

A lifestyle intervention or metformin prevented or delayed the onset of metabolic syndrome in persons at risk

Orchard TJ, Temprosa M, Goldberg R, *et al*. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005;142:611–9.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Endocrine ★★★★★☆

Q In persons with impaired glucose tolerance, does an intensive lifestyle intervention (ILS) or treatment with metformin plus standard lifestyle recommendations prevent onset or promote resolution of metabolic syndrome?

METHODS

Design: randomised placebo controlled trial (The Diabetes Prevention Program randomised trial).

Allocation: concealed.*

Blinding: blinded (clinicians, participants, data collectors, and outcome assessors for metformin and placebo).*

Follow-up period: mean 3.2 years.

Setting: 27 centres in the US.

Participants: 3234 participants ≥ 25 years of age (mean age 51 y, 68% women) without diabetes who had a body mass index ≥ 24 kg/m² (≥ 22 kg/m² for Asian Americans) and a plasma glucose concentration 5.3–7.0 mmol/l (95–125 mg/dl) (≤ 7.0 mmol/l [≤ 125 mg/dl] for Native Americans) in the fasting state and 7.8–11.1 mmol/l (140–199 mg/dl) after a 75 g oral glucose load. 53% of participants had metabolic syndrome at baseline.

Intervention: ILS (n = 1079; 530 without metabolic syndrome), standard lifestyle recommendations plus glucose control with metformin (850 mg twice daily) (n = 1073; 503 without metabolic syndrome), or placebo (n = 1082; 490 without the metabolic syndrome). The ILS aimed at achieving and maintaining a weight reduction of $\geq 7\%$ of initial body weight through a low calorie, low fat diet and moderate physical activity. Standard lifestyle recommendations emphasised the importance of reducing weight and increasing physical activity.

Outcomes: incidence and resolution of metabolic syndrome.

Patient follow-up: 100% (intention to treat analyses).

*See glossary.

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MAIN RESULTS

The cumulative incidence of metabolic syndrome was lower in the ILS and metformin groups than in the placebo group (table). Resolution of metabolic syndrome was greater in the ILS group than in the placebo group (38% v 18%, $p = 0.002$); metformin and placebo groups did not differ for resolution (23% v 18%, $p > 0.05$).

CONCLUSIONS

In persons with impaired glucose tolerance, an intensive lifestyle intervention or treatment with metformin plus standard lifestyle recommendations was more effective than standard lifestyle recommendations alone for preventing or delaying onset of metabolic syndrome.

Abstract and commentary also appear in *ACP Journal Club*.

Commentary

The Diabetes Prevention Research Group previously reported in a separate analysis that both ILS and metformin were effective in reducing risk of progression to type 2 diabetes, with ILS being approximately twice as effective as metformin.¹ Metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III, represents a cluster of cardiovascular risk factors that are associated with excess visceral abdominal fat and insulin resistance. Much of the excessive cardiovascular risk associated with impaired glucose tolerance is explained by concomitant presence of metabolic syndrome. The trial by Orchard *et al* found that the results for incidence of metabolic syndrome paralleled those for new onset diabetes, with ILS and metformin being more effective than placebo. However, ILS reduced cumulative incidence of 4 out of the 5 metabolic syndrome components (ie, all except low high density lipoprotein [HDL] cholesterol concentration), while metformin only reduced the cumulative incidence of 2: large waist circumference and high fasting plasma glucose concentration. The relatively modest targeted weight loss (7% of initial body weight) and amount and intensity of exercise (target 150 min/wk) with ILS might explain why HDL cholesterol was not affected; greater volume and intensity of exercise are probably needed to increase HDL cholesterol.²

Nevertheless, this trial provides additional evidence for the value of an individualised, structured, supervised ILS to reduce incidence of multiple cardiovascular risk factors that collectively constitute metabolic syndrome.

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1 Knowler WC, Barrett-Connor E, Fowler SE, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.

2 Kraus WE, Houmard JA, Duscha BD, *et al*. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med* 2002;347:1483–92.

Intensive lifestyle intervention (ILS) or metformin plus standard lifestyle v placebo plus standard lifestyle for prevention of metabolic syndrome*

Outcome at mean 3.2 years	Comparisons	Cumulative incidence	RHR (95% CI)	NNT (CI)†
Incidence of metabolic syndrome	ILS v placebo	38% v 61%	41% (28 to 52)	4 (3 to 7)
	Metformin v placebo	50% v 61%	17% (0 to 31)	9 (5 to 41)

*RHR = relative hazard reduction. Other abbreviations defined in glossary. †NNTs provided by author.