

## Metformin Use in Adolescents

LAUREN GRAY, DO, *University of Colorado Family Medicine Residency, Denver, Colorado*

JAY H. LEE, MD, *Denver Health Medical Center, Denver, Colorado*

JOAN NASHELSKY, MLS, *University of Iowa Center for Human Rights, Iowa City, Iowa*

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### Clinical Question

Does metformin (Glucophage) therapy reduce the development of diabetes mellitus and other morbidities in adolescents who are obese?

### Evidence-Based Answer

There are no studies evaluating whether metformin prevents or delays the onset of diabetes in adolescents who are obese. In adults, metformin is as effective as lifestyle interventions in preventing increases in A1C and fasting glucose levels, but it is less effective in preventing or delaying the onset of overt type 2 diabetes. Metformin use reduces body mass index (BMI) for up to six months in adolescents who are obese (Strength of Recommendation [SOR]: C, based on disease-oriented randomized controlled trials [RCTs]) and reduces insulin resistance, the prevalence and severity of steatosis, and non-alcoholic fatty liver disease. (SOR: C, based on disease-oriented RCTs.)

### Evidence Summary

There are no studies evaluating whether metformin therapy reduces the development of diabetes or other morbidities in adolescents who are obese. Metformin delays the onset of type 2 diabetes in adults, although it is not as effective as intensive lifestyle interventions. The Diabetes Prevention Program Outcomes Study compared the effects of intensive lifestyle modification, metformin therapy, and placebo on the incidence of diabetes in 3,234 overweight adults over 10 years.<sup>1</sup> Compared with placebo, lifestyle modification reduced the incidence of diabetes by 34 percent (95% confidence interval [CI], 24 to 42 percent; 4.8 cases per 100 person-years; number needed to treat [NNT] = 16); metformin

use reduced the incidence of diabetes by 18 percent (95% CI, 7 to 28 percent; 7.8 cases per 100 person-years; NNT = 31) compared with placebo (11 cases per 100 person-years). Metformin prevented increases in A1C and fasting glucose levels as effectively as intensive lifestyle interventions.

Four short-term studies demonstrated the beneficial effects of metformin in adolescents who are obese by reducing BMI, insulin resistance, and nonalcoholic fatty liver disease, but studies using patient-oriented outcomes are lacking. A multicenter RCT studied the effects of metformin on BMI in 77 adolescents who were obese and 13 to 18 years of age (sex not specified).<sup>2</sup> All participants took part in a lifestyle intervention program. After 48 weeks, BMI decreased in the metformin group compared with the control group (−0.9 versus +0.2 kg per m<sup>2</sup>, respectively; *P* = .03). This effect persisted until 24 weeks after discontinuation of the drug, then waned.

A second RCT studied the effects of metformin in addition to personal goal-setting on weight loss in 85 adolescents who were obese, 12 to 19 years of age, and had insulin resistance.<sup>3</sup> After six months, BMI decreased among the girls receiving metformin compared with those receiving placebo (−0.40 versus +1.04 kg per m<sup>2</sup>; *P* = .02).

A European RCT examined insulin resistance in 70 adolescents who were obese and 10 to 17 years of age (sex not specified) in whom six months of lifestyle intervention was ineffective.<sup>4</sup> Investigators measured insulin resistance using the homeostatic model assessment ( $[\text{fasting insulin (mIU per L)} \times \text{fasting glucose (mmol per L)}] \div 22.5$ ). After six months, patients who received metformin had an average decrease in insulin

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resistance of 73 percent compared with 54 percent in the control group ( $P = .048$ ).

A final RCT examined the effects of metformin on the prevalence and severity of nonalcoholic fatty liver disease diagnosed by ultrasonography in 50 adolescents 12 to 18 years of age who were obese and insulin-resistant.<sup>5</sup> After six months, participants who received metformin had a significantly lower prevalence of steatosis (61 versus 90 percent;  $P < .04$ ) and improved fatty liver severity scores.

### Recommendations from Others

The American Diabetes Association recommends lifestyle changes such as weight management and increasing physical activity to prevent the development of diabetes in adolescents who are obese.<sup>6</sup> The American Association of Clinical Endocrinologists recommends metformin or thiazolidinediones, in addition to lifestyle changes, in younger patients who are at moderate risk of developing diabetes.<sup>7</sup>

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Address correspondence to Lauren Gray, DO, at [lauren.g303@gmail.com](mailto:lauren.g303@gmail.com). Reprints are not available from the authors.

Author disclosure: No relevant financial affiliations.

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