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Opinion

The Use of Sodium-Glucose Cotransporter 2 Inhibitors in Non-Alcoholic Fatty Liver Disease

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Opinion

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of progressive liver abnormalities from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) to advanced fibrosis, cirrhosis, and/or hepatocellular carcinoma [1]. Parallel to the rising burden of obesity and metabolic syndrome, NAFLD has emerged as the leading cause of chronic liver disease at an estimated global prevalence of 24% [2]. Besides its known clinical burden for liver-related morbidity and mortality, NAFLD is potentially linked with other extra-hepatic chronic diseases and may be considered a multisystem condition. Particularly, NAFLD increases the risk of type 2 diabetes, cardiovascular diseases, chronic kidney disease, and all-cause mortality [1]. Potential pathophysiologic mechanisms underlying the detrimental effects of NAFLD include hyperglycemia, systemic inflammation, and increased oxidative stress [3]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetic agents that inhibit the reabsorption of sodium and glucose in the proximal tubules of the kidney [4]. Commonly used SGLT2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin. Large-scale randomized placebo-controlled trials have demonstrated the benefits of SGLT2 inhibitors in reducing adverse cardiovascular/renal events in patients with cardio-metabolic conditions, including diabetes, obesity, and chronic kidney disease [5]. In regard to liver function, numerous studies have revealed that SGLT2 inhibition reduced the levels of partate aminotransferase (AST) as well as alanine aminotransferase (ALT) in patients with type 2 diabetes and established cardiovascular disease [6], highlighting the potential role of SGLT2 inhibitors in patients with NAFLD.

The use of SGLT2 inhibitors is associated with reductions in liver fat content in NAFLD. In a meta-analysis of patients with type 2 diabetes and NAFLD, SGLT2 inhibitors improved hepatic steatosis and reduced levels of ALT [7]. In the E-LIFT trial which included 52 patients with type 2 diabetes and NAFLD, empagliflozin treatment reduced liver fat, as measured by MRI-derived proton density fat fraction [8]. While these results seem to support the role of SLGT2 inhibitors in NAFLD, it is important to note that prior investigations are carried out in patients with diabetes. Although the reductions in ALT and AST were independent of levels of glycated hemoglobin in the EMPA-REG OUTCOME trial [6], the effects of SGLT2 inhibitors on NAFLD and hard cardiovascular endpoints in the absence of diabetes remain unknown. Further to this is the uncertain mechanisms underlying the improvement of NAFLD with SGLT2 inhibitors. While the glucose-lowering effects of SGLT2 inhibitors have been postulated as a major mechanism through which SGLT2 inhibitors alleviate hepatic dysfunction, the absence of protection against hepatic dysfunction with other potent hypoglycemic agents, including DPP4 inhibitors and metformin, speak against this hypothesis and highlight that there might be other potential mechanisms responsible for the observed benefits of SGLT2 inhibitors. As our understanding of SGLT2 inhibitors progresses, their pleiotropic effects are becoming increasingly apparent. Recent studies have shown that treatment with SGLT2 inhibitors significantly reduced the levels of pro-inflammatory cytokines that are associated with NAFLD, including interleukin-6 (IL-6) and C-reactive protein (CRP) [9,10]. SGLT2 inhibitors also exhibit antioxidant properties, protecting tissue damage/fibrosis due to oxidative stress, and might also ameliorate atherosclerotic changes which are well-known to be associated with NAFLD [11]. Taken together, SGLT2 inhibitors are a promising therapeutic strategy for NAFLD. Further clinical trials are warranted to establish the benefits of SGLT2 inhibitors in patients with NAFLD regardless of the presence of diabetes to halt the rapidly growing pandemic of NAFLD and its assorted comorbidities/complications.

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