Brisk walking is as effective as a structured exercise plan in diabetes

Exercise is an important component in the treatment of diabetes, but the benefits of lifestyle intervention are often limited by poor compliance.

This study randomised 92 patients with type 2 diabetes to either an individualised structured exercise programme or to 60 minutes of brisk walking three times a week for a period of 12 months.

Changes in HbA1c, blood pressure, lipids, insulin sensitivity, body composition, physical fitness, programme adherence rate and health-related quality of life were assessed. Both exercise regimens had similar effects on these parameters, indicating that a relatively simple walking programme is as effective as a more individualised medical fitness programme. There was a high drop-out rate from both programmes, however, with less than half actively participating for the full 12 months. Overuse injuries and lack of motivation were the main reasons for failing to continue with the programmes.


Retinopathy at low levels of fasting glucose

A recent analysis has indicated that diabetic retinopathy is prevalent at levels of fasting glucose below the cut off level for diagnosis of type 2 diabetes.

Data from three large-scale population-based studies including a total of 12,664 people showed a prevalence of diabetic retinopathy of 11.5 %, 9.6 % and 15.8 % in the three studies.

There was no clear cut-off level of fasting glucose for development of retinopathy, and many patients with retinopathy had fasting blood glucose below 7.0 mmol/l, the cut-off for the International Diabetes Federation (IDF) definition of type 2 diabetes.

The authors conclude that their findings indicate that the criteria for diagnosis of diabetes may need to be reassessed.

**Intensive treatment reduces mortality in type 2 diabetes**

Post-trial follow-up from the Steno-2 study demonstrated a maintained reduction in mortality following intensive control of multiple cardio-metabolic risk factors in patients with type 2 diabetes.

In the Steno 2 study, 160 patients with type 2 diabetes were randomised to either intensive therapy or conventional diabetes therapy for 7.8 years. The intensive treatment strategy included lifestyle education and tight glycaemic control and treatment of known risk factors (including blood pressure and lipids) using a multiple drug regimen.

Patients were subsequently followed for 5.5 years post-trial, and the time to death from any cause was analysed. Fewer patients who received intensive treatment died during this 13-year follow-up period, compared with those who received conventional treatment during the trial (24 vs. 40; hazard ratio, 0.54). Intensive therapy was also associated with a significantly lower risk of death from cardiovascular causes, of cardiovascular events and progression to end-stage renal disease.


**Moderate Postsurgical Blood Glucose Target Appears Effective**

Moderate glucose control during first days following CABG led to better outcomes than did liberal control, by a review of > 4,000 patients at one U.S. centre. Patients maintained on tight glucose control, however, with an average level of <7.0 mmol/l during the first 3 days after CABG, had no significant outcome advantage over those on liberal control at a mean level of >10 mmol/l.

Based on this as well as published studies, the ideal blood glucose target after CABG is 8.3 mmol/l, with a target range of 6.7-8.3 mmol/l. Gorav Ailawadi said at the American Association for Thoracic Surgery meeting.

Moderate glucose control, defined as a mean blood glucose level during the first 3 days after surgery of 7.0-10.0 mmol/l, was linked to a significant reduction in mortality and major complications. The goal is 6.7-8.3 mmol/l, but not above 10.0 mmol/l.

Although it’s unclear why tight control may not be as effective as moderate control, Ailawadi suggested that perhaps patients have more hypoglycaemic episodes in the tight-control group. But although the study included 4,658 patients, it had only 134 patients in the tight-control group, along with 2,785 in the moderate-control group and 1,739 in the liberal-control group.

The Normoglycaemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, which included 6,100 ICU patients, found that a glucose target of less than 10 mmol/l led to significantly better survival than did a target of 4.5-6.0 mmol/l (N. Engl. J. Med. 2009;360:1283-97).

One study randomized 400 on-pump cardiac surgery patients to tight postoperative glucose control with a target of 4.4-5.5 mmol/l or to conventional treatment with a blood glucose goal of less than 11.1 mmol/l and an achieved mean level of 8.7 mmol/l. At 30 days' follow-up, the incidence of the primary end point – a composite of death, sternal infections, prolonged ventilation, cardiac arrhythmias, stroke, and renal failure was identical in the two groups. But the group on tight control had a trend toward more deaths that nearered significance (P = 0.061), and a significantly higher rate of stroke (Ann. Intern. Med. 2007;146:233-43).

An unpublished study that randomized cardiac surgery patients to tight postoperative glucose control with a target mean level of 5.0-6.7 mmol/l compared with a target mean of 6.7-10.0 mmol/l, and showed no significant difference in the rates of major adverse CV events between the two groups. Harold L. Lazar, at Boston University summarized the results. He also noted that the 2009 report from the Blood Glucose Guideline Task Force of the Society of Thoracic Surgeons set an “optimal glucose range” during and after adult cardiac surgery of 6.7-10.0 mmol/l (Ann. Thorac. Surg. 2009;87:663-9). A reason the task force selected this range was “to make it easier for people to be in compliance,” he said.

Multivariate analysis that controlled for clinical differences revealed that moderate glucose control was linked to a significant 40 % reduced mortality and a 30 % reduced rate of complications compared with the liberal-control group. The tight-control group had a 50 % reduced mortality compared with the liberal-control group, but the difference was not significant, and the tight-control group had the same rate of complications as the liberal-control group.
Pioglitazone Shown to Prevent Atherosclerotic Progression in Type 2 Diabetes

Treatment of type 2 diabetes (T2DM) with pioglitazone resulted in significant prevention of coronary atherosclerosis progression, compared with glimepiride, in a prospective, randomised study of 543 patients.

Intravascular ultrasound performed at 18 weeks in 360 patients revealed that the glimepiride group had highly significant progression of the primary efficacy parameter of mean change in percent atheroma volume (PAV) from a baseline of 0.73 %. Those on pioglitazone, however, had a reduction of PAV, of 0.16 %, which was statistically unchanged from baseline: Steven Nissen et al (PERISCOPE).

After 18 months treatment, patients assigned to glimepiride had unequivocal progression of coronary atherosclerosis, whereas pioglitazone-treated patients had no progression. “To our knowledge, this is the first study in which a diabetes therapy has been shown to slow or prevent progression of coronary atherosclerosis.”

A subgroup analysis revealed no statistical differences in PAV in pre-specified subgroups, including age, gender, BMI, SBP, statin use, duration of diabetes, or baseline HbA1c. Patients in the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) trial were randomised to 1-4 mg/day of glimepiride or 15-45 mg/day of pioglitazone, titrated to maximally tolerated dose by 16 weeks. The patients, aged 35-85 years, were undergoing angiography for clinical indications at the time of enrolment at 97 academic and community centres in North and South America, and had to have a baseline HbA1c of 6 %-9 %.

HbA1c levels fell in both treatment groups, although pioglitazone produced a significant and more sustained benefit. The mean difference in HbA1c was small, 0.19 %, favouring pioglitazone.

Significant differences in systolic and diastolic blood pressure were observed, favouring pioglitazone. Systolic BP increased 2.3 mm/Hg in the glimepiride group and was unchanged in the pioglitazone group, a significant difference. Diastolic pressure rose 0.9 mm Hg in the glimepiride group and fell 0.9 mm Hg in the pioglitazone group.

In terms of biochemical parameters, pioglitazone patients showed significant improvements in HDL cholesterol, compared with glimepiride patients, with increases of 16% and 4%, respectively; high-sensitivity C-reactive protein, with decreases of 45 % and 18 %; and triglycerides, which fell 15.3 % with pioglitazone treatment and rose 0.6 % with glimepiride.

LDL cholesterol rose slightly in the glimepiride patients, but there was no significant difference between groups.

Although the trial was not powered to assess major cardiovascular events, an adjudicated composite end point of CV death, nonfatal MI, or nonfatal stroke occurred in 2.2 % of the glimepiride patients and 1.9 % of the pioglitazone patients. Non-CV death occurred in 0.4 % and 0 % and coronary revascularisation in 11 % and 10.7 %. Owing to the small size of the trial, none of these differences approached statistical significance.

Both regimens were well tolerated, but revealed a different pattern of adverse events. Events that were significantly higher in the glimepiride group than the pioglitazone group were hypoglycaemia (37 % vs. 15 %, respectively) and angina (12 % vs. 7 %). Those that were more frequent in the pioglitazone group than the glimepiride group were oedema (11 % vs. 18 %), bone fractures (0 % vs. 3 %, respectively), and weight gain (1.6 kg vs. 3.6 kg).

Baseline characteristics evaluated were similar between the pioglitazone (n = 270) and glimepiride (n = 273) groups, with regard to age (mean 60 years), diabetes duration (6 years), and BMI (32 kg/m²). Significantly more patients in the glimepiride group had hypertension (92 % vs. 83 %) and were current smokers (19 % vs. 11.5 %).

Discussant B. Greg Brown, University of Washington, Seattle, said, “We don’t know for sure that there are clinical benefits associated with this improvement in stenosis severity, but the trends look favourable.” He then asked Nissen if the findings have changed his opinion regarding the glitazone class of drugs.

Nissen responded that the two available drugs – rosiglitazone and pioglitazone – have very different effects in terms of their lipid effects, with rosiglitazone raising HDL by 18 %-20 % and pioglitazone having very little effect. Moreover, while both drugs target the gene that lowers blood sugar, they otherwise have extraordinary different effects. “We have to study each of these compounds individually,” he said. “Many drugs in this class have failed due to toxicity because their genetic effects are unpredictable.

“I think what happened here is that pioglitazone has the right constellation of effects to produce a beneficial effect, whereas rosiglitazone clearly produces harm,” he said. Cont.
The two drugs were chosen because they work by “diametrically opposed mechanism,” Nissen said in a press conference. “We wanted to test an insulin-providing therapy [glimepiride] against an insulin-sensitising therapy [pioglitazone].”

The most important message of PERISCOPE is that comparative effectiveness trials must be performed in all diabetes treatment strategies. “We can’t just focus on pricking the finger, getting the blood sugar down, and saying that’s the goal of therapy. The goal of therapy is to prevent the complications of diabetes. And the most serious complication is heart disease.”

The 2 major types of bariatric procedures for obese patients — bypass surgery and restrictive surgery — have different effects on gut hormone secretion, and thus on insulin secretion and sensitivity. These effects should be considered when choosing a surgical approach for severely obese patients with type 2 diabetes according to a review in the January 20 issue of Annals of Internal Medicine.

Familiarity with these effects can help physicians decide among the different surgical procedures and avoid postoperative hypoglycaemia, said Marion L. Vetter, from University of Pennsylvania in Philadelphia, and colleagues.

The review article was based on a literature search of 4 decades’ worth of studies on bariatric surgery and diabetes. Most of the studies had serious methodological weaknesses, the authors state. Few were randomized controlled trials, and important data were missing in a number of the studies. A total of 10 studies met minimum criteria for quality and had follow-up rates of at least 80%.

Bariatric surgery was found to reduce the patients’ body mass index by 10 to 15 kg/m² and their weight by 30 to 50 kg in these studies. In 1 study, Roux-en-Y gastric bypass (RYGB) - the procedure considered the current gold standard - was associated with a 25% reduction in total body weight at 10 years, whereas restrictive procedures such as laparoscopic adjustable gastric banding and vertical banded gastroplasty were associated with 16% and 14% weight loss, respectively. Diabetes resolution was reported in 60% to 80% of patients treated surgically.

Bariatric surgery procedures achieve resolution of type 2 diabetes in 49% to 98% of patients. These procedures have different effects on the enteroinsular axis (connection between the gut and pancreatic islet cells), including effects on incretins (glucagon-like peptide 1 [GLP-1] and glucose-dependent insulino tropic peptide) and non-incretin gut peptides (peptide YY [PYY] and Ghrelin). Intestinal bypass procedures that expedite nutrient delivery to the distal ileum, such as biliopancreatic diversion and RYGB, increase GLP-1 and PYY levels; in contrast, restrictive procedures do not increase incretin or PYY levels. After surgery, Ghrelin levels are determined by the remaining amount of Ghrelin-producing tissue and by whether vagal innervation is intact.

The authors postulate that augmented levels of GLP-1 probably account for the antidiabetic effect of procedures that bypass the small bowel. It is also thought that altered secretion of anorexigenic peptides (i.e. GLP-1 and PYY) may mediate a reduction in appetite and sustained weight loss that occurs more often after intestinal bypass procedures.

Collectively, caloric restriction and alterations in the enteroinsular axis probably affect both insulin secretion and sensitivity. Physicians must anticipate the rapid improvements in insulin action after bariatric surgery and adjust diabetes regimens accordingly to avoid hypoglycaemia. In addition to identifying the antidiabetic mechanisms of bariatric surgery, future research should focus on making medical management safer, particularly if the patient takes GLP-1 analogues or DPP-IV inhibitors, state the authors.

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