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Hot Topic Commentary

SGLT-2 Inhibitor and GLP-1 Receptor Agonist Treatment for Patients with Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus: Is Their Combination the Optimal Treatment Option?

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Nonalcoholic fatty liver disease (NAFLD) is a growing epidemic, representing the most common chronic liver disease worldwide.[1] NAFLD is highly associated with type 2 diabetes mellitus (T2DM) and obesity, conditions that increase morbidity and mortality.[2] A background of T2DM has also been shown to be predictive of cirrhosis and hepatocellular carcinoma occurrence in patients with T2DM, and cirrhotic patients with diabetes seem to have a higher risk of hepatic decompensation with manifestations of hepatic encephalopathy.[3] In addition, it should not be underestimated the significantly increased risk for cardiovascular disease (CVD) and chronic kidney disease (CKD) in subjects with NAFLD, regardless of T2DM presence.[4,5]

Newer antidiabetic drugs, like sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have attracted scientific interest in the last decade, because of their multiple pleiotropic effects, with emphasis on cardio- and reno-protection with both drug classes.[6] Their potential role in the treatment of NAFLD has been widely discussed recently.[7]

A previous meta-analysis demonstrated that both drug classes provided a significant improvement in liver enzymes and steatosis in patients with NAFLD.[8] Two recent meta-analyses confirmed the beneficial effects of these drug classes on liver enzymes and liver fibrosis, along with significant improvements in the overall metabolic profile and glycemic control.[9,10] What is more, a recently published retrospective study documented that 5-year treatment with SGLT-2 inhibitors in patients with T2DM and NAFLD resulted in a significant improvement in liver steatosis and fibrosis, and that addition of a GLP-1RA was safe.[11] It has also been speculated that their diuretic effects might be of great value for cirrhotic patients with refractory ascites.[12] Some anecdotal data retrieved from small case series support this hypothesis.[13]

Regarding GLP-1RAs, a previous population-based retrospective cohort study found that treatment with this antidiabetic drug class resulted in a significant decrease in the risk of individual decompensation events, including ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, esophageal variceal hemorrhage, and hepatic encephalopathy.[14] However, when SGLT-2 inhibitors and GLP-1RAs were directly compared, no significant difference in decompensation rates was observed.[14] Combining SGLT-2 inhibitors and GLP-1RA has been shown to be safe and highly efficacious in patients with T2DM, providing a greater reduction in glycated hemoglobin levels, body weight, and systolic blood pressure, compared with each drug class alone.[15] In addition, the cardiovascular benefit obtained by combining a SGLT-2 inhibitor and GLP-1RA seems to be greater than that obtained with a SGLT-2 inhibitor or GLP-1RA alone.[16]

Unfortunately, except for the observations made by Akuta and colleagues[11] in a small cohort of patients with NAFLD,[11] there is no evidence of a synergistic effect of a SGLT-2 inhibitor plus GLP-1RA on liver steatosis and/or fibrosis in patients with NAFLD. The greater reductions of glycated hemoglobin level and body weight shown in previous randomized controlled trials and meta-analyses, should be considered a major step in achieving increased benefits with treatment of liver steatosis by combining a SGLT-2 inhibitor and GLP-1RA.[15] In addition, greater reductions in subcutaneous fat and the visceral fat mass, should be expected with such a combination, along with a greater reduction in intrahepatic fat content, although that has to be confirmed in future trials.[17,18] Remarkably, only an observational study in a total of 24 patients with NAFLD and T2DM showed that addition of a SGLT-2 inhibitor to an incretin-based regimen with GLP-1RA or a DPP-4 inhibitor resulted in a significant decrease in alanine aminotransferase levels that led to nor-

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonists; NAFLD, nonalcoholic fatty liver disease; SGLT-2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes mellitus.

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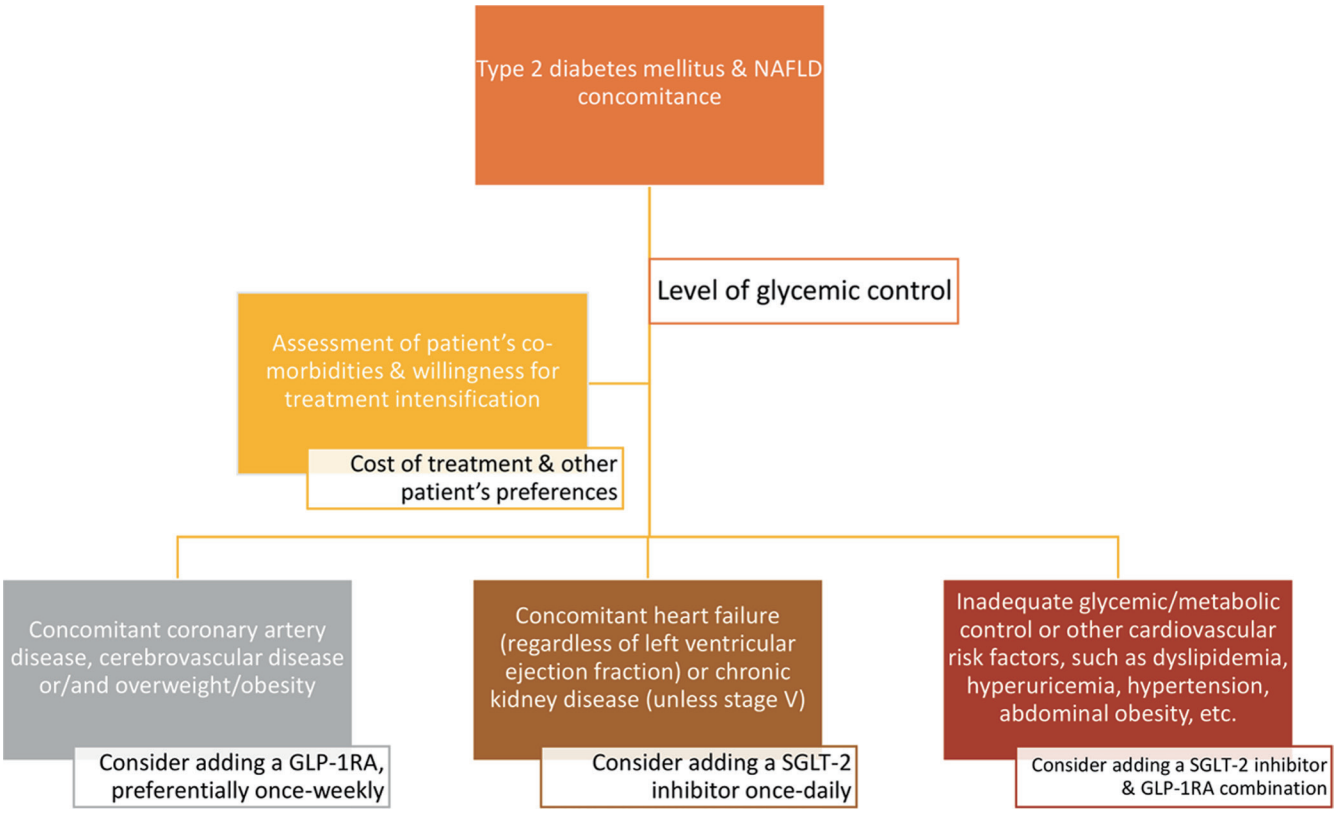

Fig. 1. A simplified treatment approach for patients with NAFLD and type 2 diabetes mellitus. NAFLD, nonalcoholic fatty liver disease.

malization and in a significant improvement in the FIB-4 index.[19]

Of course, it has to be admitted that the safety and efficacy of a great number of drug classes and investigational agents for the treatment of NAFLD with or without comorbidities testing are currently under investigation in clinical trials.[20] Peroxisome proliferator-activated receptor agonists, pyruvate carrier (MPC) inhibitors, farnesoid X receptor agonists, liver X receptor alpha inhibitors, fibroblast growth factor analogs/activators, dual GLP-1 and glucose-dependent insulinotropic peptide receptor analogs or agonists, thyroid hormone receptor (THR-β)-selective agonists, antioxidants, fibrosis-targeted treatment options, and their combinations, are being assessed for their potential incorporation into the armamentarium of NAFLD treatments.[20] Of note, some are also being tested in combination with either SGLT-2 inhibitors or GLP-1RAs.[20]

Therefore, it appears that such a combination would be of great value for patients with NAFLD and comorbidities, such as obesity, CVD, or even CKD (a simplified treatment approach is shown in Fig. 1). However, no studies have yet assessed the impact of such a combination on histological outcomes in patients with NAFLD and T2DM to confirm whether an SGLT-2 inhibitor/GLP-1RA combination might have beneficial synergistic effects on liver steatosis and fibrosis. Well-designed, prospective studies are required to answer this sound, scientific question. In addition, cost-effectiveness analyses are needed.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

DP and TM wrote the draft, DP critically revised the manuscript before submission.

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