Management & prevention of type 2 diabetes

Glucagon-like peptide-1 receptor agonists: A better option for treating and preventing steatohepatitis?

Naveed Sattar
Professor of Metabolic Medicine, University of Glasgow, Glasgow

The pathogenesis of type 2 diabetes is underpinned by ectopic fat in key organs, with the liver being one of the most easily recognised in clinical terms, often via mildly raised transaminase levels or enhanced echogenicity on hepatic ultrasound. Indeed, the vast majority of people with type 2 diabetes have excessive liver fat sufficient to be categorised as non-alcoholic fatty liver disease (NAFLD; >5% fat). In most people, this excess liver fat is not a major concern other than the fact that it causes hepatic insulin resistance, as progression to more advanced liver disease will not occur (Sattar et al, 2014). However, in some people, NAFLD will progress to non-alcoholic steatohepatitis (NASH), and then the risk of cirrhosis and even hepatocellular carcinoma are meaningfully increased. Hence, we would like to know which of our patients will progress to NASH and how to identify them. The hepatologist, in turn, would like to offer treatments that can alleviate NASH or slow its progression, and do so in a safe manner.

In terms of identifying people at increased risk of NASH, several different and often complex algorithms have been put forward. Most, however, are unlikely to be widely used in primary care or in general outpatient clinics. Therefore, Sattar et al (2014) recently suggested that the simplest and most pragmatic clinical warning sign of impending NASH is the aspartate transaminase/alanine transaminase (AST/ALT) ratio, which is normally well below 0.8. In people with known NAFLD (and thus, by definition, most people with type 2 diabetes), when this AST/ALT ratio is rising towards 0.8, or certainly towards 1.0, referral to the hepatologist for more detailed assessment of NASH risk is warranted. In most people, however, mild elevations in ALT (and when ALT levels are higher than AST and the ratio is <0.8) should be dealt by reinforcement of dietary advice to alter weight trajectory (ideally weight loss), and to cut down on alcohol, irrespective of the current intake level.

In terms of treatments, other than lifestyle change, we have long been waiting for a "magic" drug to lessen or reverse features of NASH in people with and without diabetes. However, potential treatments to date have had side effects sufficient to make some cautious about their use. Certainly pioglitazone will lessen NAFLD and impede NASH development (Aithal et al, 2008), but its associated risks of weight gain and heart failure mean that its uptake has been limited. An arguably better treatment for NASH would be one that not only lowers liver fat levels but also lowers blood glucose and weight, as well as being safe. With this in mind, the results of the short-term randomised trial by Armstrong et al (summarised alongside), which demonstrated histological resolution of NASH by liraglutide with no significant safety issues, is to be welcomed, especially since glucagon-like peptide-1 receptor agonist treatment is now well established in diabetes management and is increasingly being used.

The authors correctly state that larger and longer-term NASH studies are needed to verify their findings and validate safety given the small size of the study. Nevertheless, the results are appealing and clinically impactful. The fact that liraglutide also appears to improve cardiovascular outcomes (see page 72) is a further benefit considering that, for reasons not yet clear, people with NASH have heightened cardiovascular risk.

Finally, future studies will also need to test whether other diabetes drugs that lower weight can be beneficial in NASH, especially since preliminary evidence shows that sodium–glucose cotransporter 2 inhibitor treatment improves liver enzyme levels (Katsuyama et al, 2016). ■

References on opposite page

Lancet

Liraglutide leads to histological resolution of NASH: Phase 2 study

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 In this double-blind, phase 2, randomised controlled trial, the authors compared the efficacy and safety of liraglutide 1.8 mg with placebo for non-alcoholic steatohepatitis (NASH).

2 A total of 52 people who were overweight and had histologically confirmed NASH were enrolled. The primary outcome was the resolution of NASH with no worsening in fibrosis, as assessed by two independent pathologists, after 48 weeks of treatment.

3 Of 23 participants who received liraglutide and underwent the final histological assessment, nine achieved the primary outcome, compared with two of 22 placebo recipients (39% vs 9%; P=0.02).

4 Conversely, two liraglutide recipients and eight placebo recipients had progression of fibrosis (9% vs 36%; P=0.04).

5 Compared with placebo, the liraglutide group had significant reductions in weight (4.4 kg) and HbA_{1c} (5 mmol/mol [0.5%]).

6 Aspartate transaminase, alanine transaminase and gamma-glutamyl transferase (GGT) levels decreased to a greater extent with liraglutide; however, the difference was significant only for GGT levels.

7 Most adverse events were mild to moderate in severity and similar in the two treatment groups, with the exception of gastrointestinal disorders, which were more frequent with liraglutide.

Armstrong MJ, Gaunt P, Aithal GP et al (2016) Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* **387**: 679–90

Diabetologia

Effect of atorvastatin on HbA_{1c} progression and subsequent CV outcomes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 Following studies showing that statin use slightly increases the incidence of T2D, these authors analysed data from this prospective trial to examine whether atorvastatin 10 mg increased HbA_{1c} in people with T2D and whether this increase reduced the statin's effects on cardiovascular (CV) risk.

2 Data were available on 2838 people who were randomised to atorvastatin or placebo and were followed up for a mean of 3.3 years.

3 Deterioration in glycaemic control (defined as an increase in HbA_{1c} of 5 mmol/mol [0.5%] or treatment intensification) occurred in 74% and 78% of atorvastatin and placebo recipients, respectively (hazard ratio [HR], 1.18; 95% confidence interval, 1.08–1.29).

4 Overall, the effect of atorvastatin on glycaemic control appeared to be modest (net increase, 1.5 mmol/mol [0.14%]) and common, rather than a large effect occurring in a particular subgroup of people.

5 Importantly, the deterioration in glycaemic control did not significantly alter atorvastatin's effect on CV risk (HR, 0.47 in people with a below-median increase in HbA_{1c} vs 0.63 in those with an above-median increase; $P=0.229$ for interaction).

6 These findings are reassuring; however, further studies with different statins and doses would be helpful, as well as studies examining the effects on microvascular complications.

Livingstone SJ, Looker HC, Akbar T et al (2016) Effect of atorvastatin on glycaemia progression in patients with diabetes: an analysis from the Collaborative Atorvastatin in Diabetes Trial (CARDS). *Diabetologia* **59**: 299–306

ADA 2016

Empagliflozin versus glimepiride as add-ons to metformin

1 The EMPA-REG H2H-SU trial found that empagliflozin 25 mg, as an add-on to metformin, led to significant reductions in mean HbA_{1c}, weight and blood pressure (BP) compared with glimepiride at week 104, with a low risk of hypoglycaemia, in individuals with T2D.

2 Participants were invited to continue in a 104-week extension. Exploratory endpoints were analysed at week 208. These were change from baseline in HbA_{1c}, occurrence of hypoglycaemic adverse events (AEs), and changes from baseline in weight and systolic and diastolic BP.

3 Of the 765 and 789 people treated with empagliflozin and glimepiride, respectively, 576 and 549 extended their treatment.

4 At week 208, the empagliflozin group showed a slight reduction in mean HbA_{1c} versus glimepiride. Rescue medication was given to more individuals in the latter group.

5 Empagliflozin significantly reduced mean weight (–3.4 kg vs 1.2 kg; $P<0.001$), systolic BP (–2.9 mmHg vs 2.5 mmHg; $P<0.001$) and diastolic BP (–1.9 mmHg vs 0.6 mmHg; $P<0.001$) compared with glimepiride.

6 Fewer confirmed hypoglycaemic AEs were reported in those treated with empagliflozin compared to glimepiride (3.1% vs 27.9%; $P<0.001$).

7 AEs consistent with urinary tract and genital infections were more common with empagliflozin than glimepiride.

Ridderstråle M, Andersen KR, Toorawa R et al (2016) Empagliflozin compared with glimepiride as add-on to metformin for 4 years in patients with type 2 diabetes. *American Diabetes Association 76th Scientific Sessions:* abstract 184-OR

Diabetes Care

Markers of beta-cell failure predict poor response to GLP-1 analogue therapy

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 The primary mechanism by which glucagon-like peptide-1 (GLP-1) receptor agonists lower blood glucose is enhancement of insulin secretion by beta-cells.

2 Therefore, it may not be surprising that this study showed that people with T2D who had clinical markers of beta-cell failure (and thus a diminished capacity to produce insulin) had a reduced response to GLP-1 analogue therapy.

3 A total of 546 people treated with liraglutide or exenatide were evaluated. In this cohort, reduced glycaemic response to GLP-1 analogues was associated with longer diabetes duration, insulin cotreatment, lower fasting C-peptide level, lower postmeal urine C-peptide:creatinine ratio and the presence of autoantibodies targeting beta-cells ($P\leq0.01$ for all).

4 Insulin cotreatment was associated with an 8.5-mmol/mol (0.8%) reduction in glycaemic response compared with non-recipients.

5 Participants with severe insulin deficiency (fasting C-peptide ≤0.25 nmol/L) had a significantly reduced glycaemic response to treatment compared to people with normal levels (mean HbA_{1c} reduction, 2 vs 15 mmol/mol [0.2% vs 1.4%]).

6 Similarly, those with autoantibodies had a reduced response (mean reduction, 5 vs 15 mmol/mol [0.5% vs 1.4%]). Even after adjustment for fasting C-peptide, autoantibodies were associated with an 8-mmol/mol (0.7%) reduction in glycaemic response.

Jones AG, McDonald TJ, Shields BM et al (2016) Markers of beta-cell failure predict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. *Diabetes Care* **39**: 250–7

> *"Importantly, the deterioration in glycaemic control did not significantly alter atorvastatin's effect on cardiovascular risk."*

References from commentary

Aithal GP, Thomas JA, Kaye PV et al (2008) Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* **135**: 1176–84

Katsuyama H, Hamasaki H, Adachi H et al (2016) Effects of sodium–glucose cotransporter 2 inhibitors on metabolic parameters in patients with type 2 diabetes: a chart-based analysis. *J Clin Med Res* **8**: 237–43

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