Oral presentation 50

Oral semaglutide improves postprandial glucose and lipid metabolism and delays first-hour gastric emptying in subjects with type 2 diabetes

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Background and aims: Subcutaneous (s.c.) administration of semaglutide, a glucagon-like peptide-1 analogue, improves postprandial glucose (PPG) and postprandial lipid (PPL) metabolism and delays first-hour gastric emptying (GE) in subjects with obesity and without type 2 diabetes (T2D). In this trial, the effects of a novel once-daily oral formulation of semaglutide on postprandial metabolism and GE was investigated in subjects with T2D.

Materials and methods: In this double-blind, cross-over trial, male and female subjects with T2D were randomised to a treatment sequence of two 12-week periods with oral semaglutide/placebo or placebo/oral semaglutide, separated by a washout period of 5–9 weeks. Oral semaglutide was dose-escalated to steady-state at 14 mg via two 4-week dosing steps of 3 mg and 7 mg. At the end of each treatment period, PPG metabolism was assessed following a standardised breakfast, PPG and PPL metabolism were assessed following a standardised fat-rich breakfast, and GE was assessed (by a paracetamol absorption test) following a standardised lunch. Primary endpoint was serum glucose AUC from 0 to 5 hours ($AUC_{0–5h}$) after start of standardised breakfast.

Results: A total of 15 subjects were randomised (13 male/2 female, mean age 58.2 years, mean HbA_{1c} 6.9%, mean BMI 30.8 kg/m^2), two of whom withdrew before completing the trial. After 12 weeks of treatment, fasting levels of glucose were significantly lower and C-peptide levels significantly higher with oral semaglutide vs. placebo. After a standardised breakfast, postprandial glucose ($AUC_{0–5h}$) and mean postprandial increments in glucose (mean incremental area under the 0–5-hour curve [$iAUC_{0–5h}$]) were significantly lower with oral semaglutide vs. placebo (**Table**). Postprandial glucagon was also significantly reduced with oral semaglutide. No significant differences were shown in fasting or postprandial serum insulin levels. Similar results for glucose metabolism were observed after a standardised fat-rich breakfast. Fasting levels of total, LDL, and VLDL-cholesterol, triglycerides (TG) and apolipoprotein B48 were significantly lower with oral semaglutide vs. placebo after 12 weeks of treatment. In addition, postprandial TG ($AUC_{0–8h}$) and mean postprandial increments in TG ($iAUC_{0–8h}$) were significantly lower for oral semaglutide vs. placebo. Postprandial VLDL-cholesterol and apolipoprotein B48 were also significantly reduced with oral semaglutide. During the first hour after a meal, GE was delayed (31% decrease in paracetamol $AUC_{0–1h}$) with oral semaglutide vs. placebo, which could explain at least part of the effect on PPG and PPL.

Conclusion: Oral semaglutide significantly improved fasting and postprandial glucose and lipid metabolism, and delayed GE during the first postprandial hour, results consistent with those seen with s.c. semaglutide.

Table. Fasting and postprandial glucose and lipid metabolism endpoints after 12 weeks of treatment

Oral semaglutide/placebo:	**ETR (95% CI)**		**ETD (95% CI)**	**Relative difference**
Standardised breakfast	**Fasting**	**Postprandial ($AUC_{0–5h}$)**	**Mean postprandial increment ($iAUC_{0–5h}$)**	
Glucose (mmol/L)	0.78 (0.70, 0.87)*	0.71 (0.63, 0.81)*	−1.25 (−2.04, −0.45)*	−86.8%
Insulin (pmol/L)	1.24 (0.86, 1.79)	0.91 (0.75, 1.12)	−44.02 (−96.86, 8.82)	−30.9%
Glucagon (pg/mL)	0.76 (0.55, 1.06)	0.71 (0.59, 0.85)*	−2.22 (−11.23, 6.79)	−76.3%
C-peptide (nmol/L)	1.20 (1.01, 1.42)*	0.99 (0.86, 1.13)	−0.18 (−0.44, 0.08)	−25.0%
Standardised fat-rich breakfast	**Fasting**	**Postprandial ($AUC_{0–8h}$)**	**Mean postprandial increment ($iAUC_{0–8h/8h}$)**	
Glucose (mmol/L)	0.77 (0.73, 0.82)*	0.77 (0.68, 0.87)*	−0.32 (−1.11, 0.47)	400.0%
Insulin (pmol/L)	1.47 (1.11, 1.96)*	1.00 (0.83, 1.22)	−33.96 (−76.95, 9.03)	−48.9%
Glucagon (pg/mL)	0.81 (0.64, 1.03)	0.77 (0.67, 0.89)*	−5.06 (−15.90, 5.77)	−36.3%
C-peptide (nmol/L)	1.25 (1.05, 1.48)*	1.01 (0.89, 1.15)	−0.18 (−0.32, −0.04)*	−48.6%
Triglycerides (mmol/L)	0.81 (0.72, 0.92)*	0.76 (0.64, 0.91)*	−0.36 (−0.68, −0.04)*	−32.1%
Free fatty acids (mmol/L)	0.95 (0.77, 1.17)	1.01 (0.82, 1.25)	0.03 (−0.02, 0.09)	−60.0%
VLDL (mmol/L)	0.80 (0.67, 0.95)*	0.79 (0.68, 0.93)*	−0.08 (−0.21, 0.06)	−32.0%
Apolipoprotein B48 (g/L)	0.75 (0.58, 0.98)*	0.70 (0.57, 0.85)*	−0.004 (−0.008, 0.000)	−44.4%

Relative difference: estimated treatment difference/estimated mean for placebo x 100%. *p<0.05. ETD, estimated treatment difference; ETR, estimated treatment ratio; iAUC, mean postprandial increment in AUC after start of meal; VLDL, very-low-density lipoprotein.

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