Metformin: new insights into an archetypal cardiometabolic drug

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Although metformin has been in clinical use as a diabetes medication for six decades, its mechanism of action remains uncertain [1]. Hepatic gluconeogenesis is reduced by metformin without increasing insulin secretion, inducing weight gain, or risking hypoglycemia. Widely regarded as an insulin sensitizer, the main glucose-lowering effect of metformin is to reduce inappropriate rates of hepatic glucose production [2]; effects on whole-body insulin sensitivity appear to be secondary to lowered blood glucose concentrations [3]. Suggestions that metformin reduces glucose production by the activation of enzyme AMP-activated protein kinase were subsequently challenged by genetic loss-of-function studies [4]. While rodent and tissue culture studies reported that metformin inhibited the stimulatory effect of glucagon on hepatic glucose production [5] clinical studies suggest a more complex picture [6]. Results of in-vitro and in-vivo studies from Gerald Shulman's Yale group propose that metformin noncompetitively inhibits the redox shuttle enzyme mitochondrial glycerophosphate dehydrogenase [7]. In turn, this results in an altered hepatocellular redox state, reduced conversion of lactate and glycerol to glucose, and hence decreased hepatic gluconeogenesis. Clinical studies with delayed-release metformin, formulated to deliver the drug to the lower bowel, have implicated gut hormones (glucagon-like peptide-1, peptide YY) in the glucose-lowering effect of metformin [8,9].

Beyond glucose-lowering, metformin is credited with cardioprotective effects [10,11]. However, the evidence base for metformin in preventing or delaying cardiovascular events has been questioned since the publication of the UK Prospective Diabetes Study (UKPDS)-34 in 1998 [12]. In a subgroup of 1704 overweight or obese patients, metformin was associated with a 39% risk reduction in myocardial infarction ($P=0.01$) and a 50% risk reduction in coronary deaths ($P=0.02$) compared with conventional (diet) therapy [12]. Detracting somewhat from these impressive – and unanticipated – benefits, an even smaller randomized substudy ($n=537$) suggested that early addition of metformin in patients on maximum dose sulfonylureas was associated with an increased risk of diabetes-related death ($P=0.039$) compared with continued sulfonylurea therapy alone. It was evident from UKPDS that the cardiovascular benefits of metformin, which were not observed with sulphonylurea-based or insulin-based

therapy, were not attributable to glucose-lowering *per se*. Favorable effects of metformin on other biomarkers for vascular disease include endothelial function, nonenzymatic glycation, proinflammatory cytokines, platelet function, and haemostasis [13,14]. Evidence for cardiovascular protection continues to accrue from animal models [15].

Until recent positive data from cardiovascular outcome trials of empagliflozin [16], liraglutide [17], semaglutide [18], and canagliflozin [19], metformin was one of only two glucose-lowering drugs (the other being pioglitazone) [20] regarded as having an evidence base – albeit with some caveats – for cardiovascular disease prevention in patients with type 2 diabetes.

Two new reports add interesting insights to metformin's role as a cardioprotective drug. The first study, from researchers at the University of Gothenburg, suggest that part of metformin's effect on blood glucose may be achieved through modulation of the gut microbiota. The totality of microbial genomes in the human gut vastly exceeds and complements the human genome [21]. Attention has been directed to the therapeutic potential of modulating the microbiome [21]. Wu *et al.* [22] sequenced the microbiome of patients with type 2 diabetes ($n=22$) before and after treatment with metformin. Compared with placebo, the gut microbiome was altered within 2 months of metformin treatment. Furthermore, metformin increased the growth of several bacterial species linked to improvements in metabolism. Transplantation of gut microbiota from metformin-treated patients to bacteria-free mice showed that the metformin-modified microbiota might – at least in part – explain the effects of metformin on blood glucose. Gastrointestinal side-effects such as diarrhoea and abdominal discomfort are the main limiting factors to metformin in clinical practice. Whether alterations of the microbiome are related to either achieving a therapeutic response to metformin or the development of gastrointestinal side-effects remain uncertain.

The second study focused on the effects of long-term metformin therapy on coronary calcium in patients with prediabetes, that is elevated fasting and postload glucose concentrations. Among more than 2000 patients who underwent serial coronary artery calcium (CAC) measurements in the Diabetes Prevention Program and the Diabetes

Prevention Program Outcomes Study, the prevalence and severity of CAC after 14 years of metformin therapy were significantly lower in men (mean age: 67 years) [23]. Compared with placebo, CAC severity was significantly lower in men receiving metformin [age-adjusted: 39.5 vs. 66.9 Agatston units (AU); $P=0.04$]. The effect was most evident in the 25–44 years age group, at 3.0 versus 17.6 AU ($P<0.05$) [23]. In multivariate analysis, the effect of metformin was unaffected by several demographic, anthropometric, and metabolic factors, by the development of diabetes, or by concomitant use of statin therapy. In contrast, however, the protective effect of metformin on CAC was not observed in women (mean age: 63 years). The authors speculate that lower levels of coronary calcification made any benefit of metformin more difficult to observe. Metformin appeared to be affecting the smallest coronary lesions suggesting that a relatively early stage of atherosclerosis was being affected. The suggestion that long-term metformin may have cardioprotective properties in prediabetic patients requires confirmation in additional studies.

We also have the results of the recently reported REMOVAL (Reducing with Metformin Vascular Adverse Lesions) trial conducted in patients with type 1 diabetes. Current guidelines from the National Institute for health and Care Excellence (NICE) incorporate an adjunctive role of metformin in selected overweight or obese patients with type 1 diabetes (<https://www.nice.org.uk/guidance/ng17/chapter/1-Recommendations#blood-glucose-management-2>). Metformin reduces insulin-dose requirement in patients with type 1 diabetes, but it has been unclear whether this is sustained beyond 1 year or any metformin is associated with cardiovascular benefits in this context [24]. In brief, REMOVAL was a 3-year multicentre double-blind, randomized placebo-controlled trial carried out in a total of 428 adults aged 40 years or older with type 1 diabetes and increased cardiovascular risk. The latter was defined as at least three of the 10 specified risk factors, including BMI of at least 27 kg/m², hemoglobin (Hb)A_{1c} more than 8.0%, strong family history of cardiovascular disease, and current smoking. Mean age was 55.5 years, diabetes duration 33.8 years, HbA_{1c} 8.05%, and BMI 28.5 kg/m². Around one-third of the patients were using insulin pumps and 73 and 82% were receiving anti-hypertensive medications and statins, respectively. After a 3-month optimization period, participants were randomized to metformin 1000 mg twice daily or placebo in addition to insulin [25]. Although the primary end point – reduction in mean far-wall carotid artery intima-medial thickness at 3 years – was not met, maximal carotid artery intima-medial thickness (a prespecified tertiary outcome) was significantly reduced (–0.013 mm/year, range: –0.024 to –0.003 mm/year; $P=0.0093$) [26]. At 3 years, metformin significantly reduced HbA_{1c} (–0.13%, $P=0.006$), this effect being evident only within the first 3 months of the study. Metformin also significantly reduced body weight (–1.17 kg, $P<0.0001$) and low-density lipoprotein cholesterol (–0.13 mmol/l, $P=0.0117$) but there

was no reduction in average insulin-dose requirement over 3 years (–0.005 U/kg, $P=0.545$). Discontinuations were twice as common overall among the metformin patients compared with placebo (27 vs. 12%) as were discontinuations due to well-recognized gastrointestinal adverse effects (16 vs. 3%). There were no differences between the groups in major or minor hypoglycemia. Biochemical vitamin-B12 deficiency was more common with metformin (12 vs. 5%). Renal function improved with an increase in mean estimated glomerular filtration rate of 4.0 ml/min/1.73 m² (range: 2.19–5.82 ml/min/1.73 m², $P<0.0001$). There was no effect of metformin on endothelial function or on retinopathy. No cases of lactic acidosis were observed [26]. The results of REMOVE suggest that metformin might provide additional benefit for patients with type 1 diabetes.

Collectively, these new studies expand knowledge of the mechanisms of action and the benefit-to-risk considerations of metformin as a cardioprotective medication beyond the classic target population of patients with type 2 diabetes.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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