

A lifestyle intervention or metformin prevented or delayed the onset of the 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: GIM/FP/GP ★★★★★★ Endocrinology ★★★★★☆☆

QUESTION

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

METHODS

Design: Randomized placebo-controlled trial (The Diabetes Prevention Program randomized 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 centers in the United States.

Participants: 3234 participants \geq 25 years of age (mean age 51 y, 68% women) without diabetes who had a body mass index \geq 24 kg/m² and a plasma glucose level 5.3 to 7.0 mmol/L (95 to 125 mg/dL) (\leq 7.0 mmol/L [\leq 125 mg/dL] for Native Americans) in the fasting state and 7.8 to 11.1 mmol/L (140 to 199 mg/dL) after a 75-g oral glucose load. Exclusion criteria included recent myocardial infarction and use of medications known to impair glucose tolerance. 53% of participants had the metabolic syndrome at baseline.

Intervention: ILS ($n = 1079$; 530 without the metabolic syndrome), standard lifestyle recommendations plus glucose control with metformin (850 mg twice daily) ($n = 1073$; 503 without the metabolic syndrome), or

placebo ($n = 1082$; 490 without the metabolic syndrome). The ILS aimed at achieving and maintaining weight reduction \geq 7% of initial body weight through a low-calorie, low-fat diet and moderate physical activity. Standard lifestyle recommendations emphasized the importance of reducing weight and increasing physical activity.

Outcomes: Incidence and resolution of the metabolic syndrome (defined as having \geq 3 characteristics [waist circumference; blood pressure; and levels of high-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose] that met the criteria of the National Cholesterol Education Program Adult Treatment Panel III [NCEP III]).

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

MAIN RESULTS

The cumulative incidence of the metabolic syndrome was lower in the ILS and metformin groups than in the placebo group (Table). Furthermore, the cumulative inci-

dence was lower in the ILS group than in the metformin group (Table). Resolution of the metabolic syndrome was greater in the ILS group than in the placebo group (38% vs 18%, $P = 0.002$); metformin and placebo groups did not differ for resolution (23% vs 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 the metabolic syndrome. Also, the intensive lifestyle intervention was more effective than metformin for preventing the metabolic syndrome.

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*See Glossary.

Intensive lifestyle intervention (ILS) or metformin plus standard lifestyle vs placebo plus standard lifestyle for prevention of the metabolic syndrome at mean 3.2 years†

Outcome	Comparisons	Cumulative incidence	RHR (95% CI)	NNT (CI)‡
Incidence of metabolic syndrome	ILS vs placebo	38% vs 61%	41% (28 to 52)	4 (3 to 7)
	Metformin vs placebo	50% vs 61%	17% (0 to 31)	9 (5 to 41)
	ILS vs metformin	38% vs 50%	29% (13 to 42)	9 (5 to 33)

†RHR = relative hazard reduction. Other abbreviations defined in Glossary.

‡NNTs provided by author.

COMMENTARY

The Diabetes Prevention Research Group previously reported in a separate analysis that both ILS and metformin were effective in reducing risk for progression to type 2 diabetes, with ILS being approximately twice as effective as metformin (1). The metabolic syndrome, as defined by NCEP 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 the metabolic syndrome. The trial by Orchard and colleagues found that the results for incidence of the metabolic syndrome paralleled those for new-onset diabetes, with ILS being more effective than metformin, which in turn was more effective than placebo. ILS reduced cumulative incidence of 4 out of the 5 metabolic syndrome components (i.e., all except low high-density lipoprotein [HDL] cholesterol level), while metformin only reduced the cumulative incidence of 2: large waist circumference and high fasting plasma glucose levels. 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 individualized, structured, supervised ILS to reduce incidence of multiple cardiovascular risk factors that collectively constitute the metabolic syndrome.

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References

1. Knowler WC, Barrett-Connor E, Fowler SE, et al. *N Engl J Med.* 2002; 346:393-403.
2. Kraus WE, Houmard JA, Duscha BD, et al. *N Engl J Med.* 2002;347: 1483-92.