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Beneficial Effects of Exercise in Type 2 Diabetes Mellitus

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Physical activity is a well-established and important therapeutic modality for persons with type 2 diabetes mellitus (T2 DM). Regular exercise improves conventional risk factors, cardiovascular fitness, insulin resistance, and glycemic control. Furthermore, there is a clear association between fitness and morbidity and mortality. This edition of *Endocrinology Rounds* reviews the evidence linking exercise and fitness with diabetes outcomes and provides guidance on the components of a safe and effective exercise-training program for persons with diabetes.

Fitness, cardiovascular events, and mortality in T2 DM

The maximal amount of oxygen consumed during exercise derived from stress testing (VO_{2max}) has been used by physiologists for years to determine the maximum exercise capacity or peak cardiovascular fitness of athletes. Mathematically, VO_{2max} represents the product of peak cardiac output and peripheral oxygen extraction at the level of working muscles and, therefore, requires a well-functioning cardiac, respiratory, and muscular system, down to the mitochondrial level. Beyond being a tool for the physiologist, there has been growing recognition that fitness is a powerful and independent predictor of mortality in both healthy populations[1] and in those with medical conditions such as cardiac disease.[2,3] People with T2 DM, even in the absence of known complications, have a reduced VO_{2max} compared to controls of similar age, body mass, and activity patterns and, thus, fitness – or the lack of it – may be a particularly important health status marker and target for intervention.

Wei et al[4] evaluated the association between low cardiorespiratory fitness and physical inactivity and mortality in men with T2 DM. These data were drawn from the prospective Aerobics Center Longitudinal Study at The Cooper Clinic in Dallas, Texas. The cohort consisted of 1,263 men (50 ± 10 years of age) with T2 DM who received a thorough medical examination between 1970 and 1993 and were followed for mortality up to the end of 1994. Cardiorespiratory fitness was measured by a maximal exercise test, self-reported physical activity at baseline was noted, and subsequent death was determined by cross-referencing with the National Death Index. During an average follow-up of 12 years, 180 patients died. After adjusting for age, presence of baseline cardiovascular disease (CVD), fasting plasma glucose level, high cholesterol level, being overweight, current smoking, high blood pressure, and family history of CVD, men in the low-fitness group had an adjusted risk for all-cause mortality of 2.1 (95% CI, 1.5 - 2.9) compared with fit men. Men who reported being physically inactive had an adjusted risk for mortality that was 1.7-fold (CI, 1.2-fold to 2.3-fold) higher than that in men who reported being physically active. The authors concluded that low cardiorespiratory fitness and physical inactivity were independent predictors of all-cause mortality in men with T2 DM.

Similar findings were demonstrated for women with diabetes in the setting of the Nurses' Health Study,[5] in which 5,125 female nurses were identified as having diabetes in the baseline cohort. Physical activity was first assessed in 1980 and updated in 1982, 1986, 1988, and 1992 through validated questionnaires. Average hours of moderate or vigorous exercise and a metabolic equivalent of task (MET) score were computed. During 14 years

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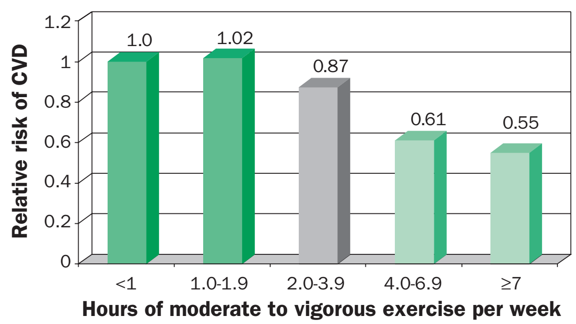
Figure 1: Occurrence of cardiovascular events in 5,125 nurses with diabetes over 14 years of follow-up stratified by exercise activity. Moderate exercise of at least 4 hours per week was associated with substantially lower risk than in those who did not exercise at all.



of follow-up, there were 323 new cases of CVD (225 cases of coronary heart disease and 98 cases of stroke). The age-adjusted relative risks according to average number of hours of moderate or vigorous activity per week (Figure 1) were:

- <1 – 1.0
- 1 to 1.9 – 0.93 (95% CI, 0.69 – 1.26)
- 2 to 3.9 – 0.82 (CI, 0.61 – 1.10)
- 4 to 6.9 – 0.54 (CI, 0.39 – 0.76)
- 7 hours – 0.52 (CI, 0.25 – 1.09) with ($P < 0.001$ for trend).

These risk estimates did not change materially after adjustment for smoking, body mass index (BMI), and other cardiovascular risk factors. In separate analyses, levels of physical activity were inversely associated with the development of coronary heart disease and ischemic stroke. Among women who did not exercise vigorously, the multivariate relative risks for CVD across quartiles of MET score (another measure of the intensity of activity) for walking were 1.0, 0.85, 0.63, and 0.56 ($P = 0.03$ for trend), indicating that a faster and more intense walking pace was independently associated with lower risk. The authors concluded that among diabetic women, increased physical activity, including regular walking, is associated with substantially reduced risk for cardiovascular events.

Both of these large studies recommend that patients with T2 DM be encouraged to participate in regular physical activity and improve cardiorespiratory fitness. However, both also suggested that randomized trials would be helpful to further define the causal relationship between fitness improvements and relevant clinical outcomes. The effect of exercise intervention on fitness in persons with diabetes is discussed in the following section.

Exercise intervention and changes in cardiovascular fitness

One of the benefits of regular aerobic training is an improvement in maximal aerobic capacity (VO_{2max}),[6] which is achieved by improvements in cardiac output, stroke volume, and peripheral extraction of oxygen. Other health benefits of regular exercise include the lowering of blood pressure and heart rate, both at rest and in response to exercise.[7,8]

A recent systematic overview of the literature by Boulé and colleagues (senior author Dr. Ron Sigal)[9] examined the effect of structured exercise training on cardiorespiratory fitness in T2 DM. Seven studies, representing data from 9 randomized trials comparing exercise and control groups, met the inclusion criteria for analysis. There was a total of 266 subjects, 40% were women, mean age was 55.7 years, and the average duration of diabetes was 4.1 years. The mean baseline VO_{2max} was 22.4 ml/kg/min (which corresponds to about 60% to 70% of the fitness level for a healthy age-matched cohort). The average exercise program consisted of 3.4 exercise sessions per week, 49 minutes per session, for 20 weeks. Exercise intensity ranged from 50% to 75% of VO_{2max}. On follow-up assessment, there was an 11.8% increase in VO_{2max} in the exercise groups compared with a 1.8% decrease in the control groups ($p<0.003$). The magnitude of improvement in VO_{2max} in the exercise groups would be expected to reduce the risk of CVD considerably.

In the one study that used a high intensity level for exercise training (ie, training heart rates adjusted to achieve 75% of the VO_{2max} measured on stress testing),[10] the final VO_{2max} increased dramatically by 40.9%, whereas the weighted average increase was only 9.5% for the studies in which exercise intensity was lower. The authors concluded that people with T2 DM show statistically significant and clinically important improvements in cardiorespiratory fitness in response to aerobic exercise interventions and that a higher intensity of exercise yields greater training effects.

Exercise intervention and glycemic control

Exercise is widely perceived to be beneficial for glycemic control and weight loss in patients with T2 DM. However, clinical trials on the effects of exercise in these patients included small sample sizes and produced conflicting results. Boulé and colleagues conducted an earlier meta-analysis that evaluated the effects of exercise intervention in adults with T2 DM.[11] Fourteen controlled trials were included, of which 11 were randomized and 3 were nonrandomized studies of exercise intervention of at least 8 weeks duration. Trials that included drug co-interventions were excluded. A total of 504 participants were included in the 14 trials. The mean (standard deviation [SD]) age of participants in studies for which this information was available was 55.0 (7.2) years, duration of diabetes was 4.3 (4.6) years, and 50% of participants were women. The exercise interventions typically prescribed 3 workouts per week, each lasting a mean (SD) of 53 (17) minutes (including 10 minutes of warm-up and cool-down) for 18 (15) weeks. The intensity of the aerobic exercise was moderate and typically consisted of walking or cycling. Two studies used resistance exercise training as an intervention and 1 study added combined resistance training with elastic bands with an aerobic training program.

For the 11 comparisons between exercise and non-exercise control groups, there were no significant baseline differences in HbA_{1c}. When the post-intervention results were pooled, HbA_{1c} was significantly lower in the exercise groups compared with the control groups (7.65% vs. 8.31%; weighted mean difference, -0.66%; P<.001). Overall, post-intervention body mass did not differ significantly between the exercise groups and control groups (83.02 kg vs. 82.48 kg; P=.76), but data from the 4 studies reporting on other anthropometric measures did suggest positive effects of exercise on abdominal obesity as represented by waist-to-hip ratio or waist circumference. The post-intervention weighted mean differences were -0.02 U (P =.05) for waist-to-hip ratio and -4.53 cm (P<.001) for waist circumference, mitigated somewhat by baseline differences in abdominal adiposity favouring the exercise groups.

The single study in the meta-analysis that directly measured abdominal obesity by magnetic resonance imaging (MRI) revealed that the aerobic training program used in that study (55 minutes, 3 times per week, for 10 weeks) resulted in a significant reduction in both abdominal subcutaneous adipose tissue (227.3 cm^2 to 186.7 cm^2; P<.05) and visceral adipose tissue (156.1 cm^2 to 80.4 cm^2; P<.05). The authors concluded that exercise training reduced HbA_{1c} to an extent that should decrease the risk of diabetic complications. The effects on body composition were promising, but inconsistent, and overall, there was no effect on body mass. Therefore, exercise should be viewed as beneficial on its own, not merely as an avenue to weight loss.

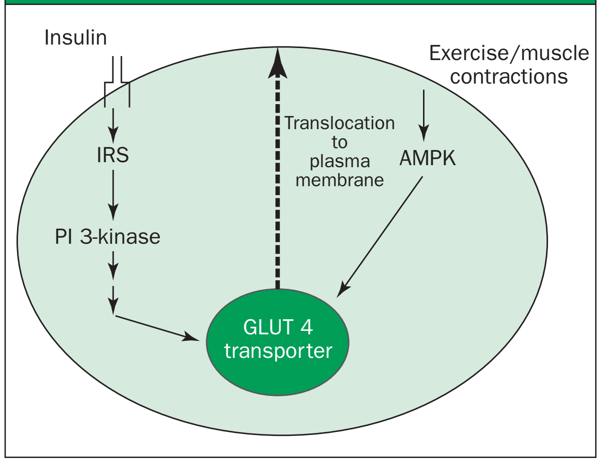
In Boulé's more recent meta-analysis of exercise and fitness,[9] the relationship between exercise intensity and changes in glycemic control were also explored. The authors found that more intense exercise produced greater improvements in HbA_{1c} and, in the one study using the most intense exercise (75% of the VO_{2max}), the HbA_{1c} was 1.5% lower in the exercise group than in the control group.[10]

Mechanisms for exercise effects

Exercise training decreases hepatic and peripheral insulin resistance and increases glucose disposal through a number of mechanisms.[12,13] Exercise and insulin work synergistically to increase glucose uptake into insulin-sensitive tissues, primarily skeletal muscle. This is facilitated by the translocation of glucose transporter 4 (GLUT 4) from the sarcoplasm to the plasma membrane of the cell (Figure 2). GLUT 4 transporters are embed into the plasma membrane after a series of complex post-insulin receptor steps, including the involvement of an insulin receptor substrate (IRS-1) and phosphatidylinositol kinase (PI 3-kinase). It has been proposed that abnormalities in IRS-1 may be involved in insulin resistance.[14] GLUT 4 transporters can also be translocated to the plasma membrane directly by exercise contractions, independent of the insulin pathway.[15,16] Since patients with T2 DM often have insulin-resistant muscles, exercise-mediated GLUT 4 activity and subsequent glucose disposal is of great importance to this patient population. Other mechanisms have also been reported, including increased activity of glycogen synthase and hexokinase, decreased release and increased clearance of free fatty acids, increased muscle glucose delivery due to increased muscle capillary density, and changes in muscle composition favouring increased glucose disposal.

Aerobic exercise benefits the T2 DM patient, both acutely, and chronically. With the exception of short-term high-intensity exercise, blood glucose tends to decrease both during and after an acute session of exercise.[17] The positive effects of the exercise episode on insulin sensitivity last for several hours post-exercise and then diminish.[18] Therefore, moderate-intensity exercise performed on a regular basis (at least every other day) is recommended for maximizing glucose control in patients living with T2 DM.[19,20]

Figure 2: Schematic diagram representing the independent pathways of insulin-mediated and exercise/muscle contraction-mediated glucose uptake in a muscle cell. Once activated, the glucose 4 (GLUT 4) transporters are translocated to the plasma membrane and facilitate glucose uptake into the cell. Activation of GLUT 4 transporters by insulin commences with insulin binding to its receptor and subsequent activation of the insulin pathway, including insulin receptor substrate (IRS) and phosphatidylinositol kinase (PI 3-kinase). Exercise/muscle contractions activate GLUT 4 transporters independently of the insulin pathway and includes activation of 5'-AMP-activated kinase (AMPK). (Adapted from Krook et al[16])



The majority of patients living with T2 DM are overweight and have a greater preponderance of adipose tissue accumulating around the abdominal region. Adipose tissue from the abdominal region (specifically the visceral depot) is very lipolytically active. The influx of excess free fatty acids from visceral adipose tissue (VAT) into the portal circulation is associated with insulin resistance.[21,22] It is very difficult to demonstrate sustained weight loss in patients living with diabetes. However, aerobic training, even in the absence of weight loss, induces a preferential reduction in VAT and associated improvements in insulin sensitivity.[10] Furthermore, the combination of aerobic and resistance training has demonstrated greater gains in insulin sensitivity as compared to aerobic training alone.[23]

Resistance training

Resistance training (ie, activities that use muscular strength to move a weight or work against a resistant load) have been shown to improve muscular strength and endurance, enhance flexibility, improve body composition, and decrease cardiovascular risk factors such as blood pressure in many different populations[8] (American College of Sport Medicine [ACSM] position). In subjects without diabetes, resistance training has also been demonstrated to improve glucose tolerance and insulin sensitivity. In Boulé's meta-analysis of exercise and glycemic control,[11] the improvement in HbA_{1c} in the resistance training groups vs. non-exercise control groups was similar to the responses seen with aerobic training, with an observed reduction in HbA_{1c} of 0.64% (95% CI, -1.29% to 0.01%). Well-designed studies on the effects of combined resistance and aerobic training are needed to better understand the impact of increasing muscle mass and reducing fat mass, especially visceral fat, on glycemic control and other metabolic abnormalities. Having said this, resistance training is already encouraged in most guidelines about exercise in diabetes.[19,24]

Designing and implementing exercise programs

There are four major components to exercise therapy, including a pre-exercise assessment, graded exercise test, exercise prescription, and progression of exercise.

The pre-exercise assessment

Screening patients for vascular and neurological complications, including peripheral vascular disease, proliferative retinopathy, nephropathy, peripheral neuropathy, and autonomic neuropathy is advised prior to commencing an exercise program. Fasting blood glucose, HbA_{1c}, and other metabolic markers should be reviewed. Additionally, care should be taken to establish any potential limitations a participant may have, such as arthritis, intermittent claudication, and any footcare concerns. All participants should be counselled on appropriate blood glucose monitoring in relation to exercise.

Graded exercise test (GXT)

For most patients, a complete GXT should be undertaken to establish both heart and blood pressure responses to exercise, along with screening for ischemic responses and arrhythmias. In general, a GXT is advisable for any previously sedentary person with diabetes who is going to undertake an exercise program, especially if the exercise intensity prescribed is moderate to vigorous. The American Association of Cardiovascular and Pulmonary Rehabilitation (AACPR) specifically recommends a pre-entry GXT for particular groups (Table 1).[24]

Exercise prescription (using the FITT principle)

For exercise to be effective for the development of improved cardiovascular conditioning, muscular strength, and endurance, the Frequency, Intensity, Time and Type of exercise (FITT) should be appropriately established. The dose of either aerobic or resistance training exercise is important in achieving improved fitness and/or improved glycemic control and can be determined from the evidence reviews discussed previously. Ideally, any person with diabetes should receive guidance, support, and supervision for the commencement and maintenance of a physical activity program.

Frequency: Training is recommended for 3 to 5 days per week with a consideration for daily exercise for obese patients (who are trying to achieve weight loss) and patients on insulin (to have predictable

Table 1: The AACPR recommends a pre-entry GXT for these groups[24]
• All people with known or suspected (on the basis of symptoms) coronary artery disease, irrespective of age
• Patients who have any microvascular or neurological diabetic complication (ie, retinopathy, nephropathy, peripheral vascular disease, autonomic neuropathy, peripheral neuropathy).
• The following asymptomatic patients: – Patients who have had T1 DM for >15 years – Patients with T1 DM who are >30 years old – Patients with T2 DM who are >35 years old – Patients who have had T2 DM for > 10 years

AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation energy expenditures). While rest days are important to reduce the occurrence of stress injuries, some form of daily activity should be promoted.

Intensity: At a minimum, exercise intensity should be prescribed at the threshold needed to improve functional capacity, but below a level that may elicit undesirable responses. In the cardiac rehab setting, exercise prescriptions are usually set at a moderate-to-vigorous intensity (ie, 60% to 80% of VO_{2max}). This is consistent with Boulé's review of exercise training in diabetes,[9] and particularly with the study by Mourier et al[10] that found a 1.5% reduction in HbA_{1c} at a training intensity of 75% of VO_{2max}. The Canadian Diabetes Association (CDA) Guidelines recommend gauging exercise intensity by heart rate (eg, moderate intensity corresponds to 50% to 70% of a person's maximum heart rate).[19] This may be a reasonable approach in many cases, however, this range can be affected significantly by the use of heart rate-lowering medications (ie, beta-blockers or calcium channel blockers) and it should be recognized that estimating maximal heart rate by simple popular formulae (eg, maximum heart rate = 220 – age) is often inaccurate. It is preferable, therefore. to actually determine symptom-limited heart rates from stress testing or electrocardiograph (ECG) monitoring of activity. It is important to note that higher-intensity exercise (ie, 80% VO_{2max}) may be associated with greater cardiovascular risk, a greater chance of injury, and lower compliance than lower-intensity exercise. Thus, initial exercise intensity should be set at the lower end of the training range and progressed gradually and carefully.

Time: The initial aerobic exercise prescription should be set at 20 minutes per session. Shorter, more frequent exercise sessions (10-minute exercise bouts) of equal total time or one continuous longer session produce equal benefits. Thus, shorter bouts of exercise may be of benefit in patients with low exercise tolerance when starting an exercise program. The goal of an exercise program is to work up to 60 minutes of exercise per session, accumulating at least 4 hours per week, with a corresponding energy expenditure of about 2000 kcal, as tolerated. The CDA Guidelines recommend the addition of resistance training exercises, as well as starting with 1 set of 10 to 15 repetitions at moderate intensity over a circuit of upper and lower body exercises.[19]

The studies reporting the greatest effect of resistance training on glycemic control had subjects progress to 3 sets of approximately 8 exercises at moderately high intensity (8 repetitions at the maximum weight that can be lifted 8 times), 3 times per week. Participants should proceed very cautiously with these higher level exercises, especially the elderly or those with underlying ischemic heart disease, since straining at maximum weight loads can have unfavourable acute effects on heart rate, blood pressure, and myocardial oxygen demand.

Type: Aerobic exercises (eg, walking, cycling, swimming etc.) for improving cardiovascular capacity and resistive exercises (eg, light weights or elastic bands) for improving muscular strength and endurance are recommended for all individuals where possible. Exercise modalities should be selected with consideration of the presence of any complications (ie, nonweight-bearing activities for patients with moderate to severe peripheral neuropathy, no resistance training for patients with moderate-to-severe proliferative retinopathy).

Progression of exercise

The progression of the exercise prescription should be done with consideration of signs, symptoms, and response to exercise. Initially, the frequency and time of the exercise prescription should be increased instead of intensity. Patients who are new to exercise, especially the obese, should avoid doing "too much too soon."

Toronto Rehab's exercise program for persons living with diabetes

The Toronto Rehabilitation Institute's Cardiac Rehabilitation and Secondary Prevention Program has developed a new exercise program for adults living with diabetes based on consultation and partnership with the Diabetes Education Centres and service providers in the area, a literature review, and extensive experience in training individuals with heart disease. The Diabetes Exercise and Healthy Lifestyle Service helps adults living with diabetes improve their strength, fitness, glycemic control, and overall quality of life. The program offers a specialized exercise program, including an exercise stress ECG with direct VO_2 measurement at entry and at discharge, twice-weekly medically-supervised exercise classes, weight management, and individualized risk stratification. Educational seminars are offered weekly that emphasize how to introduce a safe and effective exercise regime into their lives (including glucose monitoring), how to make improved lifestyle choices, and how to minimize potential risks and complications. Aerobic exercise prescriptions are set at a moderate to vigorous intensity (ie, 60%-80% VO_{2max}) and involve walking, jogging, or cycling activities as appropriate. Resistance training exercises comprised of a circuit of 10 exercises using individually-prescribed free weights and elastic bands (at 60% of maximum tolerated load) are introduced at week 8 of the program. Anthropometric, metabolic, and fitness markers are monitored throughout the program.

Conclusion

Low fitness is a major modifiable risk for persons living with diabetes. Numerous epidemiologic studies have shown a clear link between poor fitness and inactivity and cardiac events and mortality. Randomized controlled trials have demonstrated the benefit of exercise in improving glycemic control, insulin resistance, other traditional risk factors, and cardiovascular fitness. Exercise training must be actively promoted as a treatment and as a preventative strategy for all persons with diabetes. Methods to improve the implementation and adherence to exercise programs require better development and are currently being studied.

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