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SGLT2 inhibition does not reduce hepatic steatosis in overweight, insulin resistant patients without type 2 diabetes

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Background and aims: Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the leading indication for liver transplant and is associated with increased cardiovascular and liver mortality, yet there are no licensed therapies. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are now widely used for their glucose lowering effects in patients with type 2 diabetes (T2D). Pre-clinical models have suggested a beneficial impact on NAFLD, but clinical data are limited and there are currently no data in patients without type 2 diabetes. We aimed to investigate the impact of SGLT2 inhibition on NAFLD in overweight, non-diabetic patients and establish the effect these agents may have on the processes that regulate hepatic steatosis *in vivo*.

Methods: We conducted an open-label, experimental medicine pilot study in insulin resistant overweight/obese individuals (n = 10), using gold-standard non-invasive assessments of NAFLD phenotype including hepatic magnetic resonance spectroscopy, 2-step hyperinsulinaemic euglycaemic clamps and stable isotope tracers to assess lipid and glucose metabolism. Investigations were performed before and after 12-weeks of treatment with the SGLT2 inhibitor, Dapagliflozin.

Results: Despite a body weight reduction of 4.4kg, hepatic steatosis was unchanged following treatment. Hepatic glucose production rates increased and there was impairment of glucose disposal during the low-dose insulin infusion. Although circulating non-esterified fatty acid levels did not change, the ability of insulin to suppress lipolysis was reduced.

Conclusions: SGLT2 inhibition for 12 weeks does not improve hepatic steatosis in patients without T2D. Additional studies in patients with established T2D or impairments of fasting or post-prandial glucose homeostasis and needed to determine whether SGLT2 inhibition represents a viable therapeutic strategy for NAFLD.