Empaglifozin induces changes in the liver metabolome of diabetic rats

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Background: Empagliflozin is a potent, highly selective sodium glucose cotransporter-2 (SGLT2) inhibitor used as an effective and well-tolerated antihyperglycaemic agent. Beyond lowering glucose, empagliflozin exerts a favorable effect on a number of nonglycaemic outcomes, including modest reductions in bodyweight and blood pressure, and it has cardioprotective and renoprotective properties in patients with T2D and established cardiovascular disease (EMPA-REG OUTCOME).

Purpose: Since liver fat content represents a risk factor for cardiovascular diseases, and empagliflozin has been recently suggested to be able to contribute to the early treatment of nonalcoholic fatty liver disease in T2D, we aimed to study the effect of the empagliflozin treatment in the liver metabolome of type 2 diabetic rats.

Methods: Male ZDF-Leprfa/fa rats were treated with 30 mg/kg/d of empagliflozin p.o for six weeks. Metabolic profiling of the hepatic tissue was analyzed using UHPLC-MS based platforms. We performed a hematoxylin/eosin staining to determine the tissue integrity and liver fat accumulation, and a Masson's trichrome staining to analyze liver fibrosis. All animals were maintained and euthanized following protocols approved by the Animal Care Committee of the University of Santiago de Compostela in accordance with European Union Directive 2010/63.

Results: Empaglifozin treatment reduced blood glucose levels to normal (128.2±6.51 mg/dL), while untreated control rats showed high glucose levels (404.3±17.49 mg/dL). Hepatic histological analysis did not show differences regarding neither fat accumulation nor fibrosis between empagliflozin treated and control rats. Circulating levels of cholesterol, HDL, LDL, GTP, GGT triglycerides remained unaltered after empaglifozin treatment vs. control. 384 metabolites were analyzed in the liver tissue samples, observing significantly increased levels of 10 types of glycerolipids, 24 phosphatidylcholines, 8 amino acids, 1 polyunsaturated fatty acid, 4 lysophosphatidylethanolamines, 7 lysophosphatidylinositols, 1 carboxylic acid and 1 nucleoside in the empagliflozin treated rats with respect to the control group. In addition, treatment with empagliflozin produced a significant decrease of 1 glycerolipid, 1 phosphatidylcholine, 1 bile acid, 1 nucleoside and the NAD oxidoreduction coenzyme.

Conclusions: We demonstrated that empagliflozin significantly modify the liver content of the different lipid species, with the most relevant altered metabolic classes belonging to glycerophospholipids, especially monoacyl-species, and aromatic amino acids. Considering the suggested potential beneficial effect of the treatment with empagliflozin in the prevention of liver fibrosis, our metabolomics data can help to evaluate the impact and the mechanism of action of SGLT2 inhibitors at hepatic level.