



Critical Appraisal

Lifestyle intervention or treatment with metformin

Which delays onset of type 2 diabetes?

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Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346(6):393-403.

Research question

Does lifestyle intervention or treatment with metformin prevent or delay onset of type 2 diabetes in high-risk patients (ie, overweight people with high fasting glucose levels and impaired glucose tolerance)? Do these two interventions differ in effectiveness?

Type of article and design

Randomized, double-blind (for the placebo and metformin intervention), placebo-controlled trial.

Relevance to family physicians

Type 2 diabetes is extremely common in our practices, as are obese people. In 2002, we reviewed the Finnish Diabetes Prevention Trial¹ that was similar to this trial, but looked only at lifestyle. It had very promising results.² Briefly, participants made four changes: they reduced total and saturated fat intake, were active 150 minutes weekly, lost 5% of

their weight, and consumed more fibre. In that and this trial, progression to type 2 diabetes was prevented in 58% of participants during the 3 years of the trial. We know that patients struggle with dysglycemia before they meet current criteria for type 2 diabetes and that some patients are incapable of making lifestyle changes at a given time. Would medications also help “prevent” diabetes, and to what degree compared with lifestyle changes?

Overview of study and outcomes

This clinical trial in 27 centres looked at overweight people (mean age 50 years, mean body mass index [BMI] 34) who had impaired glucose tolerance (plasma glucose concentration of 7.8 to 11.0 mmol/L 2 hours after a 75-g oral glucose load) and impaired fasting glucose (plasma glucose concentration of 5.3 to 6.9 mmol/L fasting). About 45% of participants were African-American, Hispanic, Native American, or Asian; 68% were women.

The 3234 participants were assigned to one of three interventions: standard lifestyle recommendations plus 850 mg of metformin twice daily, standard lifestyle recommendations plus placebo twice daily, or an intensive program of lifestyle modification. Standard lifestyle recommendations were provided

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as written information and an annual 20- to 30-minute individual session that emphasized a healthy diet, weight reduction, and increased physical activity. The intensive lifestyle intervention targeted a 7% weight loss and consisted of a 16-lesson program on diet, exercise, and behaviour modification. It was taught by case managers on a one-to-one basis with bimonthly contacts and quarterly group sessions.

Primary outcome was onset of type 2 diabetes as diagnosed by an annual oral glucose tolerance test or a semiannual fasting glucose test. Mean duration of follow up was 2.8 years. The blinded treatment phase was terminated 1 year early because incidence of diabetes was substantially reduced by treatment.

Results

Results are shown in **Table 1**.

- Incidence of diabetes was 58% lower in the intensive lifestyle group and 31% lower in the metformin group compared with the placebo group.
- At least 80% of the prescribed study medication was taken by 77% of the placebo group and 72% of the metformin group. Gastrointestinal complaints were greatest in the metformin group.
- By the end of the 16-lesson program, 50% of the intensive lifestyle group had lost 7% or more of their weight.
- The advantage of intensive lifestyle intervention over metformin in reducing the primary end point (diabetes) increased with age (8% reduction in incidence if 25 to 44 years, 41% if 45 to 59 years, 69% if ≥ 60 years) and in those with a lower BMI (63% if BMI was 22 to <30 and 56% if BMI was 30 to <35 compared with -4% if BMI was ≥ 35).
- No hospitalizations or deaths were attributed to study interventions.

Analysis of methodology

In this randomized trial with intention-to-treat analysis, medications and placebo were administered in a double-blind fashion.

Table 1. Outcomes of the three treatment arms

OUTCOME	STANDARD INTERVENTION	METFORMIN AND STANDARD INTERVENTION	INTENSIVE LIFESTYLE INTERVENTION
Weight reduction (kg)	0.1	2.1	5.6*
Reduction in fat intake (%)	0.8	0.8	6.6*
Incidence of diabetes per 100 patient-years	11	7.8	4.8
Estimated cumulative incidence of diabetes at 3 y (%)	28.9	21.7	14.4
NNT to prevent one case of diabetes at 3 y	—	14	7
NNT—number needed to treat * $P < .001$.			

Controls received counseling, quarterly follow up, and annual review sessions that, while achievable, would represent a difficult-to-replicate criterion standard in typical practice. Groups were similar at baseline, although rate of onset of diabetes in the placebo group was slightly higher than rates typical of other trials. Follow up was complete: 92% of participants attended scheduled visits within 5 months of study termination. Subgroup analyses showed that intensive lifestyle interventions consistently lowered incidence of diabetes, but the trial was not powerful enough to assess differences in subgroups.

Application to clinical practice

This trial confirms results of other trials showing that intensive lifestyle changes can delay onset of type 2 diabetes.^{1,2} This trial, however, used even more intensive interventions: one-on-one individualized teaching and monthly individual follow up. It included a more ethnically diverse population than previous studies. The utility and practicality of intensive lifestyle programs have been questioned because the resources required to implement them might not be attainable.³ The fact that intensive lifestyle intervention appeared to have a greater effect in certain

populations suggests that such programs can be targeted at certain patients.

The benefits of metformin should not be overlooked. Although not as effective as intensive lifestyle intervention and perhaps without as many secondary positive effects, metformin is probably easier to implement and adhere to. Metformin might be an option for patients who are unable to achieve the lifestyle targets outlined by the Diabetes Prevention Program.

Bottom line

- The Diabetes Prevention Program confirms the benefits of intensive lifestyle changes in delaying onset of type 2 diabetes in high-risk patients. Compared with standard practice, an intensive program followed for 3 years can reduce incidence of diabetes by 58%.
- The intensive lifestyle intervention consisted of a 16-lesson program that covered diet, exercise, and behaviour modification taught one on one, monthly contacts, and quarterly group sessions. Goals were to lose at least 7% of initial body weight and to perform a minimum of 150 minutes of moderate physical activity weekly. Although the intervention was successful in many cultures, ages, and races, it might be difficult to achieve in typical practices.
- Metformin (850 mg twice daily) combined with standard lifestyle interventions was not as effective as intensive lifestyle change in preventing onset of diabetes (31% vs 58% reduction, respectively), but it was more effective than standard lifestyle interventions alone. Metformin could be an option for patients unable to adhere to or attain the targets required by the intensive lifestyle intervention.

References

1. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen HH, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343-50.
2. Evans M. Can we prevent high-risk patients from getting type 2 diabetes? *Can Fam Physician* 2002;48:279-81.

Points saillants

- Le Programme de prévention du diabète confirme les bienfaits de changements de mode de vie intensifs pour retarder l'apparition du diabète de type 2 chez les patients à risque élevé. Par rapport à la pratique standard, un programme intensif pendant trois ans peut réduire l'incidence du diabète de 58%.
- L'intervention intensive dans le mode de vie comportait un programme de 16 leçons qui traitaient de l'alimentation, de l'activité physique et des modifications au comportement, enseignées sur une base individuelle par des rencontres mensuelles et des séances de groupe trimestrielles. Les objectifs étaient de perdre au moins 7% du poids corporel initial et de faire au minimum 150 minutes d'activité physique modérée par semaine. Même si l'intervention a été fructueuse auprès de cultures, d'âges et d'origines ethniques différents, elle pourrait être difficile à implanter dans des pratiques typiques.
- De la metformine (850 mg deux fois par jour), combinée à des interventions standard sur le mode de vie, n'était pas aussi efficace que des changements intensifs au mode de vie dans la prévention de l'apparition du diabète (31% par rapport à 58% de réduction, respectivement), mais cette méthode était plus efficace que les seules interventions standard sur le mode de vie. La metformine pourrait être une option pour les patients incapables de se conformer aux objectifs exigés par une intervention intensive dans le mode de vie ou de les atteindre. ❁

3. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997;20(4):537-44.

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