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Effects of Sodium Glucose Cotransporters (SGLT2) Inhibitorstype 2 on Hepatosis in Patients Type 2 Diabetes Mellitus

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Abstract

Diabetes mellitus is a major public health disorder that affects more than 400 million subjects, with a prevalence ranging from 7.2 to 11.4% in the general population,worldwide [1, 2]. Diabetes is associated with various metabolic disorders and vascular damage of great extent [3] and thus, the management of the diabetic patient should aim in the attenuation of hyperglycemia and other concomitant cardiovascular conditions [4-7]. Current antidiabetic treatment options were unable to offer consistent cardiovascular benefits. Apart from metformin and glucagon-like peptide 1 analogues, the rest of the available hypoglycemic agents have not provided consistent benefits from the cardiovascular standpoint. Furthermore, the impact of these drugs on other cardiovascular risk factors is either neutral or beneficial, and in some cases even harmful [8-15].Sodium-glucose co-transporters (SGLT) 2 inhibitors area novel antidiabetic class of drugs that offer a different approach for the amelioration of hyperglycemia than the other antidiabetic drug classes. SGLT-2 inhibitors block the reabsorption of glucose in the renal proximal tubule,resulting in decreased glucose reabsorption, increased urine excretion of glucose and attenuation of glycemic parameters [6, 7]. Through their unique mechanism of action, SGLT-2 inhibitors seem to offer several beneficial effects on a cluster of other cardiovascular risk factors. These drugs are associated with a mild increase in sodium urine excretion; this combined with the osmotic effect of the excreted glucose, results in a mild diuretic effect that leads to hemodynamic improvements. A mild decrease in blood pressure accompanied with a mild reduction in body weight is noted with SGLT-2 inhibition. In addition, beneficial effects with these drugs are observed in serum acid levels, triglycerides and high-density lipoprotein cholesterol levels. Ameliorating effects are also noted in other established cardiovascular risk factors such as diabetic nephropathy, non-alcoholic fatty liver disease and arterial stiffness [8, 9].

Key words: antidiabetic drug, clinical trial, liver, SGLT2 inhibitor.

The pleiotropic effect of SGLT-2 inhibitors on the aforementioned abundance of cardiovascular risk factors has raised several expectations for their cardiovascular profile. As of this issue, two cardiovascular studies on these novel drugs exist and have provided encouraging results. Empagliflozin in the EMPA-REG study and (to a lesser extent) canaglifllozin in CANVAS study have shown remarkable benefits in cardiovascular morbidity and mortality [10, 11]. Furthermore, SGLT-2 inhibitors seem to attenuate heart failure and renal outcomes [2, 3]. In this special issue of Cardiovascular and Hematological Diseases-Drug Targets, we aim to present current data on the multidimensional profile of SGLT-2 inhibitors and discuss the benefits and potential contradictory findings with this class of drugs. Manolis *et al.* discuss in detail the mechanism of action of SGLT-2 inhibitors and comprehensively explain the SGLT-2 inhibitors-induced increased excretion of glucose, sodium, water and of other substances that might result in important outcome benefits. They further describe the effect of SGLT-2 inhibition on other organs and systems, as well [2]. The antidiabetic profile of the drugs is presented by Kihm *et al.* in the following review. The authors report the results from studies of several SGLT-2 inhibitors used as monotherapy or as add-on treatment to preexisting antidiabetic drugs. They noted a significant reduction in fasting plasma glucose and glycated hemoglobin of approximately 0.5 to 1% (in absolutes values). Importantly, it is stated that SGLT-2 inhibitors are not inferior to other hypoglycemic drugs in terms of glycemic control, with insignificant differences in glycated hemoglobin between SGLT-2 inhibitors-treated patients and other actively treated groups [5]. Subsequently, Tsioufis *et al.* in their review present the blood pressure-lowering effect of SGLT-2 inhibitors (mostly due to increased diuresis) from studies with office and ambulatory blood pressure measurements that range from 3 to 5 mmHg in systolic and 1 to 2 mmHg of diastolic blood pressure. Furthermore, it is stated that with their use, a mild body weight reduction of 2 to 3 kg is achieved, that is sustained with long-term treatment [6]. The significant cardiovascular and mortality risk reductions are reported by Lovic *et al.* who discussed the data obtained from the two aforementioned cardiovascular trials and from one large observational study indetail. Among the favorable data presented, the authors report the concerning higher amputation risk observed with canagliflozin use, as well [3]. Following this article, Doumas *et al.* and Papademetriou *et al.* comprehensively present data and potential underlying mechanisms of the attenuating impact of SGLT-2 inhibitors on renal and heart failure outcomes, respectively [10, 11]. In the article by Doumas *et al.* it is stated that SGLT-2 inhibitors are associated with a significant delay in the progression of diabetic kidney disease, with empagliflozin and canagliflozin achieving a remarkable deceleration of estimated glomerular filtration rate decline (0.9 ml/min/year) and amelioration of albuminuria status, respectively [8]. Papademetriou *et al.* present the benefits of SGLT-2 inhibition in heart failure outcomes and support that these findings could potentially be attributed to the ameliorating effect of SGLT-2 inhibitors on blood pressure, visceral obesity, arterial stiffness, diastolic dysfunction and importantly to the SGLT-2 inhibitorsinduced increase in ketones bioavailability [7]. Tziomalos *et al.* report in detail the impact of these drugs on stroke risk factors and the contradictory neutral impact of SGLT-2 inhibitors on stroke risk, implying that other factors may be in play that need to be unveiled [3]. Last, Karagiannis *et al.* discuss the concerns of a potential increase in the risk of euglycemic diabetic ketoacidosis with this novel class of drugs. The authors present randomized controlled trials, meta-analyses, case series and case reports and note that most ketoacidosis cases were observed in patients with type 1 diabetes, due to off-label use of SGLT-2 inhibitors, or in patients previously misdiagnosed as having type 2 diabetes, who in fact suffered from late autoimmune diabetes of adults.

The recent CANVAS study provided similar results with the EMPA-REG trial and suggests a class effect of SGLT-2 inhibitors on morbidity and mortality outcomes. These remarkable findings could establish this class of drugs as an optimal second-line treatment option after metformin monotherapy. The concerning findings in terms of stroke and amputations risk will place at the epicenter of the scientific interest, the identification of patients' groups that might be more prone to these events, such as patients with increased hematocrit levels or severe peripheral artery disease. Ongoing cardiovascular and renal trials will potentially provide further credence for this novel and very promising class of drugs. In this special issue of Cardiovascular and Hematological Diseases-Drug Targets, we aim to present current data

on the multidimensional profile of SGLT-2 inhibitors and discuss the benefits and potential contradictory findings with this class of drugs. Manolis *et al.* discuss in detail the mechanism of action of SGLT-2 inhibitors and comprehensively explain the SGLT-2 inhibitors-induced increased excretion of glucose, sodium, water and of other substances that might result in important outcome benefits. They further describe the effect of SGLT-2 inhibition on other organs and systems, as well [24]. The antidiabetic profile of the drugs is presented by Kihm *et al.* in the following review. The authors report the results from studies of several SGLT-2 inhibitors used as monotherapy or as add-on treatment topreexisting antidiabetic drugs. They noted a significant reduction in fasting plasma glucose and glycated hemoglobin of approximately 0.5 to 1% (in absolutes values). Importantly, it is stated that SGLT-2 inhibitors are not inferior to other hypoglycemic drugs in terms of glycemic control, with insignificant differences in glycated hemoglobin between SGLT-2 inhibitors-treated patients and other actively treated groups [5]. Subsequently, Tsioufis *et al.* in their review present the blood pressure-lowering effect of SGLT-2 inhibitors (mostly due to increased diuresis) from studies with office and ambulatory blood pressure measurements that range from 3 to 5 mmHg in systolic and 1 to 2 mmHg of diastolic blood pressure. Furthermore, it is stated that with their use, a mild body weight reduction of 2to 3 kg is achieved, that is sustained with long-term treatment [11].

1 Type 2 diabetes further accelerates NAFLD progression from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.2 Moreover, NAFLD associates with an increased risk of cardiovascular diseases, including cardiomyopathy and certain cardiac arrhythmias, thereby contributing to the excess morbidity and mortality in people with both type 2 diabetes and NAFLD.[2] Hepatic fibrosis is a strong predictor of NAFLD-related mortality2 and clinically relevant advanced fibrosis stages, F3 and F4, can be present in up to 20% of persons with NAFLD and type 2 diabetes.[1] While the 'gold-standard' diagnosis of fibrosis still requires liver biopsy,2 several imaging methods have been introduced including vibration controlled transient elastography or magnetic resonance elastography. These methods are mostly restricted to use in specialized centres[3] as they require specific technical equipment, qualified and trained personal,making them difficult to perform in large multinational clinical trials involving hundreds of study sites. Thus, non-invasive indices calculated from demographic, anthropometric and laboratory parameters provide an opportunity to estimate the prevalence and effects of interventions on liver fibrosis in large cohorts.[3] In addition, hepatic steatosis, the primary criterium of NAFLD diagnosis, may be estimated by non-invasive indices.[4,5] Sodium glucose co-transporter 2 inhibitors are associated with a modest weight loss and improved cardiovascular and renal outcomes.[6,7] Recent small-scale randomized controlled trials have shown that empagliflozin also improved hepatic steatosis and beneficial effects of empagliflozin on histological components including fibrosis were suggested from an uncontrolled pilot trial.[6] The underlying mechanisms remain largely unknown; however, apart from weight loss, they may even include improvement of adipose tissue function with amelioration of local inflammation and/or oxidative stress.11. The present study examined the effects of empagliflozin treatment in a large cohort of persons with type 2 diabetes with established cardiovascular disease (a) on indices of hepatic steatosis and fibrosis, (b) on glycaemia and body weight, as well as (c) on cardiorenal outcomes and all-cause mortality in groups at different steatosis and fibrosis risk.

Finally, this analysis addressed the question whether baseline steatosis and fibrosis risk scores are associated with the incidence of cardiorenal events in this patient population. To this end, an exploratory post-hoc analysis was performed in the EMPA-REG OUTCOME study, previously showing lower rates of cardiovascular events and deaths from any cause with empagliflozin at a median observation time of 3.1 years.[7] The design of EMPA-REG OUTCOME has been previously decribed.[7] Adult individuals with type 2 diabetes and established cardiovascular disease were included; elevated liver enzymes >3x upper limit of normal were exclusion criteria. The main objective of this post-hoc analysis was to compare the effects of empagliflozin and placebo on Dallas steatosis index (DSI)10 and hepatic steatosis index (HSI)11 as well as on NAFLD fibrosis score (NFS) and Fibrosis-4 score (FIB-4). All randomized participants, who received ≥1 dose of the study drug. The effects on risk scores as well as glycated haemoglobin (HbA1c) and weight were evaluated using a mixed-effect model repeated measurement

model, which included baseline HbA1c and baseline of score (or weight) as linear covariates and their interaction with visit in addition to baseline estimated glomerular filtration rate (Modification of Diet in Renal Disease Study) category, geographical region and baseline body mass index category. Treatment, subgroup (if applicable) and visit were also entered as fixed effects as well as all two- and three-way interactions thereof. In addition, the model included a fixed categorical effect for 'time of randomization' to account for each patient's theoretical ability to 'reach' certain weeks in this study arising from the study design. Because of small group sizes, participants at baseline intermediate and high risk (based on FIB-4) were pooled for analysis of time courses of parameters in FIB-4 low and high fibrosis risk categories and HSI low and intermediate risk categories were combined for all subsequent analyses. All time to first event analyses were performed with multivariate Cox regression models that included terms for sex, baseline age, estimated glomerular filtration rate, body mass index, HbA1c, geographical region, subgroup, and treatment _ subgroup interaction. Continuous baseline characteristics of fibrosis and steatosis risk groups are given as mean ± standard deviation, categorical variables as number and proportions. All other data are expressed as adjusted means (95% confidence interval) or adjusted means ± standard error.

The recent CANVAS study provided similar results with the EMPA-REG trial and suggests a class effect of SGLT-2 inhibitors on morbidity and mortality outcomes. These remarkable findings could establish this class of drugs as an optimal second-line treatment option after metformin monotherapy. The concerning findings in terms of stroke and amputations risk will place at the epicenter of the scientific interest, the identification of patients' groups that might be more prone to these events, such as patients with increased hematocrit levels or severe peripheral artery disease. Ongoing cardiovascular and renal trials will potentially provide further credence for this novel and very promising class of drugs.

Conclusions: Empagliflozin may reduce steatosis but not fibrosis risk in individuals with type 2 diabetes and cardiovascular disease.

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