Editorial

Glucagon-like peptide-1 receptor agonists for treatment of nonalcoholic steatohepatitis: new insights from subcutaneous semaglutide

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Nonalcoholic fatty liver disease (NAFLD) is the commonest cause of chronic liver disease globally. It affects around 25% of the general adult population, and up to ~70–80% of patients, who are obese or have type 2 diabetes mellitus (T2DM) (1,2). Over the past decades, it has become increasingly clear that NAFLD is a "multisystem" disease, requiring a multidisciplinary and holistic approach (3). Indeed, this common liver disease is not only associated with liver-related complications, but also with an increased risk of incident extra-hepatic diseases, such as T2DM, cardiovascular disease, chronic kidney disease, and extra-hepatic malignancies (4-7).

There is currently no approved therapy for NAFLD or nonalcoholic steatohepatitis (NASH). General therapeutic strategies have been proposed to treat this burdensome liver condition, including lifestyle modifications to lose body weight; correction of modifiable cardiometabolic risk factors implicated in the progression from simple steatosis to NASH and cirrhosis; and prevention of NAFLD-related extra-hepatic manifestations (8). However, in the last years, several agents have been investigated in phase 2 randomized controlled trials (RCTs) as possible treatment options for NAFLD or NASH. Among these agents, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have received a lot of attention. Experimentally, it has been reported that activation of GLP-1 receptors may reduce liver fat content by improving insulin resistance, *de novo* lipogenesis, mitochondrial function and lipotoxicity (8). Treatment with GLP-1RAs promotes a significant weight reduction (on average 4–5 kg), mostly by improved appetite control and reduced energy intake, thereby resulting in improvement of hepatic and systemic insulin resistance (8). Some preclinical NASH studies also suggested that GLP-1RAs reduce hepatic inflammation, independent of weight loss (8). In addition, given that cardiovascular disease is the predominant cause of death in people with NAFLD (1,7), it is also important to remember that large RCTs on GLP-1RAs have shown that these drugs reduce all-cause mortality and exert cardioprotective and nephroprotective effects in patients with T2DM (9), thereby representing an attractive bonus for their long-term use in people with T2DM and NAFLD.

Recently, a multicentre, randomized, double-blind, placebo-controlled, parallel-group phase 2 trial of subcutaneous semaglutide in patients with biopsy-proven NASH has been published in *New England Journal of Medicine* by Newsome *et al.* (10). In this trial, 320 middle-aged obese patients with NASH (mean age: 55 years; mean body mass index: 35 kg/m^2; 61% women; 62% had established T2DM) were randomly assigned to receive once-daily subcutaneous semaglutide at a dose of 0.1 mg (80 patients), 0.2 mg (78 patients), and 0.4 mg (82 patients) or to receive placebo (80 patients) for 72 weeks (10). At baseline, 28% of these patients had stage F1 fibrosis, 22% had stage F2, and 49% had stage F3 (10). At the end of the trial, the percentage of patients with NASH resolution

with no worsening of fibrosis (i.e., the primary endpoint of the study) was significantly higher in each semaglutide group (40%, 36%, and 59% of patients in the 0.1-mg, 0.2-mg, and 0.4-mg groups, respectively) compared to placebo (17%), with the highest percentage seen in the 0.4-mg group (P<0.001 *vs.* placebo) (10). Conversely, the percentage of patients with improvement in fibrosis stage and no worsening of NASH (the secondary endpoint) did not significantly differ between the semaglutide and placebo groups (49%, 32%, and 43% of the patients in the 0.1-mg, 0.2-mg, and 0.4-mg groups *vs.* 33% in the placebo group) (10). Semaglutide-treated participants also showed a significant reduction in serum liver enzyme levels (10). In addition, semaglutide resulted in dose-dependent reductions in body weight (10). The mean percent changes in body weight were –5% in the semaglutide 0.1-mg group, –9% in the 0.2-mg group, –13% in the 0.4-mg group, and –1% in the placebo group (10). Semaglutide was safe and well tolerated with a rate of adverse events not exceeding that of either placebo, except for a higher frequency of mild-to-moderate and transient gastrointestinal disorders (10).

These interesting results corroborate and expand the current evidence derived from some previously published phase 2 RCTs testing the use of GLP-1RAs as a treatment option for patients with NAFLD/NASH, regardless of the presence or absence of T2DM. For instance, treatment with subcutaneous liraglutide (1.8 mg daily for 48 weeks) was evaluated in the phase 2 Liraglutide Efficacy and Action in NASH (LEAN) trial involving 52 overweight or obese patients with biopsy-confirmed NASH, who were recruited from four UK medical centres (11). This trial showed that patients treated with liraglutide had a greater histological resolution of NASH (relative risk 4.3, 95% CI: 1.0–17.7; P=0.019) compared with those assigned to placebo (11). Moreover, 9% of patients in the liraglutide group *vs.* 36% of patients in the placebo group had progression of liver fibrosis (P=0.04) (11). 48 weeks' treatment with liraglutide was also associated with significant reductions in body weight compared with placebo (11).

Dulaglutide is another long-acting GLP-1RA that was recently tested in the D-LIFT (Dulaglutide on Liver Fat) trial, which is a 24-week, open-label, parallel-group RCT aimed at examining the effect of this drug on liver fat content (as assessed by magnetic resonance imaging proton density fat fraction [MRI-PDFF]) in a tertiary care centre in India. This small phase 2 RCT involved 64 patients with established T2DM of whom 32 were randomly assigned to dulaglutide and 32 to placebo (12). Compared with placebo, treatment with dulaglutide (1.5 mg weekly) was significantly associated with an absolute and relative reduction in liver fat content of –3.5% (95% CI: –6.6% to –0.4%) and –26.4% (95% CI: –44.2% to –8.6%), respectively (12).

Interestingly, all the above-mentioned RCTs were included in an updated meta-analysis that incorporated a total of 11 placebo-controlled or active-controlled phase-2 RCTs testing the efficacy of different GLP-1RAs (exenatide, liraglutide, dulaglutide or semaglutide) for treatment of NAFLD or NASH. This meta-analysis concluded that treatment with GLP-1RAs for a median of 26 weeks was associated with a significant reduction in the absolute percentage of liver fat content, as assessed by magnetic resonance-based techniques (n=7 studies included; pooled weighted mean difference: –3.92%, 95% CI: –6.27% to –1.56%; P<0.0001), as well as with greater histological resolution of NASH without worsening of fibrosis (n=2 studies using liraglutide or semaglutide; pooled random-effects odds ratio 4.06, 95% CI: 2.52–6.55; P<0.0001) (13). A difference although not statistically significant was also observed in the percentage of patients who had an improvement in fibrosis stage without worsening of NASH (pooled random-effects odds ratio 1.50, 95% CI 0.98–2.28; P=0.06) (13). This meta-analysis confirmed that treatment with GLP-1 RAs was associated with a significant reduction in body weight (nearly 4.0 kg) (13). So, it is difficult to discern if the beneficial hepatic effects (as schematically summarized in *Figure 1*) of semaglutide, liraglutide or other GLP-1RAs in people with NAFLD/NASH are, at least in part, independent of weight loss.

Among the most important strengths of the phase 2 RCT published by Newsome *et al.*, we mention that it is placebo-controlled, the sample size is sufficiently large (n=320 participants with biopsy-confirmed NASH) and the period of treatment is relatively long (i.e., 72 weeks that is the longest period of treatment with a GLP-1RA so far). Furthermore, it is also important to point out that the results of this phase 2 RCT represent the highest rate of NASH resolution ever reported in previously published NASH therapeutic trials.

However, some critical points deserve to be discussed. First, there are currently only two placebo-controlled RCTs (10,11) assessing the efficacy of GLP-1RAs (liraglutide or semaglutide) on resolution of NASH and/or improvement in fibrosis stage (which are the two histological endpoints requested by drug regulatory agencies for approval of pharmacotherapies for NASH). So, no robust data exist with liver histological endpoints to comment on the efficacy

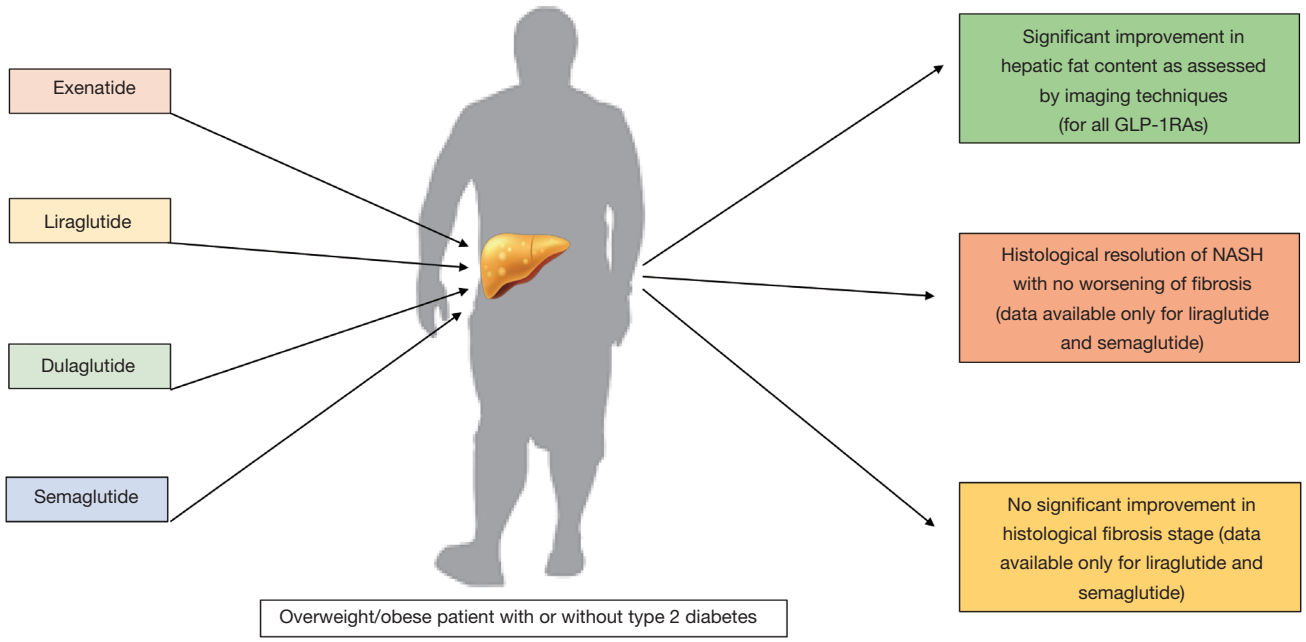

Figure 1 Possible hepatoprotective effects of GLP-1RAs for treatment of NAFLD or NASH. GLP-1RAs, glucagon-like peptide-1 receptor agonists; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

of GLP-1RAs in patients with NASH. Second, in the trial by Newsome *et al.* the participants were randomly assigned to receive once-daily semaglutide at a dose of 0.1, 0.2, 0.4 mg or placebo (10). However, it should be noted that the approved dose of semaglutide for the treatment of T2DM is 0.5 mg or 1.0 mg once-weekly (14). A dosage of semaglutide of 2.4 mg once weekly was recently used in some large trials for treating overweight or obesity (15), but this dosage is not approved by drug regulatory agencies yet. Hence, the transferability and applicability of the findings of the trial by Newsome *et al.* to routine clinical practice remain currently uncertain. Third, most of the published RCTs included individuals with NAFLD and T2DM (~70% of participants), implying that larger randomized trials in nondiabetic individuals with NAFLD are needed.

Notwithstanding these aspects, we believe that the recent phase 2RCT published by Newsome *et al.* provides further support for the long-term use of GLP-1RAs (singly or combined with other drugs acting on different molecular pathways implicated in NASH pathogenesis) as an attractive therapy for patients with NAFLD or NASH. However, well-designed phase-3 RCTs with sufficiently long follow-ups and adequate liver histological endpoints are required to better characterize the efficacy of GLP-1RAs for treatment of this common and burdensome liver disease.

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References

1. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet 2021;397:2212-24.
2. Younossi Z, Tacke F, Arrese M, et al. Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology 2019;69:2672-82.
3. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. Lancet Gastroenterol Hepatol 2021;6:578-88.
4. Mantovani A, Petracca G, Beatrice G, et al. Nonalcoholic Fatty Liver Disease and Risk of Incident Diabetes Mellitus: An Updated Meta-Analysis of 501,022 Adult Individuals. Gut 2021;70:962-9.
5. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. Gut 2020. doi: 10.1136/gutjnl-2020-323082. [Epub ahead of print].
6. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut 2021. doi: 10.1136/gutjnl-2021-324191. [Epub ahead of print].
7. Adams LA, Anstee QM, Tilg H, et al. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138-53.
8. Petroni ML, Brodosi L, Bugianesi E, et al. Management of non-alcoholic fatty liver disease. BMJ 2021;372:m4747.
9. Kristensen SL, Rorth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776-85.
10. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113-24.
11. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387:679-90.
12. Kuchay MS, Krishan S, Mishra SK, et al. Effect of dulaglutide on liver fat in patients with type 2 diabetes and NAFLD: randomised controlled trial (D-LIFT trial). Diabetologia 2020;63:2434-45.
13. Mantovani A, Petracca G, Beatrice G, et al. Glucagon-Like Peptide-1 Receptor Agonists for Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: An Updated Meta-Analysis of Randomized Controlled Trials. Metabolites 2021;11:73.
14. American Diabetes A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44:S111-24.
15. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med 2021;384:989.

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