

# Supervised Exercise Improved Fitness in Diabetic Patients

Results of a clinical trial suggest that intervention lowered blood pressure — but did not reduce weight — in men and women with type 2 diabetes.

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osing weight and becoming more active are significant challenges for overweight people with type 2 diabetes. Our group recently published results of a clinical trial in *Diabetes Research and Clinical Practice*.<sup>1</sup> We postulated that an effective weight-loss strategy may involve (1) dietary counseling, (2) supervised exercise, (3) maximum tolerated doses of metformin — the only potent glucose-lowering medication not associated with weight gain<sup>2,3</sup> — and (4) minimum doses of other glucose-lowering medications, most of which are associated with weight increase. We anticipated that dietary counseling, supervised exercise and a maximized metformin dose would offset compromised glycemic control risk by reducing use of other glucose-lowering medications.

Clinical trials have shown that supervised exercise improves glycemic control among men and women with type 2 diabetes; substantial weight loss, however, was not concurrently achieved.<sup>4</sup> Most trials have been less than 12 weeks in duration, which is arguably too short for the impact of exercise to become apparent.

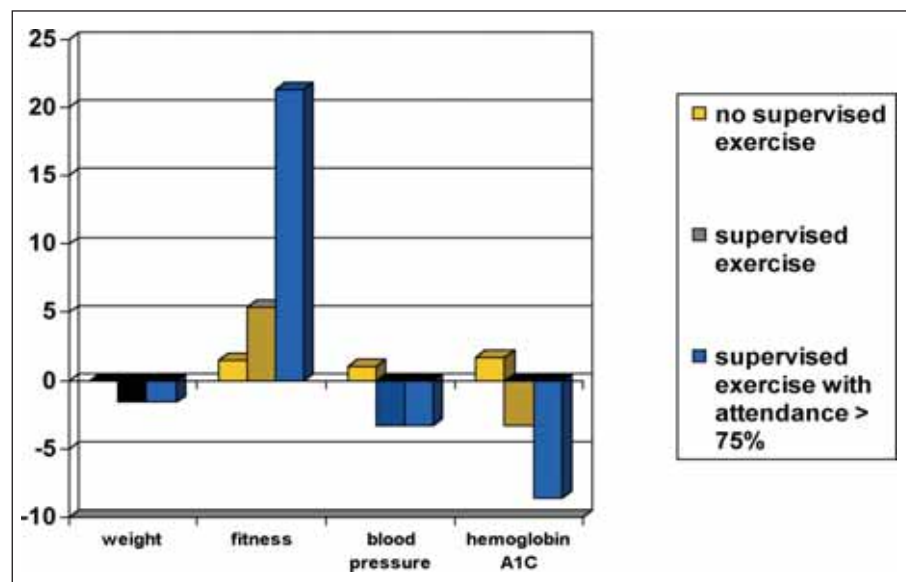


Figure 1. Impact of supervised exercise on weight, fitness, blood pressure and HbA1c in men and women with type 2 diabetes.

Using a 2 X 2 factorial design, we concurrently examined the impact on weight and HbA1c of a 24-week supervised exercise program and liberalization of preprandial glucose thresholds for adjustment of glucose-lowering medication other than metformin.

We also assessed the impact of supervised exercise on fitness and blood pressure. Among men with type 2 diabetes, there is a steep inverse gradient between fitness and mortality, independent of body mass index (BMI) and other cardiovascular risk factors.<sup>5</sup> In these

people, blood pressure control is as important or more important than glucose control for the prevention of cardiovascular complications.<sup>2,6</sup>

### RECRUITMENT AND METHODS

Primary patient recruitment was conducted through specialized diabetes clinics that are affiliated with McGill University in Montreal. All participants received one-on-one dietary counseling every 4 weeks for 24 weeks. A registered dietitian performed counseling in accordance with Canadian Diabetes Association guidelines, which emphasize consumption of low-glycemic index vegetables, whole grains and adequate protein. Metformin was increased according to individual toleration. The maximum dosing was 850 mg three times daily.

Patients were randomized to immediate or delayed participation in a 24-week supervised exercise program, consisting of small group sessions with an exercise physiologist. Sessions were conducted three times a week for the first 8 weeks, twice a week for the next 8 weeks and once a week for the final 8 weeks. Patients were expected to continue exercising at least three times a week throughout the program, increasing unsupervised sessions as the frequency of supervised sessions declined.

During the supervised sessions, exercise included the use of treadmills, bicycles and cross-trainers. Patients were asked to maintain a heart rate between 65% and 85% of their maximum heart rate achieved during baseline exercise stress testing. Those in the delayed participation group initiated the program after the final outcome assessments. They were offered the delayed program in gratitude for their participation in the study.

### PREPRANDIAL GLUCOSE THRESHOLDS

Patients were randomized to liberalized or conventional preprandial glucose thresholds for adjustment of glucose-lowering medications other than metformin. All patients were instructed to measure capillary blood glucose measurements twice daily before meals. These values were averaged at 2- to 4-week intervals. Glucose-lowering medications were adjusted based on the average preprandial values. In the liberalized group, medications were increased only if the 2-week average preprandial glucose was  $\geq 10$  mmol/L and lowered if the average glucose value was  $< 10$  mmol/L.

In the conventional group, the threshold for adjustment of glucose-lowering medication other than metformin was 7 mmol/L. The liberalized threshold (10 mmol/L) reflects the renal threshold for glucose excretion in type 2 diabetes. We did not allow preprandial glucose values above this level because our intent was

not to induce weight loss through osmotic diuresis. Glucose-lowering medications were added in the following sequence or withdrawn in the reverse sequence: metformin, sulfonylurea, thiazolidinedione and insulin. At each visit, a urine dipstick test was performed for the detection of glycosuria.

### ANALYSIS

Immediate and delayed supervised exercise groups were compared in terms of changes in weight, HbA1c level, fitness (exercise time during maximal exercise stress test) and blood pressure (mean arterial blood pressure =  $2/3$  systolic blood pressure +  $1/3$  diastolic blood pressure). We also compared the 10 mmol/L with the 7 mmol/L threshold-defined groups in terms of changes in weight and HbA1c levels.

To confirm that our protocol led to a difference in preprandial glucose levels between the 10 mmol/L and 7 mmol/L arms, we then compared mean 90-day preprandial glucose level based on capillary blood glucose assessments. To confirm that randomization to the 10 mmol/L threshold arm was not associated with an increased likelihood of osmotic diuresis, we compared frequency of glycosuria between threshold-defined groups.

Forty-two of 50 men and women formally evaluated for participation were enrolled. The most frequent reason for ineligibility was very low exercise capacity (ie,  $< 5$  metabolic equivalents). Patients were middle-aged and overweight (ie, average BMI of 36 kg/m<sup>2</sup>) and about one-third were extremely obese (ie, BMI  $> 40$  kg/m<sup>2</sup>). At baseline, blood glucose was well controlled (ie, mean HbA1c approximately 7%). About half of the patients were treated with metformin alone and the remainder were treated with a combination of metformin and sulfonylurea therapy. Average blood pressure was 130/80 mm Hg. Four patients reported a history of cardiovascular disease but no recent history of angina.

### SMALL AMOUNT OF WEIGHT LOSS

Patients in the immediate supervised exercise group lost a small amount of weight, increased their level of fitness and improved both their blood pressure and glucose control (Figure 1). Compared with those not randomized to a supervised exercise program, however, only improvement in blood pressure was statistically significant. Average attendance at exercise classes was 64% overall and 72% after exclusion of those who withdrew from the program. Nine participants attended  $> 75\%$  of scheduled exercise sessions; these patients experienced significant weight loss and improvements in fitness and blood pressure (Figure 1).

Median 90-day average preprandial glucose was significantly higher in the 10 mmol/L threshold arm (ie, 8.4 mmol/L) than in the 7 mmol/L arm (ie, 6.9 mmol/L). Frequency of glycosuria, however, was not significantly different between the two groups, and at 24 weeks, there was no significant difference between weight change (-1.2% in 10 mmol/L threshold group vs -0.3% in 7 mmol/L threshold group) or HbA1C level (-0.8% in 10 mmol/L threshold group vs 0% in 7 mmol/L threshold group).

### INTERPRETATION

In this pilot trial, neither the addition of a 24-week program of supervised exercise nor the liberalization of preprandial thresholds for increases in glucose-lowering medication were associated with significant reduction in weight, over that achieved through dietary counseling with maximal tolerated dose of metformin. In all groups, even over a 24-week period, weight reduction was <2%. The absence of weight increase, however, is an important achievement for men and women with diabetes.

Despite the absence of substantial weight loss, there were benefits associated with participation in the supervised exercise program. Overall, those randomized to a supervised exercise program experienced a greater reduction in blood pressure than those not randomized to such a program. This difference was likely driven by regular attendance at exercise classes. Improvement in blood pressure was similar overall for the supervised exercise group and the subgroup who attended  $\geq 75\%$  of supervised exercise classes.

Additionally, the improvement in fitness was 5% overall for the supervised exercise group but >20% among those who attended  $\geq 75\%$  of exercise classes. When we included all available data in a linear regression model — examining the impact of change in fitness on change in blood pressure — we determined that a 10% increase in fitness was associated with a 2.3% reduction in mean arterial blood pressure.

One previous trial found that a 24-week structured exercise program (ie, treadmills, stationary bicycles and rowing machines) significantly lowered blood pressure among men and women with type 2 diabetes.<sup>7</sup> Two other exercise trials that involved walking-based interventions did not demonstrate this same effect,<sup>8,9</sup> which suggests that exercise more intense than walking may be most effective in lowering blood pressure among men and women with type 2 diabetes.

Although liberalization of preprandial thresholds for glucose-lowering medication was not associated with greater weight loss, glycemic control did not deteriorate

as measured by HbA1c levels. Current preprandial glucose targets may, then, be raised — permitting use of less glucose-lowering medication — without adversely impacting HbA1c levels; this, however, requires further study. In the only previous trial that we identified addressing the issue of preprandial glucose thresholds in type 2 diabetes patients, randomization to a preprandial threshold of 6.5 mmol/L resulted in greater intensification of medication but no greater improvement in HbA1c levels at 1-year follow-up, compared with randomization to a preprandial threshold of 7 mmol/L.<sup>10</sup>

### CONSISTENT ATTENDANCE

Consistent attendance during a supervised exercise program was associated with a large improvement in fitness, and those in the supervised exercise program experienced clinically important reductions in blood pressure. ■

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