Metformin in type 1 diabetes

Paul Connelly¹
BSc (Hons), MB ChB, Core Medical Trainee

Gerry McKay¹
BSc (Hons), FRCP, Consultant Physician

John R Petrie¹,²
BSc (Hons), PhD, FRCP, Professor of Diabetic Medicine

¹Glasgow Royal Infirmary, Glasgow, UK
²University of Glasgow, UK

Correspondence to:
Dr P Connelly, Glasgow Royal Infirmary,
84 Castle Street, Glasgow, G4 0SF, UK;
email: paul.connelly@nhs.net

Introduction
Type 1 diabetes is a disorder of immune tolerance affecting insulin-producing beta cells in the islets of Langerhans. Intensive insulin therapy is the foundation of clinical care in accordance with evidence of reduced long-term complications from the Diabetes Control and Complications Trial (DCCT).¹

However, this approach is associated with the increased frequency and severity of hypoglycaemia as well as weight gain. Moreover, despite advances in glucose monitoring and insulin delivery, population-based data indicate that HbA1c remains poorly controlled in many individuals with reduced life expectancy of 11 years in men and 13 years in women.²,³ Adjunct therapy with insulin-sparing pharmacological agents has been proposed as a means of improving metabolic control while minimising insulin’s unwanted effects.

Metformin is a drug with potential in this context. It is widely considered to be the first-line oral glucose-lowering agent for the treatment of type 2 diabetes following evidence of cardiovascular benefit in a sub-study of the UK Prospective Diabetes Study (UKPDS). Moreover, addition of metformin to insulin in individuals with type 2 diabetes in the HOME trial (Hyperinsulinemia: the Outcome of its Metabolic Effects) attenuated weight gain, reduced insulin dose requirements, improved glycaemic control, and reduced rates of macrovascular disease (a secondary endpoint).

Pharmacology
The primary effect of metformin in type 2 diabetes is the inhibition of hepatic gluconeogenesis. There is some evidence that it may also improve peripheral glucose utilisation, reduce intestinal glucose absorption, and lower LDL and VLDL cholesterol.

Suppression of gluconeogenic gene expression via the activation of the cellular sensor and regulator of energy homoeostasis, AMP-activated protein kinase (AMPK), is widely regarded as an important mechanism, although recent data suggest this may be secondary to non-competitive inhibition of the mitochondrial redox shuttle enzyme glycerophosphate dehydrogenase (mGPD; Figure 1).⁴ Reduced cytoplasmic dihydroxyacetone phosphate (DHAP) increases the NADH:NAD⁺ ratio in hepatocytes as illustrated in Figure 1. This inhibits hepatic gluconeogenesis and improves glucose utilisation via activation of AMPK and a decrease in NADH:NAD⁺ ratio in hepatocytes. Metformin inhibits hepatic gluconeogenesis through the inhibition of mGPD by preventing the utilisation of gluconeogenic precursors.

Figure 1. Metformin inhibits hepatic gluconeogenesis through the inhibition of mGPD by preventing the utilisation of gluconeogenic precursors.
The benefits of intensive insulin therapy are well-recognized, but the addition of metformin has been suggested to further improve outcomes. A meta-analysis of 197 studies, including randomised trials covering a total of 192.8 patient years of follow up, found only nine relevant randomised trials. There was a significant reduction of 6.6 units/day of insulin in those randomised to metformin adjunct therapy, with an accompanying non-significant absolute reduction in HbA1c of 0.11%. These results likely represent the downward titration of insulin dose aimed at avoiding hypoglycaemia as adjunct therapy is introduced.

Active therapy with metformin was also associated with weight reduction of 1.7–6.0kg in three of six studies and reduction in total cholesterol by 0.31–0.41mmol/L in three of seven studies. These effects could potentially be of benefit for people with type 1 diabetes.

Research into the impact of metformin upon cardiovascular risk in type 1 diabetes has to date been limited despite apparent benefits in type 2 diabetes. Recently, in a single centre, randomised double-blind control trial, addition of metformin over six months in patients with type 1 diabetes resulted in significant improvements in flow-mediated vasodilation, a physiological measure of endothelial dysfunction, which were independent of weight reductions (-2.27kg vs placebo; 95% CI -3.9; -0.5). It has been suggested on the basis of this and earlier studies that metformin may have direct and potentially beneficial effects on the cardiovascular system.

Currently, the international double-blind randomised control trial, REDucing with MetfOrmin Vascular Adverse Lesions in type 1 diabetes (REMOVAL; NCT01483560), is in progress. This study aims to assess whether three years of metformin therapy reduces progression of atherosclerosis in adults aged 40 years and over with at least three cardiovascular risks factors. Additionally, cardiovascular function and insulin sensitivity are being assessed over shorter time periods within the Effects of Metformin on Cardiovascular Function in Adolescents with Type 1 Diabetes study (EMERALD; NCT01808690) and the Metformin on Vascular and Mitochondrial Function in Type 1 Diabetes (MeT1; NCT01813929) study.

Evidence of safety and tolerability
The most frequently associated adverse effects of metformin are gastrointestinal symptoms that occur in up to 30% of recipients; these subside over time in the majority of users, particularly with slow up-titration.

More seriously, metformin has been associated with rare, but potentially fatal, lactic acidosis. In a Cochrane review, comprising data from 347 trials and including 70 490 patient years of follow up, the upper 95% confidence interval limit for the incidence of lactic acidosis was 4.3 cases per 100 000 patient years which did not differ from the background risk in diabetes. Nevertheless, NICE guidance suggests reviewing the dose of metformin in patients with serum creatinine >130μmol/L or eGFR <45ml/minute/1.73m² and discontinuing this drug in patients with serum creatinine >150μmol/L or eGFR <30ml/minute/1.73m² to ameliorate this potential risk.

In the meta-analysis by Vella et al., increased rates of hypoglycaemia were observed with metformin. Although this was only significant in two trials, better baseline glucose control may increase the risk of insulin-induced hypoglycaemia. Careful advice regarding blood glucose monitoring and insulin dose adjustment should be given if initiating metformin therapy in type 1 diabetes.

Discussion
Metformin is a safe, inexpensive and a largely well-tolerated medication. It reduces insulin dose requirement and may promote weight reduction. Its addition to insulin therapy therefore has the potential to offset some of the disadvantages of intensive insulin therapy.

Recent draft NICE guidance recommends the addition of metformin to insulin therapy in adults with type 1 diabetes and BMI >25kg/m² who wish to improve glucose control while minimising their insulin dose. However, pending the results of on-going clinical trials, we do not consider that there are any absolute indications for metformin prescription in type 1 diabetes. We speculate that the benefits of metformin may outweigh its risks in some individuals with the increasingly recognised phenomenon of ‘double diabetes’, characterised by significant weight gain, high insulin requirements and a family history of type 2 diabetes. Longer-term studies are required to test the hypothesis that metformin might have cardiovascular benefits in type 1 diabetes.

Declaration of interests
JRP is Chief Investigator of the REMOVAL (NCT01483560) clinical trial of metformin in type 1 diabetes which is funded by the Juvenile Diabetes Research Foundation. The trial receives support in kind (donation of active and placebo study medication) from Merck-Germany.

GMcK is Principal Investigator for the Glasgow REMOVAL study site.

References
References are available in Practical Diabetes online at www.practicaldiabetes.com.
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