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COMMENTARY

Potential New Therapeutic Implications of Semaglutide: New Colours of the Rainbow?

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ABSTRACT

Semaglutide is a potent glucagon-like peptide 1 receptor agonist for the management of type 2 diabetes mellitus. In addition to this, it has emerging potential clinical implications. First, there is accumulating preliminary data on its potential role in type 1 diabetes mellitus. In this setting, we need to know which patient subgroups may benefit more. Furthermore, its role in non-alcoholic fatty liver and in non-alcoholic steatohepatitis is emerging. Other potential therapeutic implications of semaglutide include kidney disease, Alzheimer disease and pulmonary diseases. Nonetheless, we still need much more information on its long-term efficacy, safety and utility in these new implications before any definitive conclusions may be drawn for everyday practice.

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Key Summary Points

There is emerging evidence on the potential role of semaglutide in type 1 diabetes mellitus.

For this implication, we need to know which subgroups of subjects will benefit more.

There is also accumulating data on the role of semaglutide in non-alcoholic fatty liver and in non-alcoholic steatohepatitis.

Other potential therapeutic implications of semaglutide in kidney disease, in Alzheimer disease and potential secondary benefits on pulmonary diseases are also discussed.

Additional information and confirmation for these options is still needed.

INTRODUCTION

Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are well-established glucose-lowering agents for the management of type 2 diabetes mellitus (T2DM) which also help in weight loss. They showed cardiovascular benefits in high-risk people [1] and, therefore, they are recommended for the treatment of people with T2DM and cardiovascular disease (CVD) risk factors, even before insulin initiation [2]. Specifically, among GLP-1 RAs, semaglutide has shown the highest efficacy in losing weight among people with T2DM and it has also been approved as a weight-lowering agent for people with obesity without diabetes [1]. Moreover, semaglutide showed cardiovascular benefits among people with T2DM with varying cardiovascular risk, reducing CVD events [3].

SEMAGLUTIDE IN T1DM

GLP-1 RAs are usually injectable medications for the management of T2DM and are not approved for subjects with type 1 diabetes mellitus (T1DM). However, the potential role of these agents in T1DM is emerging. Two large, phase 3, randomised, placebo-controlled trials have demonstrated that long-term adjunctive therapy in T1DM with liraglutide caused significant reductions in glycated haemoglobin (HbA_{1c}), insulin doses and body weight, compared with placebo [4, 5]. Of note, the greater HbA_{1c} reduction was observed among people with T1DM with positive C-peptide. However, the increased rates of symptomatic hypoglycaemia and hyperglycaemia with ketosis that have been observed discouraged the use of these agents in T1DM. Clearly, insulin is mandatory in T1DM, but we also need to improve CVD mortality in T1DM. Given that CVD and all-cause mortality remain high in people with T1DM, especially for those with early-onset T1DM, new non-insulin management approaches which reduce hyperglycaemia and have proven CVD benefits in T2DM could be probably tried in T1DM as well [6, 7].

In this context, new data is useful. Recently, Dandona et al. presented data on the efficacy of semaglutide in newly diagnosed individuals with T1DM [8]. Among 10 newly diagnosed adults with T1DM aged between 21 and 39 years with a mean (± standard deviation, SD) HbA_{1c} of 11.7 ± 2.1% and residual C-peptide secretion (0.65 ± 0.33 ng/ml), semaglutide initiation within 3 months of T1DM diagnosis resulted in discontinuation of prandial insulin in all participants within 3 months and elimination of basal insulin in seven patients within 6 months. These findings remained at the end of the 12-month follow-up period [8]. Moreover, improved glycaemic control along with an increase in C-peptide (at 12 months mean HbA_{1c} was 5.7 ± 0.4%, fasting C-peptide increased to a mean of 1.05 ± 0.40 ng/ml) was observed. The initial dose of semaglutide was low, 0.125 mg once weekly, in order to avoid a dangerous hypoglycaemia and the maximum final dose was 0.5 mg weekly. The carbohydrate intake was also restricted [8]. It has been suggested that semaglutide at the early stage of T1DM could probably improve β-cell function, thus extending the honeymoon period and resulting in discontinuation of insulin [8]. However, these interesting and revolutionary preliminary results are based on 10 people only, and so they need to be further confirmed with prospective, randomised clinical trials with larger numbers of people.

Specific T1DM groups, such as people with double diabetes, could probably benefit from a therapy with GLP-1 RAs [9]. People with T1DM with clinical features of insulin resistance are characterised as double diabetes. They are overweight and they usually have a family history of T2DM [9]. Moreover, they rarely achieve optimal glycaemic control despite higher insulin doses and therefore they are at increased risk for micro- and macrovascular complications [9]. On the basis of clinical evidence derived from subjects with T2DM, it has been proposed that people with T1DM with double diabetes could probably benefit from a therapy with GLP-1 RAs regarding CVD, probably with a different dose of GLP-1 RAs [1, 9].

SEMAGLUTIDE IN NON-ALCOHOLIC FATTY LIVER

Emerging evidence points to a beneficial effect of semaglutide on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). These entities are commonly observed in people with T2DM and treatment options are currently insufficient. Given that NAFLD/NASH is associated with increased risk of morbidity and mortality, new treatment options are needed. In a 72-week double-blind phase 2 trial including people with biopsy-confirmed NASH and liver fibrosis of stage F1, F2 or F3 [10], the efficacy and safety of semaglutide once daily compared to placebo was tested. Treatment with semaglutide resulted in a significantly higher percentage of people with NASH resolution than placebo [10]. In another study, semaglutide added to metformin improved NAFLD (diagnosed and staged by ultrasound imaging) in subjects with T2DM after 52 weeks of treatment [11]. Beyond improvement of insulin resistance and liver enzymes, a decrease of fat mass and visceral adipose tissue was observed [11]. A potential cause of this improvement could be weight loss with subsequent improvement of metabolic parameters and CVD risk factors, such as diabetes, hyperlipidaemia and hypertension. Until now, there is no medication indicated for the treatment of NAFDL/NASH, and lifestyle changes are the current suggested interventions [12].

In another double-blind, placebo-controlled phase 2 trial of adults from 38 centres with biopsy-confirmed NASH and NASH-related compensated cirrhosis [12], treatment with 2.4 mg semaglutide once weekly did not significantly improve liver fibrosis and did not achieve NASH resolution vs. placebo after 48 weeks of treatment. However, liver enzymes and liver steatosis, as well as cardiometabolic risk factors (weight, triglycerides, very low-density lipoprotein cholesterol, and HbA_{1c} among subjects with T2DM) were improved, without new safety concerns beyond the already known (nausea, vomiting, diarrhoea) [12]. Finally, in a recent meta-analysis [13], semaglutide use in people with NAFLD or NASH showed a significantly improvement in liver enzymes and metabolic parameters after 24 weeks of treatment. Moreover, liver stiffness was reduced. However, adverse events, namely gastrointestinal and gallbladder diseases, were more frequent than with placebo [13]. Similarly, an ongoing study is investigating the effect of semaglutide in subjects with non-cirrhotic NASH compared with placebo [14]. Whether semaglutide improves liver histology in NASH and fibrosis stage 2 or 3 and reduces the risk of liver clinical events or whether it has an effect on fibrosis-related biomarkers remains to be answered [14].

SEMAGLUTIDE IN NEURODEGENERATIVE DISEASES

More interestingly, semaglutide has been proposed to positively affect aging-related neurodegenerative diseases, such as Alzheimer's disease (AD) [15]. Recently, Wang et al. [16] proposed that semaglutide could promote glucose metabolism in the brain through the SIRT1/GLUT4 (sirtuin 1/glucose transporter 4) signalling pathway and thus have a positive effect in AD mice and cells. T2DM and AD seem to share common pathogenic pathways. Metabolic dysfunction in T2DM may lead to accumulation of β-amyloid peptide (Aβ), a hallmark of AD [16]. Semaglutide has been suggested to play a protective role against Aβ in AD by enhancing autophagy and inhibiting apoptosis [15]. Whether semaglutide has a positive effect on early AD is now being tested in ongoing clinical trials (EVOKE: a randomised double-blind placebo-controlled clinical trial investigating the effect and safety of orally administered semaglutide in subjects with early AD and EVOKE plus) [17].

SEMAGLUTIDE IN KIDNEY DISEASE

Other potential pleiotropic effects of semaglutide are also being investigated. The role of semaglutide in kidney disease is not quite clear, although evidence implies its beneficial effect on renal disease. A nephroprotective effect of

semaglutide in mice has already been proposed [18]. Furthermore, a pooled analysis of SUSTAIN 6 (a trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with T2DM) and PIONEER 6 (a trial investigating the cardiovascular safety of orally administered semaglutide in subjects with T2DM) clinical trials among people with T2DM at high CVD risk suggested that the treatment with semaglutide may reduce the rate of estimated glomerular filtration rate (eGFR) decline compared with placebo [19]. Potential mechanisms suggested for this beneficial effect of semaglutide might be the reduction of oxidative stress, anti-inflammatory effects as well as hemodynamic effects [19]. Whether semaglutide could play a beneficial role in the progression of renal impairment in people with T2DM and chronic kidney disease is currently being investigated in the FLOW trial (effect of semaglutide versus placebo on the progression of renal impairment in subjects with T2D and chronic kidney disease) and remains to be answered [20].

SEMAGLUTIDE IN PULMONARY DISEASES

Of note, semaglutide also possibly has a beneficial effect on pulmonary diseases. In a meta-analysis of 28 randomised controlled trials, the use of semaglutide among people with T2DM and overweight or obesity was linked to an 18% reduced risk of overall respiratory diseases. These findings regarding pulmonary diseases could be considered positive side effects of semaglutide, rather than therapeutic new implications of the agent. Potential mechanisms may include weight loss that improves lung function and improvement of glucose metabolism with reduction of systemic inflammation and improvement of endothelial dysfunction [21]. More importantly, these results need to be further evaluated in future clinical trials with pulmonary disease as the primary outcome [21].

CONCLUSIONS

There are important emerging therapeutic implications of semaglutide. These include a beneficial effect on NAFLD and NASH, which would improve their currently insufficient treatment, as well as a potential role in the therapy of T1DM. However, further research is needed to explore which people with T1DM could benefit from a therapy with GLP-1 RAs. Data suggest that particularly obese people with T1DM and other CVD risk factors could most benefit from such therapy. Taken together, if data are confirmed, the therapy of T1DM, at least at the beginning of the disease, could change, resulting in a tremendous improvement of the quality of life of people with T1DM. Moreover, ongoing studies aim to explore the emerging role of semaglutide in kidney disease and AD. However, although the aforementioned emerging data are very interesting and promising, they are based on initial studies. Therefore, further research is warranted to confirm these potentially new therapeutic implications of semaglutide.

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Declarations

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REFERENCES

1. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes—state-of-the-art. Mol Metab. 2021;46:101102.

2. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65:1925–66.

3. Husain M, Bain SC, Jeppesen OK, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. Diabetes Obes Metab. 2020;22:442–51.

4. Mathieu C, Zinman B, Hemmingsson JU, et al. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE treat-to-target randomized trial. Diabetes Care. 2016;39:1702–10.

5. Ahrén B, Hirsch IB, Pieber TR, et al. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. Diabetes Care. 2016;39:1693–701.

6. Popovic DS, Stoian AP, Papanas N. Glucagon-like peptide-1 receptor agonists for improving cardiorenal outcomes in type 1 diabetes mellitus? Endocrine. 2023;80:232–3.

7. Popovic DS, Koufakis T, Papanas N. The recent trends in all-cause and cardiovascular mortality among people with type 1 diabetes mellitus—success is still far away, and we must do better! Curr Vasc Pharmacol. 2023;21:219–21.

8. Dandona P, Chaudhuri A, Ghanim H. Semaglutide in early type 1 diabetes. N Engl J Med. 2023;389:958–9.

9. Popovic DS, Papanas N. Double diabetes: a growing problem requiring solutions. Exp Clin Endocrinol Diabetes. 2022;130:268–74.

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. Volpe S, Lisco G, Fanelli M, et al. Once-weekly subcutaneous semaglutide improves fatty liver disease in patients with type 2 diabetes: a 52-week prospective real-life study. Nutrients. 2022;14:4673.

12. Loomba R, Abdelmalek MF, Armstrong MJ, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol. 2023;8:511–22.

13. Bandyopadhyay S, Das S, Samajdar SS, Joshi SR. Role of semaglutide in the treatment of nonalcoholic fatty liver disease or non-alcoholic steatohepatitis: a systematic review and meta-analysis. Diabetes Metab Syndr. 2023;17:102849.

14. ClinicalTrials.gov. NCT04822181. https://www.clinicaltrials.gov/study/NCT04822181?cond=NAFLD&term=ESSENCE&rank=1. Last accessed 22 Sept 2023.

15. Chang YF, Zhang D, Hu WM, et al. Semaglutide-mediated protection against Aβ correlated with enhancement of autophagy and inhibition of apotosis. J Clin Neurosci. 2020;81:234–9.

16. Wang ZJ, Li XR, Chai SF, et al. Semaglutide ameliorates cognition and glucose metabolism dysfunction in the 3xTg mouse model of Alzheimer's disease via the GLP-1R/SIRT1/GLUT4 pathway. Neuropharmacology. 2023;240: 109716.

17. ClinicalTrials.gov. NCT04777396. https://clinicaltrials.gov/study/NCT04777396?cond=Alzheimer%20Disease&term=Semaglutide&rank=3. Last accessed 8 Oct 2023.

18. Dalbøge LS, Christensen M, Madsen MR, et al. Nephroprotective effects of semaglutide as mono- and combination treatment with lisinopril in a mouse model of hypertension-accelerated diabetic kidney disease. Biomedicines. 2022;10:1661.

19. Tuttle KR, Bosch-Traberg H, Cherney DZI, et al. Post hoc analysis of SUSTAIN 6 and PIONEER 6 trials suggests that people with type 2 diabetes at high cardiovascular risk treated with semaglutide experience more stable kidney function compared with placebo. Kidney Int. 2023;103:772–81.

20. ClinicalTrials.gov. NCT03819153. https://clinicaltrials.gov/study/NCT03819153?cond=Renal%20disease&term=Semaglutide&rank=5. Last accessed 8 Oct 2023.

21. Yu M, Wang R, Pei L, et al. The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: a meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2023;15:164.