Type 2 diabetes: Drugs initially increase glucose production

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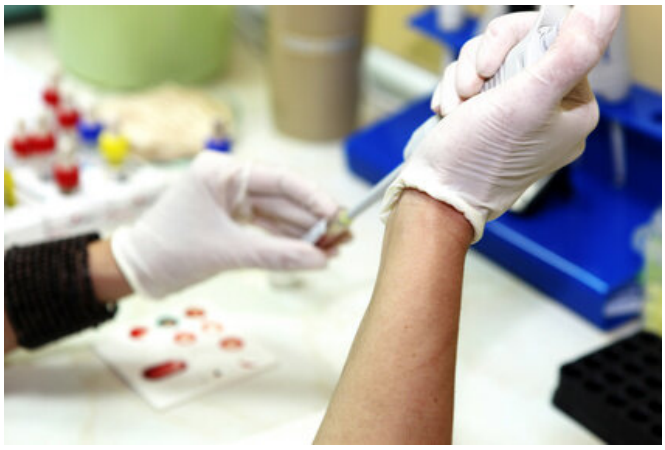

MedUni Vienna study explains the mode of action of the successful SGLT2 inhibitors. Credit: Medical University of Vienna

Although SGLT-2 inhibitors are central to the treatment of diabetes, their exact mode of action was hitherto unknown. In a study conducted by a research group led by Peter Wolf, Martin Krssak and Michael Krebs from MedUni Vienna's Department of Medicine III, magnetic resonance spectroscopy (MRS) was used to show that there is a direct correlation between the elimination of glucose via the kidneys and new glucose production in the liver. A single dose of the SGLT-2 inhibitor dapagliflozin gives rise to a beneficial regulation mechanism, in which glucose loss due to drug-induced SGLT-2 inhibition is exactly balanced out by an equal increase in new glucose production in the liver. The study has been published in the leading journal *Diabetes Care*.

Dapagliflozin is a drug from the group of SGLT-2 inhibitors, which are standardly used in the treatment of diabetes. They increase the amount of glucose that is excreted in the urine. This reduces blood glucose levels and patients also lose weight. A beneficial impact on fatty liver, which is prevalent among diabetics, has also been described after a twelve-week course of the drug. Remarkably, this group of drugs also seems to have a protective effect on the heart and kidneys. However, the acute impact upon lipid and energy metabolism had not yet been studied in any detail.

A research group led by Peter Wolf, Martin Krssak and Michael Krebs from the Division of Endocrinology and Metabolism at the Department of Medicine III has now conducted a study using MRS, in which they observed six diabetic patients and a control group of ten healthy volunteers after they had taken dapagliflozin. It was found that, in the short term, the amount of additional glucose produced in the liver exactly matched the amount lost in the urine due to the action of the drug. This suggests that the increased elimination of glucose via the kidneys immediately triggers a series of regulation mechanisms that affect the metabolism in several organs and could therefore play a role in the beneficial effect of this drug.

The study was produced in collaboration with the Center of Excellence for High-Field MRI of MedUni Vienna's Department of Biomedical Imaging and Image-guided Therapy. Using high-resolution magnetic resonance imaging, it was possible to quantify serial measurements of glucose and fat storage in the liver in a non-invasive way. In combination with the infusion of tracers (such as a marked glucose solution, for example) it is possible to use this 'virtual biopsy' to identify a change in the glucose and lipid metabolism in vivo and to study the acute, short-term impact of drugs.

More information: Peter Wolf et al. Gluconeogenesis, But Not Glycogenolysis, Contributes to the Increase in Endogenous Glucose Production by SGLT-2 Inhibition, *Diabetes Care* (2020). DOI: 10.2337/dc20-1983