Metformin as adjuvant therapy in type 1 diabetes

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How I wish I had bought shares in the manufacturers of metformin. If ever a drug has had a renaissance it has to be metformin. For several decades, it was beloved of UK diabetologists (though often only for add-on therapy to sulphonylureas) but scorned by the USA, who were worried about inducing a repetition of deaths from lactic acidosis, as had been seen with its sister biguanide, phenformin. Now the list of indications for metformin keeps growing: first-line therapy in type 2 diabetes, combination therapy with insulin when these patients progress to secondary failure, prevention of diabetes in people with impaired glucose tolerance, ovulation induction in women with polycystic ovarian syndrome, and now an adjuvant therapy in type 1 diabetes.

Two papers have looked at this combination – with adolescents on multiple injection therapy and adults on continuous subcutaneous insulin infusion (CSII) treatment. The adolescents were pubertal with an HbA_{1c} between 8% and 11% despite being on insulin at a dose of >1 u/kg. The adults had all been on CSII for over a year and had better control than the adolescents (HbA_{1c} 7.4% at the start of trial).

In both studies the insulin requirements were reduced, and in the adolescent group HbA_{1c} fell slightly and weight decreased (compared with a small increase in the placebo group). The usual gastrointestinal side-effects were experienced by a few patients, but generally the metformin was well tolerated.

Obviously, these findings will need to be confirmed by others, but certainly in insulin-resistant individuals, such as pubertal adolescents and overweight type 1 patients (apparently 30% of newly diagnosed children with type 1 diabetes in the USA are overweight), this would be a logical adjuvant therapy. Safety is not likely to be an issue as significant nephropathy is uncommon at this age. Whether adding tablets to an already arduous regimen would be acceptable to patients (especially teenagers) remains to be seen, but pubertal weight gain, particularly among girls, is greater in teenagers with type 1 diabetes than in teenagers the same age without diabetes, and anything that might lessen that and improve control at the same time may well be attractive.

DIABETES CARE

Metformin is safe for use with insulin infusions

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 This study assessed the insulin-sparing effect of oral metformin in combination with continuous subcutaneous insulin infusion (CSII) in the treatment of patients with type 1 diabetes.

2 A randomised, double-blind placebo-controlled study was undertaken in 62 patients who were given either metformin or placebo in association with CSII for 6 months.

3 Metformin led to a reduction in daily insulin requirements (–4.3 ± 9.9 units), compared with an increase in the placebo group (1.7 ± 8.3 units); and to a reduction in basal insulin requirements (–2.6 ± 3.2 units), compared with an increase in the placebo group (1.9 ± 5.7 units).

4 HbA_{1c} was unchanged and the number of hypoglycaemic events was similar in the two groups .

5 Significant reductions were seen in total and LDL cholesterol in the metformin group.

6 This study found metformin to be a safe insulin-sparing agent in combination with CSII.

Meyer L, Bohme P, Delbachian I et al (2002) The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. *Diabetes Care* **25**: 2153–8

DIABETES CARE

Adjuvant metformin reduces HbA_{1c} and insulin dosage

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 Teenagers with diabetes have higher HbA_{1c}, lower insulin sensitivity and increased weight gain compared with adults with diabetes.

2 To determine the effects of metformin on insulin sensitivity, HbA_{1c}, fasting glucose, insulin dosage and BMI in adolescents with type 1 diabetes, a randomised, placebo-controlled 3-month trial of metformin therapy was undertaken in 27 adolescents with type 1 diabetes who were on high insulin dosage and had an HbA_{1c} > 8%.

3 At trial onset, HbA_{1c} was 9.2 ± 0.9%, insulin dosage was 1.2 ± 0.2 units/kg/day, fasting glucose was 10.6 ± 2.4 mmol/l and BMI was 24.2 ± 3.9 kg/m^2, with no difference between the metformin and placebo groups.

4 At the end of treatment, HbA_{1c} was 0.6% lower for the metformin group than for the placebo group ($P < 0.05$).

5 The metformin group needed lower daily insulin dosages (–0.14 ± 0.1 vs placebo 0.02 ± 0.2 units/kg/day). This did not cause a significant change in BMI. Fasting glucose levels also improved significantly with metformin. There was no difference in insulin sensitivity between the groups.

6 In this study, metformin reduced both HbA_{1c} and insulin dosage without causing a subsequent weight gain in teenagers with type 1 diabetes. No changes in insulin sensitivity were recorded.

Hamilton J, Cummings E, Zdravkovic V et al (2003) Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance. *Diabetes Care* **26**: 138–43