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Should metformin be prescribed to overweight adolescents in whom dietary/behavioural modifications have not helped?

Report by

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An obese, 12 year old girl comes for review in clinic. A year ago when you first saw her you gave comprehensive advice regarding dietary modification, and exercise. She has continued to gain weight with a BMI greater than the 99th centile. You arrange for an oral glucose tolerance test to be performed which shows her to be hyperinsulinaemic with fasting insulin of 20 mIU/L, and 120 min insulin of 200 mIU/L. She has normal fasting and 120 min blood glucose measurements. You wonder whether prescribing metformin may help her to lose weight.

Structured clinical question

In obese hyperinsulinaemic adolescents [patient] is metformin [intervention] effective in promoting weight loss [outcome]?

Search strategy and outcome

Secondary (Cochrane library, 2004) and primary (Medline, Embase) sources were included in the search.

Search strategy: “Obesity” AND “Adolescent” AND “Metformin”.

Search outcome: 276 hits (14; 61; 201; each search respectively), of which 2 (2; 2; 0) studies were directly relevant to this question.

See table 3.

Commentary

Child and adolescent obesity is a significant and growing health problem frequently encountered in general paediatric clinics, with recent data having shown that obesity in childhood and adolescence increases cardiovascular mortality in adulthood.¹

Clinical approaches to childhood obesity have concentrated on diet and exercise programmes, and the benefit of drug treatment for the severely obese remains largely untested. This is particularly an issue during adolescence, when puberty induces reduced insulin sensitivity,² the development of sexually dimorphic patterns in blood pressure³ and lipids,⁴ and increased deposition of visceral fat.⁵ Obesity in childhood has been shown to increase the risk of the insulin resistance syndrome (consisting of obesity, hypertension, dyslipidaemia, and atherosclerosis, leading to increased risk of cardiovascular disease in adult life), with one third of obese children and adolescents having been shown to have the insulin resistance syndrome.^{6–7}

Metformin, a biguanide, offers significant potential to intervene to reduce or reverse the metabolic and endocrine changes associated with obesity during puberty. Metformin acts by suppression of endogenous glucose production in the liver, but may also have an insulin sensitising effect in peripheral tissues through an effect on the key intracellular enzyme AMP kinase.⁸

Metformin has been shown to reduce weight as well as reducing hyperinsulinaemia and hyperglycaemia in type 2 diabetes in adults.⁹ Similar benefits on hyperinsulinaemia and BMI have been reported in non-diabetic obese adults,^{10–11} in addition to a reduction in progression from impaired glucose tolerance to frank diabetes.¹² In women with polycystic ovarian syndrome (PCOS), metformin has been shown to reduce hyperandrogenaemia and reduce total cholesterol as well as improving symptoms.¹³ There is also very early evidence that metformin may reduce the risk of cancer associated with obesity in adults with type 2 diabetes, possibly through activation of the tumour suppressor protein kinase LKB1.¹⁴

We looked at research in to whether pharmacological approaches may be most appropriate for very obese hyperinsulinaemic adolescents (approximately 2–3% of early adolescents of both sexes have BMI $\geq +3$ SD¹⁵).

We found two small short term randomised controlled trials that specifically answered our question. In the first, an eight week placebo controlled randomised trial in 24 obese hyperinsulinaemic non-diabetic 13–17 year adolescents, Kay

Table 3 Metformin in overweight adolescents

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Kay <i>et al</i> (2001) ¹⁶	24 hyperinsulinaemic non-diabetic obese 13–17 year adolescents Randomised to metformin or placebo	8 week randomised placebo controlled trial (level 1b)	Weight reduction (measured in kg)	Metformin group had a greater weight loss (kg) (6.5% [plus/mn] 0.8% v 3.8 [plus/mn] 0.4% p=0.01, greater decrease in body fat (p=0.01)	Metformin (850 mg BD for 8 weeks) Small study Subjects only followed up for brief time—8 wk
Freemark <i>et al</i> (2001) ¹⁷	29 obese hyperinsulinaemic non-diabetic 12–19 year olds with a BMI >30 kg/m ² Randomised to metformin or placebo	6 mth randomised placebo controlled trial (level 1b)	Reduction in BMI	Metformin caused a decline of 0.12 standard deviations (BMI) in study participants (–1.3%) compared with a rise of 0.23 SD in placebo controls	Metformin 1 g/day for 6 mth Small study

*et al*¹⁶ reported that subjects receiving high dose metformin 850 mg twice daily) had an additional 2.7% reduction in weight compared with those receiving placebo. In the second, Freemark and Bursey reported in a study of 29 obese hyperinsulinaemic non-diabetic 12–19 year olds that metformin (1 g per day) taken for six months resulted in a decline in BMI of 0.12 SD compared with a rise of 0.23 SD in placebo controls.¹⁷ No significant harmful side effects were reported in any of these patient groups.

Despite their small size, which should caution about the generalisation of their findings, both these studies showed that metformin use results in small improvements in BMI in obese hyperinsulinaemic non-diabetic adolescents.

However, the most significant benefits of metformin use in obese hyperinsulinaemic pubertal adolescents are likely to be changes in body composition and cardiovascular risk profiles—which have not yet been adequately assessed. There is early evidence that metformin may produce changes in body composition that are greater in effect size and more significant than the relatively modest changes in BMI noted previously.

CLINICAL BOTTOM LINE

- Metformin has shown small improvements in weight reduction in obese, hyperinsulinaemic, non-diabetic, adolescents. (Grade B)¹⁸
- The benefits and risks of metformin treatment in the severely obese remains largely untested, with long term efficacy and safety in children remaining unknown. (Grade D)

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