Does a combined program of dietary modification and physical activity or the use of metformin reduce the conversion from impaired glucose tolerance to type 2 diabetes?

Trial: Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.

Question

Can treatment with lifestyle modification (changes in diet and physical activity) or metformin reduce the conversion from impaired glucose tolerance (IGT) to type 2 diabetes? Do these treatments differ in effectiveness?

Trial details

Design: A three-arm multicentre, stratified, randomised controlled trial.

Setting: 27 centres in the United States.

Patients: 3234 (mean age, 50.6 years; 45.3% non-white; 67.7% female). Inclusion criteria were age 25 years or older; body mass index 25 kg/m^2 or more if white, 24 kg/m^2 or more if Native American, or 22 kg/m^2 or more if Asian; fasting plasma glucose level of 5.3–6.9 mmol/L or < 6.9 mmol/L if Native American; a 2-hour plasma glucose level of 7.8–11 mmol/L after a 75 g glucose tolerance test (GTT); and no previous history of diabetes except gestational diabetes. Patients taking medication affecting glucose tolerance or with a disease which would affect life expectancy or participation in the activity recommendations were excluded.

Intervention: The three groups were standard lifestyle recommendations plus twice-daily placebo (control group); intensive lifestyle program plus twice-daily placebo (lifestyle group); and standard lifestyle recommendations plus metformin (metformin group). The intensive program aimed to reduce patients' weight by at least 7% by dietary means and to have them engage in physical activity of moderate intensity for at least 150 minutes a week.[1,2] The program was taught in 16 one-to-one lessons followed by individual and group sessions. The standard lifestyle intervention included similar information to the intensive program, but this was given as a written brochure and advice at the annual visit. Patients taking metformin were given one 850 g tablet plus one placebo per day for the first month and two metformin tablets daily thereafter.

Main outcome measures: Progression from impaired glucose tolerance (IGT) to diabetes on the basis of six-monthly fasting plasma glucose measurements and an annual 75 g oral GTT. If a result met the 1997 American Diabetes Association (ADA) definition of diabetes,[3] the test was repeated within six weeks. If the repeat result also met the ADA definition, the primary endpoint was reached. Otherwise, the patient continued in the assigned group.

Main results: The trial was stopped one year early after an average follow-up of 2.8 years. Compared with the control group, the rate of type 2 diabetes was reduced by 58% (95% CI, 48%–66%) in the lifestyle group and by 31% (95% CI, 17%–43%) in the metformin group. The three-year cumulative incidence was 14.4% in the lifestyle group, 21.7% in the metformin group and 28.9% in the control group. The general pattern of the results did not vary by age, sex or race. At the final visit, 38% of the lifestyle group had reduced weight by 7% or more, average fat intake had declined by 6.6% from a baseline of 34.1% of total energy, and 58% were achieving the activity goal. More than 70% of patients took at least 80% of their medication. Hospitalisation and death rates were not different among the three groups.

Conclusion: Both lifestyle modification and metformin reduce progression rates from impaired glucose tolerance to diabetes but lifestyle changes were more effective than metformin. The number needed to treat to prevent one case of diabetes in three years is 6.9 for lifestyle and 13.9 for metformin.

Commentary

Rationale for the trial

The prevalence of type 2 diabetes and its precursor stages is increasing. In 1999, the prevalence of diabetes was 7.4% and of impaired glucose tolerance (IGT) and abnormal fasting blood glucose (FBG) level was 16.4% in Australians aged 25 years and older.[4] People with IGT have an increased risk of macrovascular disease, but not of microvascular disease. IGT is associated with obesity, sedentary lifestyle and increasing age, and is more common in some racial and ethnic groups. The only well conducted previous study of lifestyle modification was smaller and included only white people.[5] Previous studies of pharmacological agents to reduce the conversion rate had been underpowered.[1]

Trial methods

This was a well-conducted study with great attention to detail. For example, the requirement that an endpoint was diagnosed based on the results of two GTTs or two FBG tests was a potential source of bias and unblinding for participants and trial staff. This was addressed by retesting a sample of patients with normal results on these tests and not disclosing the result until progression to diabetes was confirmed.[1] Patients were randomly assigned to groups only after completing an extensive run-in phase. An intention-to-treat analysis was done. Sample size for the trial was based on having a 90% power to detect a 33% reduction in the expected incidence of diabetes (6.5% per year). Greater methodological detail is available elsewhere.[1,2]

Although the focus was on progression to diabetes, reversion to normoglycaemia was also reported. At one year, more than 20% of the control group and 40% of the lifestyle group had normal values for both fasting and post-load glucose levels, and this declined to about 20% and 30%, respectively, at three years' follow-up. This highlights the need for a control group when evaluating interventions. Without this, most of the reversion in the intervention group might have been attributed to the intervention. Instead, it is clear that much of the reversion is related to "regression to the mean".[6] That is, when a group defined using a cut-off

point in a measure with substantial intra-individual variability is retested, the average value on the second test will be closer to the total population mean.[6]

New information

This study is the first to test lifestyle against pharmacological prevention for type 2 diabetes and also the first to include groups that are often under-represented — the elderly, women and non-white people. The results confirm the findings of the previous lifestyle trial[5] and extend their generalisability. Whether the interventions actually prevent diabetes, or simply delay its onset, or what happens if the interventions stop, cannot be answered by either study.

The variability of glucose levels has been previously described. However, the size of this trial means that the magnitude of the reversion to normal is probably a good estimate of what would happen in the clinical setting in patients who were retested. The size of the variability also has implications for interpreting the results of national surveys such as AusDiab,[4] as it means that the proportion of people with abnormal glycaemia found on a single test overestimates the proportion who would have had the abnormality confirmed on a later test.

Implications for clinical practice

This study shows that 5–6 kg weight loss combined with dietary modification to reduce fat intake to less than 30% of energy and increasing activity for 150 minutes per week will halve the conversion rate to diabetes in people with IGT. Because the mean baseline body mass index (BMI) was 34.0 kg/m^2, losing 5–6 kg reduced this to about 31.5 kg/m^2, which is still in the obese range. Patients should not be given the false impression that they must achieve a body weight in the healthy range (BMI of 18.5–24.99 kg/m^2) before any benefits occur.

As Native Americans and Pacific Islanders were included, it is reasonable to conclude that the results of this study would apply to Indigenous Australians, who have high levels of diabetes and cardiovascular mortality.[7]

At present, it is not possible to separate the effects of dietary and activity change on the outcomes, so both need to be recommended together. The intervention for the control group was similar to what a general practitioner might do during a consultation. A lot of support was given to help the lifestyle group patients achieve their lifestyle changes,[2] which means that this is not a cheap intervention. The challenge for clinical practice is to provide this support either directly or by referral to community groups and to advocate for environmental changes that support beneficial lifestyle changes.

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Competing interests

None identified.

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