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Letters to the editor

Semaglutide for the treatment of post transplantation diabetes mellitus in patients following liver transplantation is safe and effective

Dear Editor,

Post-Transplant Diabetes Mellitus (PTDM) is a frequent consequence of solid organ transplantation with an incidence of over 30% [1]. Similar to the findings in non-transplant settings, PTDM has been shown to be associated with an increased risk of cardiovascular disease and infectious complications [1]. With PTDM reduced patient survival and accelerated graft loss have been reported. Risk factors for PTDM include many of the immunosuppressive medications themselves as well as the well-known risk factors for type 2 diabetes mellitus (T2DM), including obesity, the metabolic syndrome and Metabolic-dysfunction Associated Steatotic Liver Disease (MASLD)/ Metabolic-dysfunction Associated Steatohepatitis (MASH). Treatment options for management of PTDM are limited with regards to the availability of strong clinical evidence.

Semaglutide is a once-weekly GLP-1RA injection and approved for treatment of adults with T2DM and is known for its high potency in reducing HbA1c, weight and blood pressure. The more frequent adverse events associated with the use of GLP-1RA were gastrointestinal reactions, such as nausea, vomiting, and diarrhea. Most events are mild to moderate in severity and lead to treatment discontinuation in less than 5% of patients. Contraindications for GLP-1RA treatment are history of chronic or idiopathic acute pancreatitis, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min per 1·73 m^2), and heart failure (New York Heart Association class IV).

We present here the data of 10 patients with PTDM following liver transplantation, without any contraindications for the use of GLP-1RA, treated with semaglutide 0.5 mg once weekly. The primary etiology following liver transplantation was MASLD and MASH in all patients, with 7 patients suffering from hepatocellular carcinoma. Patients in this case report received semaglutide as part of usual care and not in trial settings. Therefore, ethical approval was waived by the local Ethics Committee of the LUMC. The case report adhered to the latest version of the declarations of Helsinki.

In 10 patients (mean±SEM, age 54±5 years), 6 months treatment with semaglutide resulted in a significant decrease of median HbA1c from 66.1 (32.2-80.2) to 48.0 (28.7-58.8) mmol/mmol (P<0.05). Blood pressure, liver enzymes, and lipids improved, but not significantly (see Table 1). A significant decrease in weight (mean 111 ± 3 to 101 ± 2 kg, P<0.05) was established. BMI and waist circumference decreased significantly, from 34.9 ± 1.2 to 31.1 ± 0.8 (P<0.05) and from 123.2 ± 3.3 to 100.7 ± 2.5 (P<0.05), respectively. There were no differences in trough levels and $AUC_{0\text{-}3h}$ of tacrolimus before and after start of semaglutide. One patient suffered from nausea the day following injection; this could be ameliorated by temporarily reducing the dosage.

In this small observational study, we suggest that GLP-1RA could be an effective treatment for PTDM. This may be especially the case in patients with tacrolimus, since this, widely used, immunosuppressant induces loss of human beta-cell maturity and beta-cell failure through activation of the BMP/SMAD signaling pathway. Glucagon-like peptide 1 receptor agonists (GLP-1RA) are a relatively new class of injectable drugs used in the treatment of T2DM [1]. GLP-1RAs mimic endogenous GLP-1, stimulating insulin release from the pancreas, suppressing glucagon secretion, slowing gastric emptying and increasing satiety. In addition, GLP-1RA have been demonstrated to have beneficial effects on MASLD/MASH [2]. These agents lack hepatic metabolism and hence have limited drug–drug interactions, but they do slow gastric emptying, potentially impairing immunosuppressant absorption. The results of our observational study confirm the previously reported potential benefits for patients after liver transplantation. Chow et al. reported in a small cohort study of 23 liver transplantation recipients a significant weight loss after 17 months. Metabolic effects and tacrolimus levels were not studied. Although most patients in this study were suffering from PTDM, changes in HbA1c after treatment were not reported [3]. Another study, focusing on the safety and efficacy of semaglutide, GLP-1 infusion improved HbA1c levels and body weight in renal transplant recipients without changes in renal graft function markers [4].

In conclusion, semaglutide seems effective, well-tolerated and safe in the treatment of PTDM in patients following liver transplantation. Therefore, GLP-1RA should be considered in patients with PTDM, especially in those with MASH cirrhosis as transplant

Table 1
Baseline characteristics and results following 6 months semaglutide.

	T=0	T= 6 months	*P*
Male/Female	7/3	-	-
Age (years)	54 ± 5	-	-
Weight (kg)	111 ± 3	101 ± 2	<0.05
Body Mass Index (kg/m^2)	34.9 ± 1	31.1 ± 1	<0.05
Systolic Blood Pressure (mm Hg)	132 ± 8	124 ± 7	NS
Diastolic Blood Pressure (mm Hg)	81 ± 4	75 ± 4	NS
HbA1c (mmol/mmol)	66.1 (32.2-80.2)	48.0 (28.7-58.8)	<0.05
Total Cholesterol (mmol/L)	5.4 ± 0.3	5.1 ± 0.2	NS
ALT (U/L)	68 ± 8	50 ± 5	NS
AST (U/L)	53 ± 5	46 ± 4	NS
Creatinine (μmol/L)	95 ± 8	100 ± 8	NS
Tacrolimus trough levels (μg/L)	4.2 ± 1	4.4 ± 1	NS
Tacrolimus $AUC_{0\text{-}3}$ (μg*h/L)	142 ± 15	151 ± 18	NS

Values are means ± SE or median (Range). ALT, alanine transaminase; AST, aspartate transaminase.

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indication, since recurrence rates are high. These findings need to be confirmed in larger studies.

Author contributions

Daphne Bot: acquisition of data, analysis and interpretation of data, and drafting of the manuscript; Bart van Hoek: critical revision of the manuscript for important intellectual content and statistical analysis; Maarten Tushuizen: study concept and design, critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical or material support, and study supervision.

Declaration of competing interest

None.

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Daphne Bot*
Bart van Hoek
Maarten E. Tushuizen
Department of Dietetics, Leiden University Medical Center, Leiden, the Netherlands
Department of Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands

*Corresponding author.
E-mail address: d.bot@lumc.nl (D. Bot).