Editorial

Glucose-lowering agents and reduced risk of incident non-alcoholic fatty liver disease: new insights

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Non-alcoholic fatty liver disease (NAFLD) is classically defined as the hepatic manifestation of metabolic syndrome (1). Histologically, NAFLD covers a range of conditions, spanning from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis (2). At present, NAFLD is the most frequent chronic liver disease seen in clinical practice in high-income countries, as it affects nearly 30% of adults in the general population, up to 70% of patients with type 2 diabetes (T2DM) and almost all patients with obesity (2).

Over the last decade, it has become evident that NAFLD is a "multisystemic" disease (2), which is not only associated with hepatic complications [i.e., hepatocellular carcinoma (HCC)], but also with a higher risk of extra-hepatic complications, including cardiovascular disease (CVD) and T2DM (2).

In spite of the clinical burden of NAFLD, there are no pharmacological treatments for NAFLD/NASH approved by main national medicines agencies to date (3). However, based on the data provided by randomized controlled trials (RCTs) (*Table 1*), the EASL-EASD-EASO and AASLD practice guidelines for the NAFLD management now recommend the use of pioglitazone (which is a member of thiazolidinediones) in non-cirrhotic adults with biopsy-confirmed NASH (4,5). That said, several other drugs have been tested in phase-2 RCTs as potential therapy for NAFLD/NASH (3). Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have received attention, as these agents are able to promote weight loss and to improve glycemic control and insulin resistance (3). In a 2021 meta-analysis, for instance, Mantovani *et al.* (6) reported that, compared to control therapy, treatment with GLP-1RAs was associated with reductions in the absolute percentage of liver fat content (as assessed by magnetic resonance-based techniques), as well as with histological resolution of NASH without worsening of liver fibrosis.

However, to date, information on the association between the use of specific agents (including thiazolidinediones or GLP-1RAs) and the risk of developing NAFLD and its advanced forms is scarce. Notably, understanding this issue could help to create novel therapeutic strategies that may reduce the clinical burden of NAFLD, which is strongly associated with an excess of premature mortality (2).

Recently, on Hepatology, van Dalem *et al.* (7) published the results of a large population-based cohort study collecting primary care data from the Clinical Practice Research Datalink database (2007–2018) with the aim to assess the potential role of different glucose-lowering agents on the risk of incident NAFLD. In this study involving 207,367 UK T2DM adults [median age: 61 years; 45% women; median body mass index (BMI): 31 kg/m^2] with an initial prescription of glucose-lowering agents, the investigators found that 2,526 patients had a new diagnosis of NAFLD (as assessed by Read codes) during

Table 1 Main RCTs that have used liver biopsy to assess the efficacy and safety of pioglitazone or GLP-1RAs in patients with NASH

Authors, ref.	Phase of study	Country	Population	Median age (years)	Details of intervention	Duration of treatment (months)	Main results
Pioglitazone							
Belfort *et al.*, *N Engl J Med* 2006;355:2297-307.	IIb (NCT00227110)	International	55 patients with impaired glucose tolerance or T2DM and histological NASH	51	Pioglitazone 45 mg/day *vs.* placebo	6	• Pioglitazone *vs.* placebo: significantly higher rate of reduction in NAS score (85% *vs.* 38%, P=0.001) • Fibrosis change from baseline did not differ between two groups (P=0.08)
Aithal *et al.*, *Gastroenterology* 2008;135:1176-84.	IIb	UK	74 non-diabetic patients with histological NASH	53	Pioglitazone 30 mg/day *vs.* placebo	12	• Pioglitazone *vs.* placebo: significantly higher rate of reduction in hepatocyte injury (32% *vs.* 10%, P=0.005), Mallory bodies (26% *vs.* 3%, P=0.004) and fibrosis (29% *vs.* 20%, P=0.05)
Sanyal *et al.*, *N Engl J Med* 2010;362:1675-85.	IIb (NCT00063622)	USA	247 non-diabetic patients with histological NASH	46	Pioglitazone 30 mg/day *vs.* Vitamin E 800 UI/day *vs.* placebo	24	• Vitamin E *vs.* placebo: significantly higher rate of improvement in NASH features (43% *vs.* 19%, P=0.001) • Pioglitazone *vs.* placebo not significantly higher rate of improvement in NASH features (34% and 19%, P=0.04) • At sensitivity analysis, both Vitamin E and pioglitazone significantly reduced all histologic features of NASH, but not fibrosis
Sharma *et al.*, *J Clin Exp Hepatol* 2012;2:333-7.	IIb	India	60 patients with histological NASH and increased transaminases >1.2 ULN	59	Pioglitazone 30 mg/day + hypocaloric diet + physical exercise *vs.* pentoxifylline 1,200 mg/day + hypocaloric diet + physical exercise	6	• Pioglitazone *vs.* placebo: significant more reduction of Brunt score from baseline (pre 2.1±0.8, post 0.9±0.9) *vs.* (pre 1.5±0.7, post 1.2±0.9), P=0.04 • No effect on fibrosis change in both groups
Cusi *et al.*, *Ann Intern Med* 2016;165:305-15.	IIb (NCT00994682)	USA	101 patients with prediabetes or T2DM and histological NASH	50	Pioglitazone 45 mg/day + hypocaloric diet *vs.* placebo + hypocaloric diet	18	• Pioglitazone *vs.* placebo: significantly higher rate of improvement in histological features (58% *vs.* 17%, P<0.001) and of resolution of NASH (51% *vs.* 19%, P<0.001)

Table 1 *(continued)*

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Authors, ref.	Phase of study	Country	Population	Median age (years)	Details of intervention	Duration of treatment (months)	Main results
GLP-1RAs							
Armstrong *et al.*, *Lancet* 2016; 387:679-90.	IIb (NCT01237119)	International	52 patients with histological NASH	51	Liraglutide 1.8 mg/day *vs.* placebo	12	• Liraglutide *vs.* placebo: histological resolution of NASH: 39% *vs.* 9%, P=0.019 • No effect on fibrosis change in both groups
Newsome *et al.*, *N Engl J Med* 2021;384:1113-24.	IIb (NCT02970942)	International	320 patients with histological NASH and different stages of fibrosis	55	Semaglutide 0.1 mg/day *vs.* semaglutide 0.2 mg/day *vs.* semaglutide 0.4 mg/day *vs.* placebo	18	• Semaglutide *vs.* placebo: the percentage of patients in whom NASH resolution was obtained without worsening of fibrosis was 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group and 17% in the placebo group (P<0.05) • No effect on fibrosis change among 4 groups

RCTs, randomized controlled trials; GLP-1RAs, glucagon-like peptide-1 receptor agonists; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes.

a mean follow-up of nearly 5 years (7). Interestingly, the risk of developing NAFLD was lower in patients receiving thiazolidinediones (mainly pioglitazone) compared with those receiving sulphonylureas, even after adjustment for age, sex, BMI, HbA1c and use of glucocorticoids (adjusted-HR: 0.32; 95% confidence interval: 0.20–0.51) (7). Conversely, no difference in the risk of incident NAFLD was observed between patients receiving GLP-1RAs and those receiving insulin therapy (adjusted-HR: 1.22; 95% confidence interval: 0.91–1.63) (7). The investigators concluded that their study further endorses the use of thiazolidinediones (pioglitazone) in specific patients at risk of developing NAFLD (7), thereby suggesting that these agents may reduce the clinical burden of NAFLD.

We believe that van Dalem *et al.* (7) should be congrats for their interesting findings. Indeed, their study confirmed, but also expanded, the findings of previous RCTs and meta-analyses (3), suggesting that pioglitazone is able to promote the resolution of NASH and to improve liver fibrosis. However, pioglitazone is not yet approved by most national medicines agencies outside the use for the treatment of T2DM, and, therefore, the off-label use of this agent for NAFLD/NASH treatment requires the patient's consent. Interestingly, pioglitazone can also reduce the risk of developing cardiovascular events (8), which are the primary cause of death amongst NAFLD patients (2). However, concerns about its side-effects (i.e., weight gain, fluid retention, risk of bone fractures) might preclude the use of pioglitazone in clinical practice. Hence, other agents have been studied as potential therapy for NAFLD.

The history of GLP-1RAs for the treatment of NAFLD/NASH is instead at the beginning and, unfortunately, the study by van Dalem *et al.* (7) does not allow to draw firm conclusions on this topic for the following reasons. First of all, it is an observational study and, hence, it cannot establish the causality of the observed findings. Second, the results of the study by van Dalem *et al.* (7) may be potentially influenced by specific biases (including the "prescription" bias) that can be only partially overcome by advanced statistical analyses. In this regard, it is important to note that, in real life, insulin therapy is usually prescribed to patients with advanced stage of T2DM, whereas GLP-1RAs is often prescribed to T2DM patients with obesity. Third, patients included in the study by van Dalem *et al.* (7) had T2DM and, hence, the results cannot be generalized to other patient populations. Lastly, the diagnosis of NAFLD was made by Read codes that can potentially lead to misclassification of NAFLD and, even, under-recording it.

In this context, it is important to remember that at present, although specific indirect markers are being studied, the gold-standard method for the diagnosis of NAFLD and its advanced forms is still liver biopsy (4,5).

Presently, as reported in *Table 1*, there are only two published phase-IIb RCTs (9,10) that have used liver biopsy to determine the efficacy of GLP-1RAs in patients with NAFLD/NASH. Notably, the resolution of NASH and/or improvement in fibrosis stage are the two main histological endpoints requested by drug regulatory agencies for approval of NAFLD/NASH pharmacotherapies. In a 48-week, double-blinded RCT enrolling 52 patients with biopsy-proven NASH randomly to receive liraglutide (n=26) or placebo (n=26), Armstrong *et al.* (9) showed that liraglutide led to the resolution of NASH (9). Conversely, liraglutide did not lead to the improvement of liver fibrosis. In a recent 72-week, double-blind RCT involving 320 patients with biopsy-confirmed NASH and liver fibrosis randomly to receive semaglutide at a dose of 0.1 mg (n=80), 0.2 mg (n=78), or 0.4 mg (n=82) or to receive placebo (n=80), Newsome *et al.* (10) showed that the percentage of patients in whom NASH resolution was observed with no worsening of fibrosis was 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group (P<0.05). Again, this RCT did not report between-group differences in the percentage of patients who experienced an improvement in fibrosis stage without worsening fibrosis as well (10). However, some relevant aspects need to be discussed regarding these findings. First, the most individuals included in these trials had NAFLD and T2DM. Hence, additional trials in nondiabetic individuals with NAFLD are required. Second, in the trial by Newsome *et al.* (10) the patients with biopsy-proven NAFLD were randomly assigned to receive once-daily semaglutide at a dose of 0.1, 0.2, 0.4 mg or placebo. This is not the current approved dosage of semaglutide for the treatment of T2DM. Third, the insufficient follow-up duration might have contributed to not demonstrating a beneficial effect of GLP-RAs on liver fibrosis. For these reasons, additional trials are timely needed to test the exact efficacy of GLP-1RAs in patients with NAFLD/NASH and to establish if these glucose-lowering agents may reduce the risk of developing NAFLD/NASH over time.

Maybe, given the multiple pathways involved in the NAFLD pathogenesis and the single response from single-agent therapies (that stands from 30% to 50%) observed in the RCTs published so far (3), the combination of different agents with various mechanisms of action may be the best way to treat NAFLD and its advanced forms (11). In this regard, for instance, the GLP-1 RA, semaglutide, is being investigated in combination with the nonsteroidal Farnesoid X receptor (FXR) agonist, cilofexor, and with the acetyl-CoA carboxylase inhibitor, firsocostat, in a phase 2 proof-of-concept trial (NCT03987074). Semaglutide is also being investigated in combination with empagliflozin (gliflozin) in a placebo-controlled, double-blind, randomized, 3-arm parallel group trial (NCT04639414). Moreover, considering the heterogeneity of NAFLD patients, it might be even more suitable to identify specific individuals for a definite therapeutic strategy (11). However, the research on this topic is still at the beginning and further studies are needed to improve our understanding for intercepting NAFLD patients who would have a higher probability of treatment response with a specific agent as monotherapy or, better, with a combination therapy (3).

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