Empagliflozin promises to bridge the gap between non-alcoholic fatty liver disease, type 2 diabetes, and cardiovascular disease

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Non-alcoholic fatty liver disease (NAFLD) represents the commonest chronic liver disease in the Western world, while its prevalence among patients with type 2 diabetes (T2D) is as much as 70% [1]. Non-alcoholic fatty liver disease shares common pathophysiologic mechanisms with T2D, mainly insulin resistance, lipotoxicity, and inflammation [2].

Besides the well-established role of T2D in the development of cardiovascular disease (CVD) [3], NAFLD has also emerged as a potential predictor of CVD. Previous data support the association between NAFLD and subclinical atherosclerosis, with a remarkable higher probability of its presence among patients with NAFLD compared to controls (OR = 1.60, 95% CI: 1.45–1.78) [4]. Increased arterial stiffness [5], coronary artery calcification [6], elevated carotid intimal media thickness [7], and impaired endothelial function [8] have been previously shown in patients with NAFLD.

Targher *et al.* have demonstrated that patients with NAFLD exhibit almost 64% greater probability of experiencing fatal or non-fatal CVD events, compared to controls (OR = 1.64, 95% CI: 1.26–2.13) [9]. Similar results were obtained from another meta-analysis conducted by Mahfood Haddad *et al.*, who demonstrated a significantly higher risk of clinical cardiovascular events in patients with NAFLD compared to controls – up to 77% (RR = 1.77, 95% CI: 1.26–2.48) [10]. According to a recently published retrospective, cohort study involving 1452 patients with NAFLD and T2D, the risk of CVD among those patients was almost 70% higher compared to patients with no liver disease (HR = 1.70, 95% CI: 1.52–1.90) and was associated with a 60% greater risk of all-cause mortality [11].

However, it is worth mentioning that the observational design of the included studies in the aforementioned meta-analyses does not permit safe conclusions to be drawn regarding the true causal relationship between NAFLD and CVD. It is still debated whether NAFLD represents a true predictor of CVD, while causality has to be proven in large-scale, prospective clinical studies [12].

Recent data suggest that liver fat content represents a risk factor for CVD [13]; however, proceeding a step further, the fibrosis stage seems to be the strongest predictor of both overall and disease-specific (including cardiovascular) mortality in patients with NAFLD/non-alcoholic steatohepatitis (NASH). Patients with liver fibrosis stage 3–4, irrespective of NAFLD activity score, exhibit the greatest risk of death among this population [14]. In general, obese/overweight patients feature greater risk of advanced liver fibrosis compared to lean patients with NAFLD, along with higher incidence rates of NASH [15]. Based on the increasing prevalence of overweight and obesity among patients with T2D, it seems that this association is becoming stronger.

A significant amount of interest lies on the pleiotropic effects of sodium glucose cotransporter 2 (SGLT-2) inhibitors. The hallmark EMPA-REG OUTCOME study revealed the potential role of empagliflozin in the management of patients with T2D at high cardiovascular risk, leading to a 38% decrease in the rates of cardiovascular death and a 35% decrease in hospitalisation for heart failure [16].

In a post-hoc analysis of the EMPA-REG OUTCOME, it was shown that alanine aminotransferase (ALT) levels decreased from baseline to week 28 with empagliflozin compared to placebo (adjusted mean difference: –2.22, 95% CI: –2.83, –1.62; $p < 0.0001$) and remained signifi-

cantly lower at week 164 (adjusted mean difference: –1.26, 95% CI: –2.12, –0.40; $p = 0.0040$). Non-significant reduction in aspartate aminotransferase (AST) levels was observed at week 164 with empagliflozin vs. placebo. Alanine aminotransferase decrease was largely independent of alteration in body weight or glycaemic control [17]. The aforementioned results are consistent with empagliflozin-induced reduction in liver fat in patients with T2D. Of note, such a small decrease in ALT levels should be carefully interpreted regarding its clinical meaningfulness.

The recently published E-LIFT trial, enrolling 50 patients (42 completed the study) with T2D and NAFLD randomly assigned to empagliflozin 10 mg/day as an add-on to standard antidiabetic treatment or placebo, demonstrated that empagliflozin led to a significant reduction in liver fat [18]. More specifically, empagliflozin resulted in a significant decrease in liver fat, by up to 4.0%, compared to controls ($p < 0.0001$), as measured by MRI-derived proton density fat fraction (MRI-PDFF), while a significant difference in liver fat, almost 5%, was observed in the empagliflozin group in the end of the treatment (16.2–11.3%, $p < 0.0001$). Empagliflozin also produced a significant decrease in AST levels at the end of the treatment (64.3–49.7 IU/l, $p = 0.001$), while it did not affect significantly ALT levels [18].

After meticulous interpretation of the results of the aforementioned studies [17, 18], along with the derived evidence documenting the cardiovascular efficacy and safety of empagliflozin [19, 20], we can speculate that empagliflozin promises to bridge the gap between NAFLD, T2D, and CVD, bolstering our armamentarium against this increasingly frequent concomitance that is associated with significant morbidity and mortality rates, especially in the Western world.

However, two certain limitations arise. First, there is no available randomised clinical trial assessing the efficacy of empagliflozin on overall and cardiovascular mortality, after detailed survival analysis, in patients with T2D and NAFLD/NASH. Secondarily, the effects of empagliflozin on AST/ALT levels and liver fat content should be cautiously interpreted, in terms of clinical significance. The efficacy of this novel agent on liver fibrosis amelioration should be evaluated in future, prospective clinical trials.

Conflict of interest

The authors declare no conflict of interest.

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