioners to prescribe exercise, given the evidence from some studies suggesting that the risk of atrial fibrillation is increased in men who exercise more often[22,23] or at high intensities.[24] Yet, the data on this topic are conflicting[25] and while it is clear that the relative risks of sudden cardiac death and acute myocardial infarction are higher during vigorous exercise compared with rest, the absolute risk of these cardiac events is extremely low, especially for those who are frequently active.[26] Indeed, there is overwhelming evidence that exercise is safe for most people and the ACSM has published a new exercise preparticipation healthy screening model to eliminate unnecessary diagnostic testing that may result in false positives and thus serve as a barrier to initiating exercise programs.[26] Some have argued[2] that expanding our knowledge of the biological links between physical activity and CVD risk would help to boost physical activity promotion efforts. Indeed, if we are to convince medical professionals to embrace exercise as a medicine and, in turn, widely prescribe it to their patients, a clear understanding of its mechanisms of action is imperative.

The overarching goal of this review is to explore ways in which exercise, a form of structured physical activity, helps to reduce the risk of CVDs. It should be stated at the onset that this review is not intended to provide an exhaustive listing of all potential mechanistic pathways through which exercise confers cardioprotection. The list of these mechanisms is quite extensive[15,27] and it is beyond the scope of this paper to review them all. Nor is it intended to provide an in-depth comparison of the effectiveness of exercise in relation to drug treatments or other lifestyle interventions (eg, diet, weight loss, or smoking cessation). Furthermore, whether a genetic predisposition for certain CVD risk factors influences the responsiveness to exercise training is an important topic that has been widely studied,[28-30] but one that will not be explored on the following pages. Instead, this review is designed to provide the reader with a short, introductory primer on the topic. To provide the appropriate context, we begin with a discussion of atherosclerosis, arguably the initiating event in CVD development and, consequently, the leading cause of CAD and stroke.

Atherosclerosis Atherosclerosis is a disease of medium-sized and large arteries characterized by chronic inflammation and fibroproliferation. Comprehensive reviews of this topic can be found elsewhere.[31,32] Briefly, the development of atherosclerosis begins with the extravasation of low-density lipoprotein (LDL) particles through a leaky and dysfunctional endothelial layer into the subendothelial space, where they are oxidized and become proatherogenic. Adhesion molecules (eg, vascular cell adhesion moledule-1 [VCAM-1], E-selectin, P-selectin) become upregulated and help recruit circulating monocytes and T cells to the lesion.[33] Monocytes bind to the endothelial cells and migrate to the subendothelial space. Once there, they engulf the oxidized LDLs and transform to lipid-loaded macrophages that contain cholesteryl esters. The formation of these "foam cells" marks the first, asymptomatic stage of atherosclerosis. Further progression of the disease involves an immunoinflammatory response,[34] followed by fibroproliferation that is mediated by the smooth muscle cells of the intima layer. The reparative process conferred by the smooth muscle cells produces a collagen-rich matrix which offers protection against plaque rupture and thrombosis,[35] although the consequence of unmitigated atherogenic stimuli is a capacious response that stiffens the vessel (contributing to high blood pressure), narrows the lumen, and results in ischemia.[36] Ultimately, smooth muscle cell dysfunction or death leads to the destabilization of a lipid-rich fibrous plaque that is fragile and prone to rupture. The coronary arteries are among the most vulnerable locations for occlusion and plaque rupture. Not surprisingly, nearly 80% of all fatal heart attacks worldwide are the result of the rupture of plaques in the coronaries.[32]

Atherosclerotic stimuli **Cholesterol** Elevated levels of serum cholesterol appear to be the major driver of atherosclerotic plaque development in humans.[31,37] Serum cholesterol is carried by lipoprotein particles that transport dietary and endogenous lipids. Dietary lipids are carried by chylomicrons, whereas endogenously produced lipids are transported by LDLs and high-density lipoproteins (HDLs). Very–low-density lipoproteins (VLDLs) carry triglycerides (referred to as triglyceride-rich lipoproteins [TRLs]) synthesized in the liver and intestines to capillary beds to provide a source of energy for target tissues.[38] As alluded to above, the engulfing of LDL-derived cholesterol by macrophages and their subsequent oxidation is the major event leading to fatty streak formation. Conversely, HDL cholesterol prevents the modification of LDLs, and is considered the major mechanism involved in transporting cholesterol away from a lesion site and back to the liver, a process referred to as "reverse cholesterol transport," thus slowing the progression of plaque.[32] Moreover, while LDL particles can leak through the endothelial wall, VLDL particles cannot, due to their size. But once in circulation, VLDLs can be hydrolyzed along the luminal surface of capillaries, producing free fatty acids and TRL remnants, which contain more cholesterol than LDLs.[32] These remnants can be taken up by macrophages without being oxidized and, therefore, are considered to have a strong atherogenic effect.[38] Thus, CVD risk can be reduced by improving the lipid "profile" (ie, lowering serum levels of LDL and triglycerides and raising HDL cholesterol).

The case for exercise Evidence from the last several decades supports the notion that exercise training has a favorable effect on the blood lipid profile.[39-41] Leon et al[39] reviewed 51 aerobic exercise interventions and found that the most commonly observed lipid change was an increase in the HDL cholesterol level (mean change across the studies reviewed was +4.6%). This improvement was observed across studies utilizing moderate-to-high intensities of exercise in which diet was held constant. Moreover, the magnitude of improvement in the level of HDL cholesterol was not associated with changes in aerobic fitness– or exercise--induced changes in body weight. Significant reductions in LDL cholesterol and triglyceride levels were observed less frequently.

In a large randomized controlled trial, Kraus et al[42] examined the effects of different amounts and intensities of aerobic exercise on blood lipids. They randomized 111 men and women with mild-to-moderate dyslipidemia to 8 months of either a high amount (jogging approximately 32 km/week) of high--intensity exercise (65%–85% of peak oxygen consumption); a low amount (jogging approximately 19.2 km/week) of high-intensity exercise; a low amount of moderate-intensity exercise (40%–55% of peak oxygen consumption); or 6-month control. The high-high group exhibited a significant improvement in the levels of HDL cholesterol (+0.11378 mmol/l) and triglycerides (–0.7344 mg/dl), but no significant change in LDL cholesterol levels, compared with lesser intensity / amount of exercise. Still, O'Donovan et al[43] observed a significant reduction in LDL cholesterol levels following 24 weeks of high-intensity (80% of aerobic capacity), but not lower-intensity (60% of aerobic capacity) aerobic exercise in previously sedentary but otherwise healthy men. A more recent meta-analysis[41] indicates that high-intensity aerobic interval training, (ie, periods of high-intensity exercise interspersed with periods of active / passive recovery) is more effective at raising HDL cholesterol levels than moderate-intensity continuous exercise, independent of dietary or pharmaceutical interventions, for subclinical or clinical populations (eg, healthy or obese individuals taking usual medications). In contrast, exercise interventions[40] that examined the effectiveness of resistance exercise (ie, strength-developing exercises using body weight or external resistance) on lipid profiles have found significant reductions in LDL cholesterol and triglycerides levels with greater volume of exercise

(eg, more sets and repetitions), but not necessarily greater intensity (eg, higher loads).

Mechanisms of action While the mechanisms explaining the beneficial effects of exercise on the lipid profile have not been entirely elucidated, it is clear that exercise improves the ability of the skeletal muscle to use lipids as the primary food substrate, resulting in a reduction in plasma lipid levels.[44] This may be accomplished, in part, through the upregulation of lecithin cholesterol acyltransferase, the enzyme involved in HDL cholesterol formation and, in turn, reverse cholesterol transport or through the upregulation of lipoprotein lipase, which hydrolyzes triglycerides into free fatty acids and promotes the cellular uptake of TRL remnants. Previous data[45] in well-trained men suggest that an energy expenditure threshold (ie, approximately 1000 kcal) must be achieved to elicit an increased lipoprotein lipase activity. This threshold is likely to vary depending on an individual's previous exercise history, disease status (healthy vs hypercholesterolemic), intensity of exercise, age, sex, and exercise modality. While exercise-induced changes in the levels of LDL cholesterol and triglycerides appear less consistently across exercise training studies than improvement in HDL cholesterol levels and may require higher intensities of aerobic exercise to achieve, it appears that activity-induced improvements in HDL cholesterol can offset any increases in LDL cholesterol and triglycerides.

High blood pressure Hypertension tends to coexist with hypercholesterolemia.[46] The higher shear forces against the endothelial wall associated with chronically elevated blood pressure result in endothelial damage, making vessels more vulnerable to the incursion of LDLs to the subendothelial space. It is also believed that vascular structural and functional abnormalities (eg, endothelial dysfunction, vascular remodeling) precede clinically diagnosed hypertension. Thus, hypertension may act as an atherogenic stimulus as well as contribute to atherosclerosis progression. Moreover, chronically high blood pressure has significant consequences for the heart.[47] Cardiac myocytes grow larger in order to offset the increased arterial pressure; however, this increased growth is associated with an increased deposition of surrounding collagen that requires greater blood supply and results in decreased ventricular compliance. Eventually, the compensatory hypertrophy of the heart leads to subendocardial ischemia and heart failure. Since mean arterial pressure is the product of cardiac output and peripheral vascular resistance, a reduction in one or both factors would, in theory, help to reduce the CVD risk.

The case for exercise Aerobic exercise is recommended by the American Heart Association / American College of Cardiology,[17] the European Society of Hypertension / European Society of Cardiology,[48] and the Canadian Hypertension Education Program[49] as a first-line treatment for the prevention, treatment, and control of elevated blood pressure or hypertension. This recommendation is bolstered by numerous randomized controlled trials that report a mean reduction of blood pressure of 5 to 7 mm Hg following aerobic exercise programs.[50]

There is general agreement across these governing bodies that exercise should be performed on most, if not all, days of the week. This is based on evidence of an immediate reduction in blood pressure following a single, acute bout of aerobic exercise; a phenomenon referred to as postexercise hypotension.[51] This reduction in blood pressure can be sustained for 24 hours after exercise.[52] Importantly, the magnitude of reduction appears to be dose-dependent, as illustrated by Eicher et al,[53] who measured ambulatory blood pressure in 45 pre- / stage 1 hypertensive men after they completed low-intensity (40% of peak oxygen consumption), moderate-intensity (60% of peak oxygen consumption), and high-intensity (100% of peak oxygen consumption) exercise on a bicycle ergometer. The high intensity elicited the largest reduction in blood pressure (11.7/4.9 mm Hg), followed by moderate intensity (5.4/2.0 mm Hg) and low intensity (2.8/1.5 mm Hg). Moreover, a significant reduction in ambulatory blood pressure (6/3 mm Hg) was observed among a group of adults with resistant hypertension (eg, blood pressure above 140/90 mm Hg despite using 3 antihypertensive agents) who exercised at a moderate intensity, 3 days per week for 8 to 12 weeks.[54] Also, in a study[55] of 17 prehypertensive men and women who underwent blood pressure assessment before and after acute exercise and following 8 weeks of aerobic exercise training, it was reported that the magnitude of reduction in blood pressure following acute exercise was associated with the magnitude of decline in resting blood pressure after chronic training. Finally, Moraes et al[56] reported significant reductions in resting blood pressure (–16/–12 mm Hg) among middle-aged hypertensive patients who were deprived of antihypertensive medications, following 12 weeks of moderate-intensity resistance training.

Together, these data suggest the following: 1) a dose-response relationship exists between aerobic exercise intensity and improved blood pressure; although 2) lower intensities of exercise can be used to achieve clinically significant reductions in blood pressure among individuals with established hypertension but resistant to drug therapy; 3) blood pressure responses to acute exercise can be used to predict the magnitude of response following chronic training; and 4) reductions in blood pressure are observed across different exercise modalities.[52]

Mechanisms of action Cardiac output and total peripheral resistance contribute to mean arterial pressure and hence provide targets for antihypertensive therapies. Yet, a major benefit of exercise training is an increase in cardiac output at rest.

Thus, the principle means through which exercise is believed to maintain or lower blood pressure is through the reduction in total peripheral resistance. A number of exercise-induced vascular and autonomic adaptations have been proposed that potentially provide major contributions to blood pressure control.[57] These adaptations are briefly discussed below.

Firstly, hypertensive patients exhibit heightened sympathetic control, which results in increased total peripheral resistance via vasoconstriction of arterial beds.[58] This may be the result of increased sensitivity of baroreceptors,[55] located in the aortic arch and carotid sinus, that are responsible for monitoring changes in blood pressure. There is evidence that baroreceptor sensitivity is influenced by exercise.[59] For example, in a group of hypertensive patients, blood pressure and muscle sympathetic nerve activity declined following 4 months of cycle exercise (3 times per week at 70% of maximum capacity), and these changes corresponded with improvements in baroreflex control such that the levels of sensitivity were reset to the levels observed in normotensives.[60]

Secondly, exercise enhances vascular function through its effects on the local vascular control mechanisms. Specifically, exercise increases the bioavailability of nitric oxide,[61] a potent vasodilator, and decreases the bioavailability of endothelin-1, a vasoconstrictor,[62] both of which are secreted by the endothelial cells. This improvement in the nitric oxide vasodilator system with exercise training is seen consistently among groups of patients with CVD and risk factors and this is manifested as an improvement in endothelial function.[63] In a recent trial, Pedralli et al[64] observed similar improvements in endothelial function among patients with prehypertension or hypertension who engaged in 8 weeks of aerobic, resistance, or combined exercise. Importantly, all groups experienced improvements in ambulatory blood pressure. Previously, Maeda et al[65] found that endothelin-1 concentrations in previously sedentary normotensive older women (aged 61–69 years) were higher than in younger women (21–28 years). However, the concentrations were reduced significantly following 3 months (5 days per week) of cycling exercise and were accompanied by reductions in blood pressure.

Thirdly, in addition to improved endothelial function, exercise training leads to increased vessel size in the conduit arteries that feed active muscle beds.[66] This adaptation serves to normalize the increases in shear stress associated with repetitive exercise bouts.[67] Indeed, 6 months of resistance training that involved mostly upper body movement led to improved vasodilatory function and brachial artery remodeling, while 6 months of aerobic exercise involving the legs led to improved vasodilatory function and size of the femoral artery.[68]

Lastly, there are some data suggesting that exercise increases the compliance of large elastic arteries (eg, the aorta and carotids) which buffer the fluctuations in pressure with each beat of the heart. When arterial compliance is reduced, ventricular afterload is increased, resulting in left ventricular hypertrophy. Tanaka et al[69] reported an improvement in arterial compliance of the carotid artery among middle- to older-aged sedentary normotensive men (mean age, 53 years) following 3 months of aerobic exercise training (4 to 6 days per week at 70%–75% of the maximum capacity). In contrast, systemic arterial compliance was unaltered in adults with isolated systolic hypertension after 8 weeks (3 days per week) of moderate-intensity (65% of the maximum capacity) cycling.[70] Similarly, 20 weeks (3 days per week) of moderate-intensity (70% of the maximum capacity) aerobic exercise failed to alter carotid arterial stiffness in a group of older hypertensives (mean age, 68 years).[71] Finally, Stewart et al[72] found that while diastolic blood pressure improved following 6 months of combined aerobic and resistance exercise in a group of older (55–75 years) hypertensive patients, no changes in systolic blood pressure or aortic stiffness were observed. These conflicting data suggest age- and hypertension-related structural changes of elastic vessels resulting in the fact that effect compliance may not be modified with exercise training.

Chronic inflammation While the entrance of LDLs into the subendothelial space is arguably the initial event in the atherosclerotic process, inflammatory cells play a major role in every stage of its development.[33,73] LDLs are oxidized by reactive oxygen species which upregulate adhesion molecules (eg, VCAM-1, intercellular adhesion molecule-1 [ICAM-1], E-selectin, and P-selectin), ultimately leading to the recruitment of monocytes and T lymphocytes to the site of the lesion.[74] These, in turn, express a family of chemoattractant cytokines (eg, interferon γ, tumor necrosis factor-α [TNF-α], and interleukin-6), which cause smooth muscle cells to impede into the subendothelial space, eventually forming a fibrous cap.[75] Vascular endothelial growth factor (VEGF) is produced by inflammatory cells in the atherosclerotic plaque. VEGF stimulates microvessel growth (along with endothelial progenitor cells [EPCs]) that is needed to supply the plaque with nutrition, but plaque rupture can lead to hemorrhage and thrombosis.[76] Also, levels of C-reactive protein (CRP), which is produced in the liver, start to rise in response to the inflammatory process, which exacerbates endothelial dysfunction.[74] As the vessel thickens at the point of the lesion, blood flow is impeded, causing ischemia. Following the plaque rupture, the subendothelial factors that are exposed stimulate platelet activation and aggregation leading to thrombus formation and potentially triggering a stroke or myocardial infarction.[73] Accordingly, treatments aimed toward lowering the factors associated with inflammation (or raising EPC expression) could affect atherosclerosis progression, enhance endothelial function, and decrease cardiovascular risk.

The case for exercise There is strong evidence that exercise has positive effects on several, but not all, of the above factors involved in the atherosclerosis process. These data have been summarized and evaluated in a recent review.[73] For instance, Schumacher et al,[77] observed an inverse relation between the amount of physical work (ie, kilojoules / minute × minutes of exercise) performed during an exercise test following 6 months of aerobic exercise training and levels of TNF-α, VCAM-1, and CRP (see below) among patients with established CAD. In a group of patients with breast cancer, Pakiz et al[78] reported an association between the number of hours engaged in moderate-to-vigorous exercise over a 16-week weight loss program that included dietary counseling and favorable changes in TNF-α levels. For those with chronic heart failure,[79] 12 weeks of aerobic exercise led to significant reductions in ICAM and VCAM. Moreover, the improvement in aerobic fitness was correlated with the magnitude of reduction in these adhesion molecules. Similarly, VEGF levels decreased by 9% and myocardial blood flow increased by 33% in post–myocardial infarction patients after 3 months of exercise training.[80]

There is also evidence that both aerobic[77,81] and resistance exercise[82] reduces the levels of CRP. In addition to the abovementioned findings from Schumacher et al,[77] Lara Fernandes et al[81] found that CAD patients who underwent 4 months of aerobic exercise (60-min sessions 3 times per week) of moderate-to-high intensity exhibited a decreased CRP level in response to an acute bout of exercise. Also, Olson et al[82] randomized young (25–44 years), overweight women free from CVD to a resistance training program (twice weekly) or a control condition. They found significant reductions in CRP levels, but not in the levels of adhesion molecules, following 1 year of training.

Finally, some data suggest that exercise increases the levels of EPC. For example, Schlager et al[83] showed that levels of EPC and maximal walking distance increased in patients with peripheral artery disease following 6 months of aerobic exercise (eg, walking intermittently to claudication). Moreover, for older patients who underwent cardiac surgery, levels of EPCs increased following just 15 days of cardiac rehabilitation that consisted of moderate aerobic exercise, but only among patients who improved the 6-minute walking distance by at least 23% from baseline.[84]

The above data suggest that there is a strong link between the magnitude of improvement in various factors involved in chronic inflammation and levels of fitness achieved through exercise training, implying a dose-response relationship. Also, in contrast to what has been previously discussed regarding the effects of exercise on blood pressure (ie, older adults with established hypertension may be resistant to exercise-induced improvements in blood pressure), the exercise-mediated effects on inflammatory markers are observed in those who have developed CVD (eg, peripheral vascular disease and coronary artery disease), thus highlighting the importance of exercise as a tool for secondary prevention.

Insulin resistance Insulin resistance is associated with the cluster of atherosclerosis risk factors described above (ie, hypercholesterolemia, hypertension, and chronic inflammation) and is thus a strong predictor of CVD in patients with type 2 diabetes.[85] In insulin-resistant states, including obesity, glucose metabolism is impaired, resulting in augmented secretion of insulin by the β cells of the pancreas.[86] At high levels, insulin stimulates the growth and proliferation of vascular smooth muscle cells,[87] it activates inflammatory pathways,[88] results in a deficiency in nitric oxide and stimulation of endothelin-1 production,[89] thus promoting vasoconstriction and atherogenesis. Since suboptimal diets act as the primary lifestyle factor that triggers insulin resistance, exercise may not be sufficient as a solitary treatment. However, there is evidence of significant impact of exercise, independent of dietary change or weight loss, on the insulin-resistant state.

The case for exercise A series of reports provide strong evidence for the importance of exercise in the treatment of type 2 diabetes. Boule et al[90] reviewed 7 randomized controlled trials that compared the effects of aerobic exercise interventions (a mean of 3 sessions per week, at 50 minutes per session for 20 weeks) compared with nonexercise controls in patients with type 2 diabetes. As expected, the exercise interventions led to an approximate 12% increase in aerobic fitness compared with no change in the controls. Interventions that employed greater exercise intensities produced greater improvements in aerobic fitness and blood glucose control, as defined by reductions in glycated hemoglobin (HbA_{1c}). The total exercise volume expressed as total weekly energy expenditure was not an important predictor of the change in either aerobic capacity or HbA_{1c}. However, the same authors[91] later suggested that a threshold of 150 minutes of weekly structured exercise per week must be achieved for significant reductions in HbA_{1c} to occur. In this way, in an updated analysis[92] of 26 randomized controlled trials that included aerobic, resistance, or combined exercise of at least 12 weeks in duration, it was reported that patients with a higher level of HbA_{1c} at the beginning of an intervention experienced greater reductions in HbA_{1c} and that the volume of weekly aerobic or combined exercise was associated with HbA_{1c} level reductions. Neither the volume nor intensity of resistance exercise (when performed as the sole modality) explained the subsequent change in HbA_{1c}. However, Church et al[93] demonstrated in a group of patients with type 2 diabetes with HbA_{1c} levels above 6.5% that adding resistance exercise performed twice weekly to a moderate-intensity aerobic exercise program (ie, 150 min/week at 50%–80%

TABLE 1 The benefits and limitations of exercise training on atherosclerotic stimuli

Atherosclerotic stimuli	Benefits	Limitations
Cholesterol	• Moderate/vigorous AE is associated with an increase in HDL-C levels (4.6%) • Independent of changes in fitness/body composition/diet • HIIT may be required for clinical populations • RE volume more important than intensity	• LDL-C and triglyceride levels not altered with AE • AE of higher intensities may be required
Blood pressure	• AE is associated with a decrease in BP (approximately 5–6 mm Hg) • Dose response: the higher the AE intensity, the greater the decrease in BP • Lower AE intensity may lead to a decrease in BP among patients with hypertension • BP is responsive to RE	• Older patients with hypertension may be resistant to exercise adaptations
Chronic inflammation	• Increased AE volume is associated with decreased levels of TNF-α, VCAM-1, and CRP • Dose response: markers improve as the level of fitness increases • RE reduces CRP levels • AE increases EPC levels in clinical populations	• AE or RE do not alter IL-8, SDF-1, or E-selectin • Inflammatory markers not altered in healthy populations
Insulin resistance	• Increased AE intensity is associated with a decrease in HbA_{1c} • 150 min/week of structured exercise needed for positive change • Combined exercise (AE + RE) is associated with a greater decrease in HbA_{1c} than AE or ER alone	• Patients with poor glycemic control or long diabetes duration may not be responsive to AE or RE

Abbreviations: AE, aerobic exercise; BP, blood pressure; CRP, C-reactive protein; EPC, endothelial progenitor cell; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; IL-8, interleukin-8; LDL-C, low-density lipoprotein cholesterol; RE, resistance exercise; SDF-1, stromal cell-derived factor 1; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion moledule-1

of the maximum intensity), was superior after 9 months with regard to decreasing HbA_{1c} than engaging in aerobic or resistance training alone.

Together, these data suggest that for exercise to have a significant effect on the insulin-resistant state, a minimum dose of approximately 150 minutes of accumulated exercise over the course of a week may be required. Additional beneficial effects may be achieved by increasing the intensity of aerobic exercise and resistance training may be most impactful when practiced in combination with an aerobic exercise intervention. Finally, those with better glycemic control and short diabetes duration may respond most favorably to exercise.

Mechanisms of action The mechanisms through which exercise can ameliorate diabetes have been well studied.[94] Evidence from experimental studies suggest a myriad redundant pathways that impact the delivery, transport of glucose across the muscle cell surface, and metabolism of glucose in the muscle cell. It should be also stated that insulin sensitivity is increased for 48 hours after the completion of 60 minutes of moderate-intensity cycling in healthy but untrained men.[95] While patients with type 2 diabetes also experience improved insulin sensitivity following exercise, the effect does not appear to be as long-lasting (eg, >15 h post exercise).[96] Briefly, regarding glucose transport, increased glucose delivery to active muscles occurs as a result of increased blood flow that is proportional to exercise intensity, and increased glucose uptake is linked to increased levels of skeletal muscle perfusion.[97] Furthermore, it has been reported[98] that glucose transporter-4 (GLUT-4) concentrations are increased by approximately 70% compared with baseline in both apparently healthy individuals and patients with type 2 diabetes following just 1 bout of cycling exercise (ie, 45–60 min at 60%–70% of the maximum effort). GLUT-4 is the glucose transporter that permits the facilitated diffusion of plasma glucose into the muscle and fat cells. Finally, GLUT-4 activity is intricately linked to glucose metabolism within the cell. While glycogen is the preferred energy source during exercise, as exercise is prolonged and glycogen stores become depleted, the muscle permeability to glucose is increased and there is a gradual shift from glycogen to blood glucose to generate the adenosine triphosphate required for exercise.[94] Altogether, by simultaneously enhancing the factors that improve the delivery, transport, and metabolism of glucose, as well as enhancing insulin sensitivity, exercise provides a powerful treatment for CVD.

Conclusion Cardiovascular disease remains the leading cause of death in the industrialized world. Luckily, increasing levels of exercise and improved aerobic fitness can dramatically reduce CVD risk. Evidence from randomized controlled trials and experimental studies suggest that structured exercise confers cardioprotection, in part, by targeting the intermediary mechanisms involved in the atherosclerotic process; namely, hypercholesterolemia, hypertension, chronic inflammation, and insulin resistance. The efficacy of exercise for improving the lipid profile, reducing blood pressure and certain markers of inflammation, and improving blood glucose control in diabetes is well supported by the literature. A summary of the benefits and limitations of exercise training on atherosclerotic stimuli is provided in TABLE 1. A general understanding of these effects can be used to help support physical activity and exercise promotion efforts in health care settings.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Weisfeldt ML, Zieman SJ. Advances in the prevention and treatment of cardiovascular disease. Health Aff (Millwood). 2007; 26: 25-37.

2 Booth FW, Gordon SE, Carslon CJ, Hamilton MT. Waging war on modern chronic diseases: primary prevention through exercise biology. J Appl Physiol. 2000; 88: 774-778.

3 Morris JN, Heady JA, Raffle PA, et al. Coronary heart-disease and physical activity of work. Lancet. 1953; 262: 1111-1120.

4 Paffenbarger RS, Gima AS, Laughlin E, Black RA. Characteristics of longshoremen related fatal coronary heart disease and stroke. Am J Public Health. 1971; 61: 1362-1370.

5 Slattery ML, Jacobs DR Jr. Physical fitness and cardiovascular disease mortality. The US Railroad Study. Am J Epidemiol. 1988; 127: 571-580.

6 Blair SN, Morris JN. Healthy hearts – and the universal benefits of being physically active: physical activity and health. Ann Epidemiol. 2009; 19: 253-256.

7 Blair SN, Kohl HW 3rd, Barlow CE, et al. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA. 1995; 273: 1093-1098.

8 Nocon M, Hiemann T, Muller-Riemenschneider F, et al. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008; 15: 239-246.

9 Kraus WE, Powell KE, Haskell WL, et al. Physical activity, all-cause and cardiovascular mortality, and cardiovascular disease. Med Sci Sports Exerc. 2019; 51: 1270-1281.

10 Pescatello LS, Buchner DM, Jakicic JM, et al. Physical activity to prevent and treat hypertension: a systematic review. Med Sci Sports Exerc. 2019; 51: 1314-1323.

11 Kaminsky LA, Arena R, Ellingsen O, et al. Cardiorespiratory fitness and cardiovascular disease – the past, present, and future. Prog Cardiovasc Dis. 2019; 62: 86-93.

12 Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. New Engl J Med. 2002; 347: 716-725.

13 Mora S, Cook N, Buring JE, et al. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation. 2007; 116: 2110-2118.

14 Saint-Maurice PF, Troiano RP, Bassett DR Jr., et al. Association of daily step count and step intensity with mortality among US adults. JAMA. 2020; 323: 1151-1160.

15 Lavie CJ, Ozemek C, Carbone S, et al. Sedentary behavior, exercise, and cardiovascular health. Circ Res. 2019; 124: 799-815.

16 Pate RR, Pratt M, Blair SN, 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. 1995; 273: 402-407.

17 Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 140: e596-e646.

18 Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41: 111-188.

19 Krist AH, Davidson KW, Mangione CM, et al; US Preventive Services Task Force. Behavioral counseling interventions to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: US Preventive Services Task Force recommendation statement. JAMA. 2020; 324: 2069-2075.

20 Bauman AE. Updating the evidence that physical activity is good for health: an epidemiological review 2000-2003. J Sci Med Sport. 2004; 7: 6-19.

21 Troiano RP, Berrigan D, Dodd KW, et al. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008; 40: 181-188.

22 Drca N, Wolk A, Jensen-Urstad M, Larsson SC. Atrial fibrillation is associated with different levels of physical activity levels at different ages in men. Heart. 2014; 100: 1037-1042.

23 Aizer A, Gaziano JM, Cook NR, et al. Relation of vigorous exercise to risk of atrial fibrillation. Am J Cardiol. 2009; 103: 1572-1577.

24 Khan H, Kella D, Rauramaa R, et al. Cardiorespiratory fitness and atrial fibrillation: a population-based follow-up study. Heart Rhythm. 2015; 12: 1424-1430.

25 Panchal G, Mahmood M, Lip GYH. Revisiting the risks of incident atrial fibrillation: a narrative review. Part 2. Kardiol Pol. 2019; 77: 515-524.

26 Riebe D, Franklin BA, Thompson PD, et al. Updating ACSM's recommendations for exercise preparticipation health screening. Med Sci Sports Exerc. 2015; 47: 2473-2479.

27 Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda). 2013; 28: 330-358.

28 Ekman C, Elgzyri T, Strom K, et al. Less pronounced response to exercise in healthy relatives to type 2 diabetic subjects compared with controls. J Appl Physiol (1985). 2015; 119: 953-960.

29 Hivert MF, Jablonski KA, Perreault L, et al. Updated genetic score based on 34 confirmed type 2 diabetes Loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. Diabetes. 2011; 60: 1340-1348.

30 Szczerbiński L, Gościk J, Bauer W, et al. Efficacy of family history, genetic risk score, and physical activity in assessing the prevalence of type 2 diabetes. Pol Arch Intern Med. 2019; 129: 442-450.

31 Ross R. The pathogenesis of atherosclerosis – an update. N Engl J Med. 1986; 314: 488-500.

32 Falk E. Pathogenesis of atherosclerosis. J Am Coll Cardiol. 2006; 47: C7-C12.

33 Libby P. Inflammation in atherosclerosis. Nature. 2002; 420: 868-874.

34 Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005; 352: 1685-1695.

35 Schwartz SM, Virmani R, Rosenfeld ME. The good smooth muscle cells in atherosclerosis. Curr Atheroscler Rep. 2000; 2: 422-429.

36 Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of atherosclerotic plaques in the four major epicardial coronary arteries in acute myocardial infarction and in sudden coronary death. Circulation. 1989; 80: 1747-1756.

37 Glass CK, Witztum JL. Atherosclerosis. The road ahead. Cell. 2001; 104: 503-516.

38 Peng J, Luo F, Ruan G, et al. Hypertriglyceridemia and atherosclerosis. Lipids Health Dis. 2017; 16: 233.

39 Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. Med Sci Sports Exerc. 2001; 33: S502-S515.

40 Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. Sports Med. 2014; 44: 211-221.

41 Wood G, Murrell A, van der Touw T, Smart N. HIIT is not superior to MICT in altering blood lipids: a systematic review and meta-analysis. BMJ Open Sport Exerc Med. 2019; 5: e000647.

42 Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med. 2002; 347: 1483-1492.

43 O'Donovan G, Owen A, Bird SR, et al. Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate- or high-intensity exercise of equal energy cost. J Appl Physiol (1985). 2005; 98: 1619-1625.

44 Horowitz JF, Klein S. Lipid metabolism during endurance exercise. Am J Clin Nutr. 2000; 72: 558S-563S.

45 Ferguson MA, Alderson NL, Trost SG, et al. Effects of four different single exercise sessions on lipids, lipoproteins, and lipoprotein lipase. J Appl Physiol (1985). 1998; 85: 1169-1174.

46 Oparil S, Zaman MA, Calhoun DA. Pathogenesis of hypertension. Ann Intern Med. 2003; 139: 761-776.

47 Berkin KE, Ball SG. Essential hypertension: the heart and hypertension. Heart. 2001; 86: 467-475.

48 Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Press. 2014; 23: 3-16.

49 Dasgupta K, Quinn RR, Zarnke KB, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2014; 30: 485-501.

50 Johnson BT, MacDonald HV, Bruneau ML Jr, et al. Methodological quality of meta-analyses on the blood pressure response to exercise: a review. J Hypertens. 2014; 32: 706-723.

51 Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension. 1993; 22: 653-664.

52 Pescatello LS, MacDonald HV, Lamberti L, Johnson BT. Exercise for hypertension: a prescription update integrating existing recommendations with emerging research. Curr Hypertens Rep. 2015; 17: 87.

53 Eicher JD, Maresh CM, Tsongalis GJ, et al. The additive blood pressure lowering effects of exercise intensity on post-exercise hypotension. Am Heart J. 2010; 160: 513-520.

54 Dimeo F, Pagonas N, Seibert F, Arndt R, et al. Aerobic exercise reduces blood pressure in resistant hypertension. Hypertension. 2012; 60: 653-658.

55 Liu S, Goodman J, Nolan R, et al. Blood pressure responses to acute and chronic exercise are related in prehypertension. Med Sci Sports Exerc. 2012; 44: 1644-1652.

56 Moraes MR, Bacurau RF, Casarini DE, et al. Chronic conventional resistance exercise reduces blood pressure in stage 1 hypertensive men. J Strength Cond Res. 2012; 26: 1122-1129.

57 Sabbahi A, Arena R, Elokda A, Phillips SA. Exercise and hypertension: uncovering the mechanisms of vascular control. Prog Cardiovasc Dis. 2016; 59: 226-234.

58 Fisher JP, Paton JF. The sympathetic nervous system and blood pressure in humans: implications for hypertension. J Hum Hypertens. 2012; 26: 463-475.

59 Fadel PJ, Raven PB. Human investigations into the arterial and cardiopulmonary baroreflexes during exercise. Exp Physiol. 2012; 97: 39-50.

60 Laterza MC, de Matos LD, Trombetta IC, et al. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. Hypertension. 2007; 49: 1298-1306.

61 Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. J Physiol. 2004; 561: 1-25.

62 Van Guilder GP, Westby CM, Greiner JJ, et al. Endothelin-1 vasoconstrictor tone increases with age in healthy men but can be reduced by regular aerobic exercise. Hypertension. 2007; 50: 403-409.

63 Maiorana A, O'Driscoll G, Taylor R, Green D. Exercise and the nitric oxide vasodilator system. Sports Med. 2003; 33: 1013-1035.

64 Pedralli ML, Marschner RA, Kollet DP, et al. Different exercise training modalities produce similar endothelial function improvements in individuals with prehypertension or hypertension: a randomized clinical trial exercise, endothelium and blood pressure. Sci Rep. 2020; 10: 7628.

65 Maeda S, Tanabe T, Miyauchi T, et al. Aerobic exercise training reduces plasma endothelin-1 concentration in older women. J Appl Physiol (1985). 2003; 95: 336-341.

66 Tinken TM, Thijssen DH, Black MA, et al. Time course of change in vasodilator function and capacity in response to exercise training in humans. J Physiol. 2008; 586: 5003-5012.

67 Tinken TM, Thijssen DH, Hopkins N, et al. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension. 2010; 55: 312-318.

68 Spence AL, Carter HH, Naylor LH, Green DJ. A prospective randomized longitudinal study involving 6 months of endurance or resistance exercise. Conduit artery adaptation in humans. J Physiol. 2013; 591: 1265-1275.

69 Tanaka H, Dinenno FA, Monahan KD, et al. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 2000; 102: 1270-1275.

70 Ferrier KE, Waddell TK, Gatzka CD, et al. Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. Hypertension. 2001; 38: 222-226.

71 Aizawa K, Petrella RJ. Acute and chronic impact of dynamic exercise on arterial stiffness in older hypertensives. Open Cardiovasc Med J. 2008; 2: 3-8.

72 Stewart KJ, Bacher AC, Turner KL, et al. Effect of exercise on blood pressure in older persons: a randomized controlled trial. Arch Intern Med. 2005; 165: 756-762.

73 Palmefors H, DuttaRoy S, Rundqvist B, Borjesson M. The effect of physical activity or exercise on key biomarkers in atherosclerosis – a systematic review. Atherosclerosis. 2014; 235: 150-161.

74 Steffens S, Mach F. Inflammation and atherosclerosis. Herz. 2004; 29: 741-748.

75 Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol. 2006; 6: 508-519.

76 Brogi E, Winkles JA, Underwood R, et al. Distinct patterns of expression of fibroblast growth factors and their receptors in human atheroma and nonatherosclerotic arteries. Association of acidic FGF with plaque microvessels and macrophages. J Clin Invest. 1993; 92: 2408-2418.

77 Schumacher A, Peersen K, Sommervoll L, et al. Physical performance is associated with markers of vascular inflammation in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil. 2006; 13: 356-362.

78 Pakiz B, Flatt SW, Bardwell WA, et al. Effects of a weight loss intervention on body mass, fitness, and inflammatory biomarkers in overweight or obese breast cancer survivors. Int J Behav Med. 2011; 18: 333-341.

79 Adamopoulos S, Parissis J, Kroupis C, et al. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J. 2001; 22: 791-797.

80 Lee BC, Hsu HC, Tseng WY, et al. Effect of cardiac rehabilitation on angiogenic cytokines in postinfarction patients. Heart. 2009; 95: 1012-1018.

81 Lara Fernandes J, Serrano CV Jr, Toledo F, et al. Acute and chronic effects of exercise on inflammatory markers and B-type natriuretic peptide in patients with coronary artery disease. Clin Res Cardiol. 2011; 100: 77-84.

82 Olson TP, Dengel DR, Leon AS, Schmitz KH. Changes in inflammatory biomarkers following one-year of moderate resistance training in overweight women. Int J Obes (Lond). 2007; 31: 996-1003.

83 Schlager O, Giurgea A, Schuhfried O, et al. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. Atherosclerosis. 2011; 217: 240-248.

84 Cesari F, Sofi F, Caporale R, et al. Relationship between exercise capacity, endothelial progenitor cells and cytochemokines in patients undergoing cardiac rehabilitation. Thromb Haemost. 2009; 101: 521-526.

85 Gast KB, Tjeerdema N, Stijnen T, et al. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. PLoS One. 2012; 7: e52036.

86 DeFronzo RA, Banerji MA, Bray GA, et al. Determinants of glucose tolerance in impaired glucose tolerance at baseline in the Actos Now for Prevention of Diabetes (ACT NOW) study. Diabetologia. 2010; 53: 435-445.

87 Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol. 2006; 7: 85-96.

88 Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002; 420: 333-336.

89 Wilkes JJ, Hevener A, Olefsky J. Chronic endothelin-1 treatment leads to insulin resistance in vivo. Diabetes. 2003; 52: 1904-1909.

90 Boule NG, Kenny GP, Haddad E, et al. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. Diabetologia. 2003; 46: 1071-1081.

91 Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA_{1c} levels in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2011; 305: 1790-1799.

92 Umpierre D, Ribeiro PA, Schaan BD, Ribeiro JP. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. Diabetologia. 2013; 56: 242-251.

93 Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A_{1c} levels in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2010; 304: 2253-2262.

94 Sylow L, Kleinert M, Richter EA, Jensen TE. Exercise-stimulated glucose uptake - regulation and implications for glycaemic control. Nat Rev Endocrinol. 2017; 13: 133-148.

95 Mikines KJ, Sonne B, Farrell PA, et al. Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol. 1988; 254: E248-E259.

96 Devlin JT, Horton ES. Effects of prior high-intensity exercise on glucose metabolism in normal and insulin-resistant men. Diabetes. 1985; 34: 973-979.

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

98 Kennedy JW, Hirshman MF, Gervino EV, Ocel JV, et al. Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects and subjects with type 2 diabetes. Diabetes. 1999; 48: 1192-1197.