PROJECT GRANT RECIPIENT AND FINAL REPORT

Funded by:	Australian Rheumatology Association ($20,000)
Recipient:	Dr Timothy Davis
Intended Department:	University of Western Australia, School of Medicine
Project:	The effect of sodium-glucose transport protein 2 inhibitor and fibrate therapies, alone and in combination, on the serum uric acid concentration in hyperuricaemic people with type 2 diabetes

We are very grateful for the grant funding received from Arthritis Australia in support of our project "The effect of sodium-glucose transport protein 2 inhibitor and fibrate therapies,alone and in combination, on the serum uric acid concentration in hyperuricaemic people with type 2 diabetes".

What were the main scientific objectives of the grant?

Key Research Question: What are the serum urate lowering effects of empagliflozin, fenofibrate and the combination of these two treatments in people with type 2 diabetes and a raised serum urate concentration?

Aim: To examine serum urate responses in hyperuricaemic people with type 2 diabetes treated with a sodium- glucose co-transporter-2 inhibitor (SGLT2i) and/or fibrate.

Hypotheses to be tested: Empagliflozin, fenofibrate and combination therapy will reduce the serum urate by ≥0.04 mmol/L, ≥0.06 mmol/L and ≥0.10 mmol/L, respectively.

What were the main scientific achievements of the grant?

In a sample of eight people with type 2 diabetes who participated in a crossover study, empagliflozin (a medication for type 2 diabetes which also promotes uric acid excretion) and fenofibrate (a lipid modifying drug which also lowers serum urate) monotherapies reduced fasting serum urate concentrations to levels at least as much as hypothesized based on previous studies, but their effects appeared additive when given in combination. This was a novel finding. The mean reduction in serum urate (0.14 mmol/L) with recommended maximum daily doses of combination therapy (empagliflozin 25 mg plus fenofibrate 145 mg) was associated with three quarters of the participants achieving a serum urate <0.36 mmol/L after all had started the study above this level.

There was, however, evidence that the combination was synergistic in its effect on kidney function. Although neither drug is nephrotoxic and neither had a statistically significant effect on the estimated glomerular filtration rate (eGFR) when given alone in our study, the significant mean eGFR reduction of 10.2 mL/min/1.73m^2 with combination therapy may have clinical implications. These would include the need for close monitoring of renal function if the combination were used for their usual indications with or without the additional potential benefits of urate lowering, and consideration of dose modification of other therapies used in people with diabetes that are affected by changes in renal function such as the widely used drug metformin.

What problems, if any, did you encounter in achieving the project's objectives, and how did you address them?

Recruitment for the study proved difficult since many people with type 2 diabetes are now receiving treatment with an SGT2i such as empagliflozin, while other exclusion criteria (such as renal impairment) are also relatively common. In addition, the duration of the study and the need for regular blood sampling over 6 weeks were factors that influenced participation. Have you disseminated, or plan to disseminate, the results of this research? Please tell us about it:

The study report has been accepted for publication in the well regarded diabetes-related journal *Diabetes Obesity and Metabolism* (a copy of accepted version is attached). The corrected proofs of the article were returned to the journal recently which means it will appear in press shortly.