Is There a Role for Metformin in the Treatment of Childhood Obesity?

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Childhood obesity often seems like an intractable problem, with a rising incidence, especially of severe obesity, over the last few decades and few effective treatment options. Lifestyle changes, including dietary modification and exercise, are effective only in a minority of patients, with significant and sustained weight loss most likely to occur in the setting of costly multidisciplinary programs. Thus, clinicians often turn to pharmacotherapy. Currently there is only 1 medication, orlistat, that is approved for childhood obesity, but its effect on weight is modest and its acceptability is limited by side effects related to decreased fat absorption.

Metformin is the mainstay of treatment of type 2 diabetes in both children and adults, with effects mainly on improving insulin sensitivity and decreasing hepatic glucose output. Since 2000, there have been a large number of studies that have examined the use of metformin as a weight-loss drug in children with obesity. Although each study has been unique in its size, design, and the patient populations studied, the theme that emerges, as summarized in a systematic review in 2014 based on 14 randomized clinical trials, is that “metformin provides a statistically significant, but very modest reduction in BMI when combined with lifestyle interventions over the short term.”

The latest addition to this literature, published in this issue of Pediatrics, is a study from Spain, “Metformin for obesity in prepubertal and pubertal children: A Randomized Controlled Trial,” which offers some benefit compared with previous clinical trials but leaves more questions unanswered than answered. The main improvement of this study is its large size (160 patients with obesity were randomly assigned) and the inclusion of equal numbers of prepubertal and pubertal subjects. Like most other studies, it lasted only 6 months. However, the authors found an effect of metformin on BMI over 6 months only in the prepubertal subjects, which was both unexpected and disappointing. The effect in drug-treated prepubertal subjects was significant when BMI SD was the outcome (a decrease from 3.4–2.6 versus a decrease from 4.0–3.4 in the placebo group; \( P = .04 \)), but the decrease in weight from 55.8 kg to 54 kg and in BMI from 28.2 to 26.5 did not reach a statistical significance compared with placebo. No effect on these parameters in the pubertal subjects was found. The authors correctly point out that because they used the same relatively small dose of metformin (500 mg twice daily) in both groups, the failure to see an effect in the pubertal group may have been due to the metformin dose being ∼50% lower on a milligram per kilogram basis. Most other published metformin-obesity studies have used escalating doses up to either 850 mg or 1000 mg twice daily. In addition, several studies have revealed a BMI reduction in teenage subjects as well as in subjects younger than age 12, so there is no evidence that puberty per se mitigates against metformin responsive ness.

One study from Colorado briefly cited by the authors offers some insight as to why metformin is not more uniformly effective in treating obesity.
These authors studied 85 adolescents with obesity aged 12 to 19 with documented insulin resistance, of whom 60 received metformin at doses escalating to 850 mg twice daily by 2 months, whereas 25 got a placebo. Although for the entire group mean BMI did not decrease significantly, the authors of this study found that 23% of subjects on metformin versus 0% on the placebo had a BMI reduction of 5% or more. Moreover, the subjects who lost weight were much more likely to have reported an excellent adherence with metformin as well as a decrease in portion size compared with those who did not reduce their BMI. The current study reported an overall adherence rate of 89%, much higher than the 60% rate in patients taking metformin in the Colorado study. Although dietary information was collected, the authors of the current study only reported on the healthy lifestyle-diet index, which they stated was in the moderate category in both groups, and apparently did not specifically question subjects about portion size. This is important because, in addition to the diarrhea and cramping often seen in patients taking metformin (mostly during the first 2 weeks), decreased appetite with an increased feeling of fullness is one of the medication’s other effects. Studies have documented this effect in both adults and in children, with the adult study demonstrating the effect to be dose-dependent. Although the exact mechanism is not understood, a study in rats suggests a direct inhibition on neuropeptide Y expression in the brain. There is no evidence found in any of the metformin trials that weight loss is dependent on improvement in insulin resistance or in other metabolic markers, which have been variable.

A common feature of the metformin obesity studies is that nearly all concluded at or before 6 months after commencement, leaving one to wonder if longer treatment would result in further BMI reduction. Although data on this point are limited, the National Institutes of Health study by Yanovski et al(6) of 6- to 12-year-old children with obesity did offer open-label metformin at doses of 1000 mg twice daily for an additional 6 months and found no further reduction in BMI. If one considers the public health implications of treating large numbers of children with obesity for extended periods of time, one might conclude that if all or most of the weight benefit is seen in the first 6 months, compliance with long-term therapy would be poor outside of a clinical trial.

The just-published Endocrine Society clinical practice guideline on pediatric obesity(6) discourages the use of any obesity medication unless the patient has failed a formal program of intensive lifestyle modification. It specifically states that “given its limited weight-loss efficacy, metformin is not considered a weight-loss treatment.” However, metformin does have the advantage of being inexpensive with a low incidence of serious side effects. It has been shown in adults to reduce the progression from elevated fasting glucose and glucose intolerance to type 2 diabetes by 31% over a mean of 2.8 years versus a reduction by 58% with a lifestyle intervention. However, it has not been demonstrated to be effective for this purpose in youth, although no large-scale studies to test this possibility have been reported to date.

What should be the take-away message from the study of Pastor-Villaescusa et al(7) and other similar studies? Although metformin should not be considered standard of care for obesity, it may have a limited role in treating carefully selected patients with prediabetes and a strong family history of type 2 diabetes, or those who have made a major effort at improving their lifestyle and are frustrated by their inability to lose weight. In such situations, it is suggested that clinicians push the dose, if tolerated, to the maximum recommended dose of 1000 mg twice daily to take advantage of the important effect of decreased appetite, which likely is a major factor accounting for its variable and modest effect on BMI.

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