

## Exercise Training for Diabetes: The “Strength” of the Evidence

Exercise is an essential component in the treatment of diabetes mellitus. Lifestyle factors affect the prevention, development, and treatment of diabetes mellitus and its close relation, the metabolic syndrome (1). The Finnish Diabetes Prevention Study (2) and the Diabetes Prevention Program (3) tested lifestyle interventions that included a physical activity program. Both studies showed the power of exercise, nutrition, and weight loss to prevent diabetes mellitus in at-risk individuals.

However, exercise comes in several flavors, and the clinician should think critically about the effects of different types of exercise training. It is useful to think of exercise training as a drug with a specific dose–response relationship (4). For example, exercise can be delivered in various “doses”: differing number of sessions per week (frequency), number of minutes per session (duration), or degree of effort (intensity). Exactly how to quantify the dose of exercise, and how different doses influence cardiovascular, musculoskeletal, or metabolic outcomes, are among the most important current issues in exercise science (5, 6).

In addition to dose, the type of exercise is important. Endurance exercise involves repetitive, rhythmic contraction of large muscle groups, as occurs in running or cycling; it also called *aerobic exercise* because it depends predominantly on oxidative energy sources to produce adenosine triphosphate. Strength training, also called *resistance training*, generally involves relatively slow, intense contractions at high force; weightlifting is the most common example. These types of exercise are similar in some ways but have important differences. For example, according to elegant studies done at the Copenhagen Muscle Research Center, little blood flows through muscle during muscle contraction, even during aerobic exercise (7). Nevertheless, endurance exercise (high frequency, multiple repetitions, and low force) induces alterations in contractile protein isoforms of skeletal muscle and stimulates mitochondrial respiratory enzymes and specific adaptations in the heart and blood vessels (6). Conversely, strength training stimulates increases in muscle protein and muscle cross-sectional area, although this adaptation is more a function of force production than of “anaerobic metabolism” (8).

In this issue, Sigal and colleagues (9) report a first pass at addressing some of these issues. In the DARE (Diabetes Aerobic and Resistance Exercise) trial, they randomly assigned 251 patients with diabetes age 39 to 70 years to 1 of 4 exercise programs: aerobic training, resistance training, combined aerobic and resistance training, or no exercise. The primary outcome measure was glucose control, as assessed by the hemoglobin A<sub>1c</sub> measurement. Secondary end points included changes in body composition, serum lipid values, and blood pressure.

The conduct of the trial was exemplary. The authors took several measures to ensure that the 4 study groups

were similar in size and participant characteristics. There was no prescribed nutrition program, and weight loss was minimal in all groups during the 22-week study. Retention and adherence to the exercise program in this study was extremely good. The groups were well matched for important baseline characteristics. Finally, the authors standardized medication use during the study. For all of these reasons, we can ascribe the changes in glucose control to the exercise interventions.

Both the aerobic and resistance training groups had lower hemoglobin A<sub>1c</sub> values than did the inactive control group—a difference of about 0.5 percentage point. Most important, as hypothesized, the combined aerobic and resistance training group had even lower hemoglobin A<sub>1c</sub> values than the groups that did only 1 form of exercise, and their hemoglobin A<sub>1c</sub> values were about 1 percentage point lower than those of the control group. Both types of exercise reduced subcutaneous abdominal fat (but not visceral fat) over 22 weeks. Surprisingly, all 4 groups had similar blood pressure and serum lipid values. The participants were large (average body mass index, about 35 kg/m<sup>2</sup>) and exercise intensity was relatively low (sufficient to maintain a heart rate of 60% to 75% of maximal), which might account for the lack of effect on lipid values and blood pressure. The high average body mass index might also account for the frequent musculoskeletal complications in the exercise groups, although it was reassuring that non-musculoskeletal event rates were low.

The observed differences in hemoglobin A<sub>1c</sub> values are clinically significant, not only for diabetes treatment but for cardiovascular risk: As Sigal and colleagues note (9), a 1–percentage point decrease in hemoglobin A<sub>1c</sub> value results in a 15% to 20% decrease in major cardiovascular events (10). Unfortunately, the authors did not report other specific measures of glucose control, such as fasting insulin and glucose levels or the response to an oral glucose challenge. These more acute abnormalities of glucose handling (which form the foundation for the diagnosis of diabetes) are particularly sensitive to skeletal muscle insulin sensitivity and are modified substantially by exercise training. Such information could have allowed the authors to provide insight into the mechanisms of the different exercise regimens. Also missing is a measure of improved physical fitness, such as peak oxygen uptake during an exercise test, which other studies of similar design and scope have provided (11).

Despite the thoughtful design and very careful execution of the DARE study, several questions remain about the best way to use exercise training to modify glucose control. For example, all intervention groups exercised 3 days per week. Therefore, participants in the combined exercise training group, who performed both strength and endurance training, spent much more time per day exer-

cising, and their total caloric expenditure must have been substantially higher than that in persons assigned to a single exercise type. We cannot tell whether the added exercise duration (and caloric expenditure) or the combination of the 2 types of exercise was responsible for the key difference in diabetes control.

A second unanswered question involves the mechanisms by which the 2 forms of exercise training alter glucose tolerance. Although aerobic exercise and resistance training have similar effects on glucose tolerance (the response to an oral load), the mechanism of this effect differs: Aerobic exercise acts through qualitative changes in skeletal muscle (fiber type and metabolic capacity), whereas resistance training acts through quantitative changes in skeletal muscle (muscle mass and fiber diameter). Therefore, aerobic exercise may modify the insulin action of each fiber without increasing fiber size, whereas resistance training may not alter insulin action on single fibers, but rather may improve glucose uptake by increasing the size of each fiber, which increases the muscle mass available to handle a glucose load. Exercise scientists are very interested in distinguishing these 2 hypotheses and measuring the relative persistence of these effects after stopping the training stimulus. If the postulated mechanisms are true, a combination of resistance and aerobic exercise might have additive effects due to the complementary mechanisms of aerobic and resistance training. Sigal and colleagues’ findings are consistent with—but do not prove—this premise.

A third unanswered question is the effect of dose. The DARE study did not address the specific importance of the amount (kilocalorie expenditure per session or week) and intensity, number of sessions per week or frequency of sessions, and total volume of exercise performed.

Answering these 3 questions and thereby determining the optimal exercise prescription for a patient with diabetes will require additional clinical trials with some measure of glucose metabolism as the primary outcome. These future studies will build on Sigal and colleagues’ work. The DARE study’s most important contribution is demonstration of the direct, clinical relevance of exercise training for the management of patients with diabetes. Despite the study’s limitations, a combined regimen of resistance and aerobic exercise is likely to be practical and safe, and it is probably the best strategy for modulating the mean glucose level, as it is to increase strength, endurance, and cardiovascular risk.

To envision the importance of exercise, imagine an inexpensive pill that could decrease the hemoglobin A<sub>1c</sub> value by 1 percentage point, reduce cardiovascular death by 25% (12), and substantially improve functional capacity (strength, endurance, and bone density). Diabetes experts would be quick to incorporate this pill into practice guidelines and performance measures for diabetes. The DARE study results should stimulate all clinicians to include exercise assessment and counseling into every clinic visit. In the shadow of a growing diabetes and obesity epidemic,

failing to prescribe exercise to patients with diabetes is simply unacceptable practice.

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