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Q / Does metformin prevent diabetes in at-risk adults?

EVIDENCE-BASED ANSWER

A / YES. Metformin therapy reduces the risk of developing diabetes for adults with one or more risk factors for at least 5 years (strength of recommendation [SOR]: **A**, consistent meta-analyses) and perhaps as long as 10 years (SOR: **B**, ran-

domized clinical trial [RCT]).

Lifestyle modification with diet and exercise is approximately twice as effective as metformin for preventing diabetes, especially in older patients (SOR: **B**, RCTs).

Evidence summary

Three meta-analyses of studies lasting from 2 months to 5 years found that metformin reduced the risk of developing overt diabetes in at-risk adults when compared with placebo (TABLE).¹⁻³

Metformin is likely effective for as long as 10 years, based on long-term follow-up of patients in the Diabetes Prevention Program (DPP). In this trial, investigators randomized 3234 at-risk patients to 3 groups: metformin 850 mg twice daily; lifestyle modification (7% weight loss, 150 minutes of physical activity per week, and a one-to-one 16-lesson curriculum covering diet, exercise, and behavior modification); or placebo.⁴ At a mean 2.8-year follow-up, the incidence of diabetes was 31% lower in the metformin group (95% confidence interval [CI], 17%-43%) and 58% lower in the lifestyle modification group than in the placebo group (95% CI, 48%-66%; $P < .001$ for both comparisons).

At the close of the DPP trial, investigators offered lifestyle intervention to all 3 groups. Patients in the original metformin group continued to take metformin (with participants unblinded to assignment); patients in the original lifestyle intervention group were offered additional lifestyle support.⁵ At a median follow-up of 10 years after initial enrollment in the DPP trial, metformin re-

duced the incidence of overt diabetes by 18% compared with placebo (95% CI, 7%-28%), and lifestyle intervention reduced it by 34% (95% CI, 24%-42%; no statistic of comparison supplied).

Lifestyle modification works better than metformin in older adults

Another analysis found that metformin was equally effective in preventing diabetes in older and younger patients, whereas lifestyle modification was more effective in older patients. Investigators followed the patients in the DPP trial for an additional 5 months and stratified the effect of metformin and lifestyle modification by age.⁶

Metformin's effectiveness didn't change significantly in older adults compared with younger adults (hazard ratio [HR] for developing diabetes at age 60-85 years vs 25-44 years=1.45; 95% CI, 0.98-2.16; $P = .06$). In contrast, lifestyle modification worked better in older adults than younger adults (HR at age 60-85 years vs 25-44 years=0.47; 95% CI, 0.28-0.78; $P < .01$).

Recommendations

The American Diabetes Association says that physicians may consider using metformin to prevent type 2 diabetes in patients at the

TABLE

Metformin to prevent overt diabetes in at-risk adults: What the research reveals

Characteristics of meta-analysis (N)	Inclusion criteria: At least one of the listed diabetes risk factors	Metformin dose	Trial duration	Risk of diabetes vs placebo (95% CI)	NNT*
2 RCTs ¹ (3324)	<ul style="list-style-type: none"> • Impaired glucose tolerance • Elevated fasting glucose 	250-850 mg bid 250 mg tid	1-3 y	OR=0.67 (0.55-0.81)	14
7 RCTs ^{1,2} (3552)	<ul style="list-style-type: none"> • Impaired glucose tolerance • Elevated fasting glucose • HbA1c, 5.7-6.4 • History of gestational diabetes • Obesity 	500-850 mg bid 125-250 mg tid	6 mo to 5 y	RR=0.77 (0.69-0.86)	37-74
6 RCTs ³ (3119)	<ul style="list-style-type: none"> • Impaired glucose tolerance • Obesity • Metabolic syndrome • Polycystic ovary syndrome • Family history of diabetes • Hypertension, peripheral vascular disease, dyslipidemia 	500-2550 mg/d	2 mo to 3 y	OR=0.6 (0.5-0.8)	13

CI, confidence interval; NNT, number needed to treat; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

*NNT with metformin to prevent one case of overt diabetes.

¹One RCT of the 7 (N=204; 6% of total patients) used the biguanide phenformin rather than metformin.

highest risk, such as patients with multiple risk factors, especially if they show progression of hyperglycemia (HbA1c \geq 6%, for example) despite lifestyle intervention.⁷ **JFP**

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