Journal of Parenteral and Enteral Nutrition
Volume XX Number X
Month 201X 1–10
© 2016 American Society
for Parenteral and Enteral Nutrition
DOI: 10.1177/0148607116672265
jpen.sagepub.com
hosted at
online.sagepub.com

Effect of Liraglutide Treatment on Jejunostomy Output in Patients With Short Bowel Syndrome: An Open-Label Pilot Study

Mark Hvistendahl, MSc[1]; Christopher Filtenborg Brandt, MD[1]; Siri Tribler, MD[1]; Rahim Mohammad Naimi, MD[1]; Bolette Hartmann, PhD[2]; Jens Juul Holst, MD[2]; Jens Frederik Rehfeld, MD[3]; Mads Hornum, MD[4]; Jens Rikardt Andersen, MD[5]; Birthe Merete Henriksen, MD[6]; Per Brøbech Mortensen, MD[1]; and Palle Bekker Jeppesen, MD[1]

Abstract

Background: An impaired hormonal "ileo-colonic brake" may contribute to rapid gastric emptying, gastric hypersecretion, high ostomy losses, and the need for parenteral support in end-jejunostomy short bowel syndrome (SBS) patients with intestinal failure (IF). Liraglutide, a glucagon-like peptide 1 receptor agonist, may reduce gastric hypersecretion and dampen gastric emptying, thereby improving conditions for intestinal absorption. *Materials and Methods:* In an 8-week, open-label pilot study, liraglutide was given subcutaneously once daily to 8 end-jejunostomy patients, aged 63.4 ± 10.9 years (mean ± SD) and with small bowel lengths of 110 ± 66 cm. The 72-hour metabolic balance studies were performed before and at the end of treatment. Food intake was unrestricted. Oral fluid intake and parenteral support volume were kept constant. The primary end point was change in the ostomy wet weight output. *Results:* Liraglutide reduced ostomy wet weight output by 474 ± 563 g/d from 3249 ± 1352 to 2775 ± 1187 g/d (P = .049, Student t test). Intestinal wet weight absorption tended to increase by 464 ± 557 g/d (P = .05), as did urine production by 765 ± 759 g/d (P = .02). Intestinal energy absorption improved by 902 ± 882 kJ/d (P = .02). *Conclusion:* Liraglutide reduced ostomy wet weight output in end-jejunostomy patients with SBS-IF and increased their intestinal wet weight and energy absorption. If larger, randomized, placebo-controlled studies confirm these effects, it adds to the hypothesis that many ileo-colonic brake hormones in conjunction may be involved in the process of intestinal adaptation. By identification of key hormones and addressing their potential synergistic effects, better treatments may be provided to patients with SBS-IF. This trial was registered at clinicaltrialsregister.eu as 2013-005499-16. *(JPEN J Parenter Enteral Nutr. XXXX;xx:xx-xx)*

Keywords

short bowel syndrome; gastroenterology; parenteral nutrition; nutrition; diarrhea; research and diseases

Clinical Relevancy Statement

Liraglutide proves to be safe and tolerable as treatment for jejunostomy patients with intestinal failure with efficacy in reducing wet weight output and improving intestinal wet weight and energy absorption. Results from this study suggests a clinical relevancy to conduct a larger liraglutide study, to better elucidate the potential for treatment of patients with short bowel syndrome, not only for price-competitive reasons but also for its effect as an "ileo-colonic-brake" hormone.

Introduction

In end-jejunostomy patients with short bowel syndrome (SBS), high ostomy losses following surgery are consequences of the reduced mucosal surface area and an impaired neuroendocrine "ileo-colonic brake" causing accelerated gastrointestinal (GI) motility,[1] gastric and intestinal hypersecretion,[2] poor functional adaptation, and consequently reduced absorptive capacity.[3] In patients with SBS with intestinal failure (IF), who are characterized by their inability to compensate orally for ostomy losses, parenteral support (PS) is lifesaving by preserving nutritional homeostasis, body composition, and function. Glucagon-like peptide (GLP) 2 and the receptor agonist teduglutide were the first ileo-colonic brake hormones to be tested in a clinical setting.[4–6] Following successful phase 2[7] and phase 3 studies,[8–10] teduglutide has now been marketed for this indication in the United States and in Europe. Other ileo-colonic brake factors, such as GLP-1[11,12] and peptide YY,[13] have been suggested to have beneficial effects in patients with SBS. Indeed, small, short-term, clinical pilot studies in patients with SBS have demonstrated a beneficial role of the treatment with native GLP-1,[14] the GLP-1 receptor agonist exanatide,[15] and even additive effects when combining GLP-1 and GLP-2 treatments.[14] Therefore, the primary aim of this pilot study was to evaluate the effect of liraglutide, a GLP-1 receptor agonist,

Downloaded from pen.sagepub.com by guest on October 4, 2016

on the reduction of jejunostomy wet weight output in patients with SBS-IF. Secondary end points were changes in intestinal wet weight absorption, intestinal energy and macronutrient absorption, electrolyte absorption, urine production, PS volume, body composition, and quality of life (QoL) in relation to liraglutide treatment.

Liraglutide is already marketed for the treatment of type 2 diabetes. Safety profiles have been evaluated thoroughly in the diabetes population, and liraglutide seems to be without carcinogenic risk, making it a potential safe drug in the treatment of the SBS-IF population.

The current annual cost of teduglutide is approximately US$300.000 per patient.[16]

Since Denmark has the highest incidence of patients with IF in the world, estimated at 500 patients in 5 million inhabitants and of whom roughly half have SBS-IF,[17] the introduction of this high-cost treatment would annually account for 6% of the total national budget for all hospital medicines.[18] In the frame of a limited budget in a tax-paid national health system, the implementation of this treatment would have significant, detrimental effects on other national healthcare services.

Although reducing intestinal malabsorption, ostomy and fecal losses, and the need for PS, our cost-benefit considerations have suggested that alternative, price-competitive treatments to teduglutide should be explored. In this respect, the cost of liraglutide is 250 times cheaper than teduglutide at around US$1200 per patient per year.

Materials and Methods

The investigator-initiated protocol was approved by the Scientific-Ethical Committee of the Capital Region of Denmark (protocol 2013-624), the Danish Health and Medicine Authority, and the Good Clinical Practice unit in Copenhagen, Denmark. The study, registered with the Danish Data Protection Agency (Journal 30-1138) and at clinicaltrialsregister.eu (EudraCT 2013-005499-16), was conducted according to the Helsinki Declaration II, and written informed consent was obtained from all participants prior to enrollment. The study was performed from March to June 2014, at the Department of Medical Gastroenterology, Rigshospitalet, Denmark. All authors had access to the study data and reviewed and approved the final manuscript.

Patients

All patients who were eligible for inclusion were aged >18 or <90 years, had an end-jejunostomy, and were continuously dependent on PS for at least 6 months prior to enrollment, with a stable body weight of <5% fluctuation. The underlying causes leading to SBS were Crohn's disease, intestinal volvulus, surgical complication, or mesenteric infarction. Habitual dosing of concomitant medication was required to be stable 4 weeks before enrollment. Exclusion criteria included pregnancy; previous or active cancer of any kind; active inflammatory bowel diseases; significant renal (>2.5 times upper normal limit of serum creatinine), hepatic, or cardiac diseases as evaluated by the investigator; or intake of glutamine or growth factors 3 months before the study.

Study Design

In this single-center, open-label, proof-of-concept pilot study, 8 patients were admitted for two 72-hour metabolic balance studies before and at the end of 8 weeks of liraglutide treatment (Figure 1). The primary and secondary end points as well as explorative effect parameters were assessed as changes from the first and second admission. Patients were instructed and supervised in all study procedures but were encouraged to behave as close to normal life as possible. The full trial period was scheduled with specific study procedures (Supplemental Table S1). On the first day of admission, a personalized 24-hour oral fluid program was created based on the preferences of the patient. The 72-hour metabolic balance study began in the morning of day –2 and ended on day 1. Treatment with liraglutide started on day 1 and continued throughout the second metabolic balance study (days 54–56). During the metabolic balance studies, oral fluid intake and PS were intended to be kept constant, but the participants were allowed to vary their solid unrestricted dietary intake. Every 2 weeks of liraglutide treatment, the patients were instructed to measure 48-hour urine at home while adhering to their personalized, oral fluid

From the [1]Department of Medical Gastroenterology CA-2121, Rigshospitalet, Copenhagen, Denmark; [2]Department of Biomedical Sciences, NNF Center of Basic Metabolic Research, Copenhagen, Denmark; [3]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark; [4]Department of Nephrology, Rigshospitalet, Copenhagen, Denmark; [5]Department of Nutrition, Exercise, and Sports, University of Copenhagen, Copenhagen, Denmark; and the [6]Department of Diagnostic Radiology, Rigshospitalet, Copenhagen, Denmark.

Financial disclosure: None declared.

Conflicts of interest: None declared.

Received for publication June 20, 2016; accepted for publication September 8, 2016.

Corresponding Author:
Mark Hvistendahl, MSc, Department of Medical Gastroenterology CA-2121, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Email: mark.hvistendahl@regionh.dk

Downloaded from pen.sagepub.com by guest on October 4, 2016

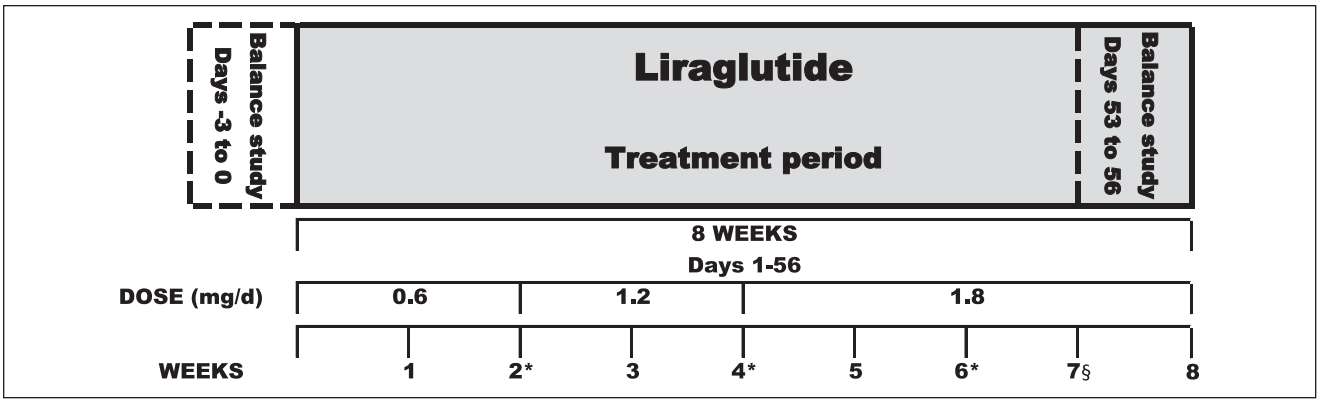

Figure 1. Study design. *The 48-hour urine measurement at home. §Four days prior to the second balance study at trial day 50, the parenteral support was fixed to match the parenteral support program during the baseline balance study.

schedule. Since the collections were done at home, the compliance to the prescribed oral fluid intake was ensured by regular telephone reminder calls from the study staff to the patients included in the study. An increased urine production compared with baseline would be interpreted as an improved hydration status. If 48-hour urine volume was 10% larger than baseline urine production, this would allow for a PS volume reduction. However, a clinical evaluation and a discussion between the patient and the investigating physician could offset the PS reduction. Patients, who reduced their PS volume in relation to liraglutide treatment, were obligated to return to their baseline PS program at the beginning of the eighth treatment week (day 50). This was done to ensure that the 2 metabolic balance studies were identical regarding provision of PS.

Liraglutide Dosing and Compliance

Liraglutide (Victoza; Novo Nordisk, DK-2880 Bagsværd, Denmark) is a recombinant, dipeptidyl peptidase-4 resistant GLP-1 receptor agonist, developed for the treatment of type 2 diabetes. Study drug was acquired from the local hospital pharmacy in ready-to-use 6-mg/mL prefilled pens. It was subcutaneously injected in the abdomen or thigh every morning. A starting dose of 0.6 mg/d for 2 weeks was followed by a dose of 1.2 mg/d for another 2 weeks. During the last 4 weeks, a 1.8-mg/d dose was given. The dose escalation could be modified based on a patient-physician telephone interview, with focus on the potential side effects; however, the doses used for this study compare with the general recommendation for type 2 diabetes. Liraglutide has recently been approved as a pharmacological aid to lose weight, but higher doses (3.0 mg) are used for this indication.[19] Compliance was evaluated by comparing a patient-filled study drug diary with the returned liraglutide pens at the end of the trial.

The 72-Hour Metabolic Balance Study

The 72-hour metabolic balance study quantified urine volume, ostomy wet weight output, and dietary intake based on duplicate meals. Energy content was measured by bomb calorimetry, nitrogen by Kjeldahl's method, lipid by a modified Van de Kamer titration technique, carbohydrate by Englyst's method, sodium and potassium by flame photometry, and calcium and magnesium by atomic absorptiometry. Further details of the metabolic balance study technique have been described before in detail.[20]

Body Weight, Body Composition, Resting Energy Expenditure, and Vital Signs

During each admission, body composition was measured by dual-energy X-ray absorptiometry (DEXA; Norland XR-800 densitometer, CooperSurgical, Trumbull, CT) and basal metabolic rate (BMR) by indirect calorimetry (Oxycon Pro; Jaeger, Hoechberg, the Netherlands). Vital signs were measured daily and included body weight, body temperature, pulse, and blood pressure.

Hormone Profiles and Gastric Emptying

On the first day of the balance study (day –2), the patients were given a standardized meal[4] after an overnight fasting of oral intake (regular PS was allowed the night before, but infusions were terminated at least 2 hours before experiments). Peripheral venous blood was collected 15 minutes before and 0, 2, 5, 10, 15, 20, 30, 45, 60, 120, and 180 minutes after completion of the meal. Patients were kept "nil-by-mouth" during the collection. The methods to determine concentration of GLP-1,[21] GLP-2,[22] glucagon,[23] glucose-dependent insulinotropic peptide (GIP),[24] gastrin,[25] and cholecystokinin (CCK)[26] have been described elsewhere. A paracetamol absorption test[27] was done by ingesting 2 g paracetamol dissolved in 200 mL water between blood sample 0 and 2 minutes. We compared the area under the curve (AUC), maximal concentration (C_{max}), and time to peak (T_{max}) before and after liraglutide treatment.

Downloaded from pen.sagepub.com by guest on October 4, 2016

Plasma Citrulline

A blood sample was taken during each 72-hour metabolic balance study after an oral overnight fasting period. Concentration of plasma citrulline was determined by a high-pressure liquid chromatography.[28]

Statistical Analysis

Data analyses were performed using Statistical Analysis Software (version 9.4; SAS Institute, Cary, NC). Unless specified otherwise, continuous data are described as mean ± standard deviation. All comparisons were performed using a paired 2-sided Student *t* test, with $P < .05$ to determine significance. A Pearson's correlation coefficient was used to test for correlations.

Results

Patient Demographics

Eight end-jejunostomy patients with SBS-IF were included and completed the study (Table 1). At baseline, systolic blood pressure was 133 ± 22 mm Hg, diastolic blood pressure was 74 ± 14 mm Hg, and resting heart rate was 66 ± 8 bpm. Serum creatinine was 113 ± 64 μmol/L (reference value, 50–90 μmol/L), plasma-bilirubin was 10.1 ± 5.9 μmol/L (reference value, 5–25 μmol/L), and plasma-C-reactive protein was 2 ± 1.8 mg/L (reference value, <1 mg/L).

Compliance and Adverse Events

All patients injected more than 97% of the prescribed liraglutide. Seven patients followed the scheduled dose escalation time points of liraglutide and reached the 1.8-mg/d dose by the end of the fourth treatment week. These patients remained on this dose for the rest of the treatment period. One patient (patient 5, Table 1) experienced side effects in the form of nausea, edema, and nose bleeding when increasing the liraglutide dose to 1.2 mg/d. Hence, this patient was kept on the well-tolerated 0.6-mg/d dose throughout the remaining study period. Adverse events during treatment were transient, mainly seen immediately in the days following liraglutide up-titration, and tended to subside. Six patients reported a sensation of reduced appetite in relation to liraglutide treatment. Four patients reported nausea. A single episode of vomiting was reported by 3 patients, and weight loss >5% of baseline body weight was reported in 1 patient. None of these events led to discontinuation of liraglutide. No serious adverse events were associated with the use of liraglutide (Supplemental Table S2).

PS Adjustments

When planning the study, it was intended that the 48-hour urine measurements at 2-week intervals could be used to downregulate patients' PS volume. However, 3 patients (patients 1, 4, and 5; Table 1) reported immediate effect of liraglutide a few hours after initiating treatment. In these patients, based on their self-reported feeling of fluid retention and swelling of extremities, deviation from the protocol PS reduction algorithm occurred (see Method section). The PS volume was reduced by 1.3 L/d (range, 0.3–3.1 L/d) within the first week of treatment for these patients. Four patients remained on the same PS program, and 1 patient took 0.4 L/d more saline after the first week.

The 72-Hour Metabolic Balance Study

Individual data on the absolute amount of dietary intake, ostomy output, the calculated absolute absorption (intake minus output), and relative absorption (absolute absorption/intake × 100%) of wet weight, electrolytes, energy, and macronutrients before and after 8 weeks of treatment with liraglutide are presented in Figure 2 and summarized in Supplemental Table S3.

Eight weeks of liraglutide treatment reduced the ostomy wet weight output by 474 ± 563 g/d ($P = .049$; from 3249 ± 1352 g/d to 2775 ± 1187 g/d). This corresponded to a relative wet weight ostomy output reduction of 13% ± 16%. The oral fluid intake was intended to be kept constant during both balance studies. Indeed this was the case, as the difference in the oral fluid intake only differed by 9 ± 57 g/d ($P = .68$; 1801 ± 660 g/d vs 1810 ± 691 g/d, respectively). The weight of the spontaneous, unrestricted dietary intake of solid food of the patients was constant and thus numerically only 19 ± 136 g/d less after liraglutide treatment ($P = .71$; 941 ± 270 g/d at baseline vs 923 ± 227 g/d after liraglutide treatment). The total weight of the dietary intake of solids and fluids was also equal during both metabolic balance studies ($P = .83$; 2743 ± 824 g/d vs 2733 ± 838 g/d, respectively). The patients' subjective feeling of appetite, measured by a 0- to 10-cm visual analogue scale (VAS),[29] tended to be reduced after liraglutide treatment by 2.3 ± 3.3 cm ($P = .09$).

On average, patients were net secretors with wet weight absorption of −506 ± 1347 g/d at baseline, which increased to −42 ± 1119 g/d after liraglutide treatment. Consequently, there was a numerical increase in intestinal wet weight absorption of 464 ± 557 g/d ($P = .05$). This increase in intestinal wet weight absorption resulted in an increase in urine production. A significant correlation between the reduction in ostomy wet weight output and the increase in urine output was seen ($P = .006$). At baseline, the urine production was 1543 ± 532 g/d, which increased to 2308 ± 1138 g/d after liraglutide treatment. The absolute increase was 765 ± 759 g/d ($P = .02$), and the relative increment was 50% ± 42%. As intended, the PS volume was maintained constant in both metabolic balance study periods (3.7 ± 2.2 L/d vs 3.7 ± 1.9 L/d, respectively; $P = .79$). The relative increment in the 48-hour urine production collected during the second, fourth, and sixth treatment weeks was 22%, 20%, and 15% compared with baseline, respectively.

Downloaded from pen.sagepub.com by guest on October 4, 2016

Table 1. Patient Demographics and Disease-Specific and Baseline Absorptive Characteristics.

Patient No.	Sex/Age, y/ Cause of SBS-IF	BMI, kg/m^2	Small Bowel Length, cm	Calculated BMR,[a] kJ/d	Measured BMR, kJ/d	Wet Weight Dietary Intake, kg/d	Wet Weight Ostomy Output, kg/d	Parenteral Support, L/d	Energy Dietary Intake, kJ/d	Energy Ostomy Output, kJ/d	Energy Parenteral Intake, kJ/d	Duration of HPN, y	Concomitant Medication of Antisecretory/ Antimotility Agents
1	F/57/CD	19.1	70	5145	5359	3.7	4.4	3.2	10,823	9638	6662	24.2	Esomeprazole (IV)
2	M/66/Mes Inf	23.5	190	5994	5503	3.0	1.6	0.9	7238	3497	0	6.7	Pantoprazole (tablet) Codeine (mixture)
3	M/74/Mes Inf	22.6	30	6486	5648	3.6	5.0	5.2	15,181	12,741	8120	4.8	Esomeprazole (IV) Codeine (mixture)
4	F/55/volvulus	19.2	100	5150	5306	1.9	3.9	8.0	9038	6771	6120	4.8	Esomeprazole (IV)
5	F/70/CD	26.5	30	5477	6633	1.2	2.9	4.0	8447	7697	4853	10.9	Esomeprazole (IV)
6	M/42/CD	19.0	150	6203	5778	3.1	4.3	3.4	12,216	7445	5857	5.5	Omeprazole (tablet) Codeine (tablet)
7	M/66/UC	25.4	200	7790	8348	2.9	1.4	2.0	10111	1977	664	13.8	Esomeprazole (IV) Codeine (mixture)
8	M/72/Compl	31.1	110	6467	5095	2.6	2.5	3.1	8126	5467	2727	4.6	Esomeprazole (IV) Codeine (mixture)
Mean ± SD	63 ± 11 years	23.3 ± 4.3	110 ± 66	6089 ± 875	5959 ± 1071	2.7 ± 0.8	3.2 ± 1.4	3.3 ± 2.2	10,147 ± 2584	6904 ± 3390	4375 ± 2936	9.4 ± 6.9	

BMI, body mass index; BMR, basal metabolic rate; CD, Crohn's disease; Compl, complication to surgery; HPN, home parenteral nutrition; IF, intestinal failure; IV, intravenous; Mes Inf, mesenteric infarction; SBS, short bowel syndrome; UC, ulcerative colitis.
[a]Calculated by the Harris-Benedict formula.

Downloaded from pen.sagepub.com by guest on October 4, 2016

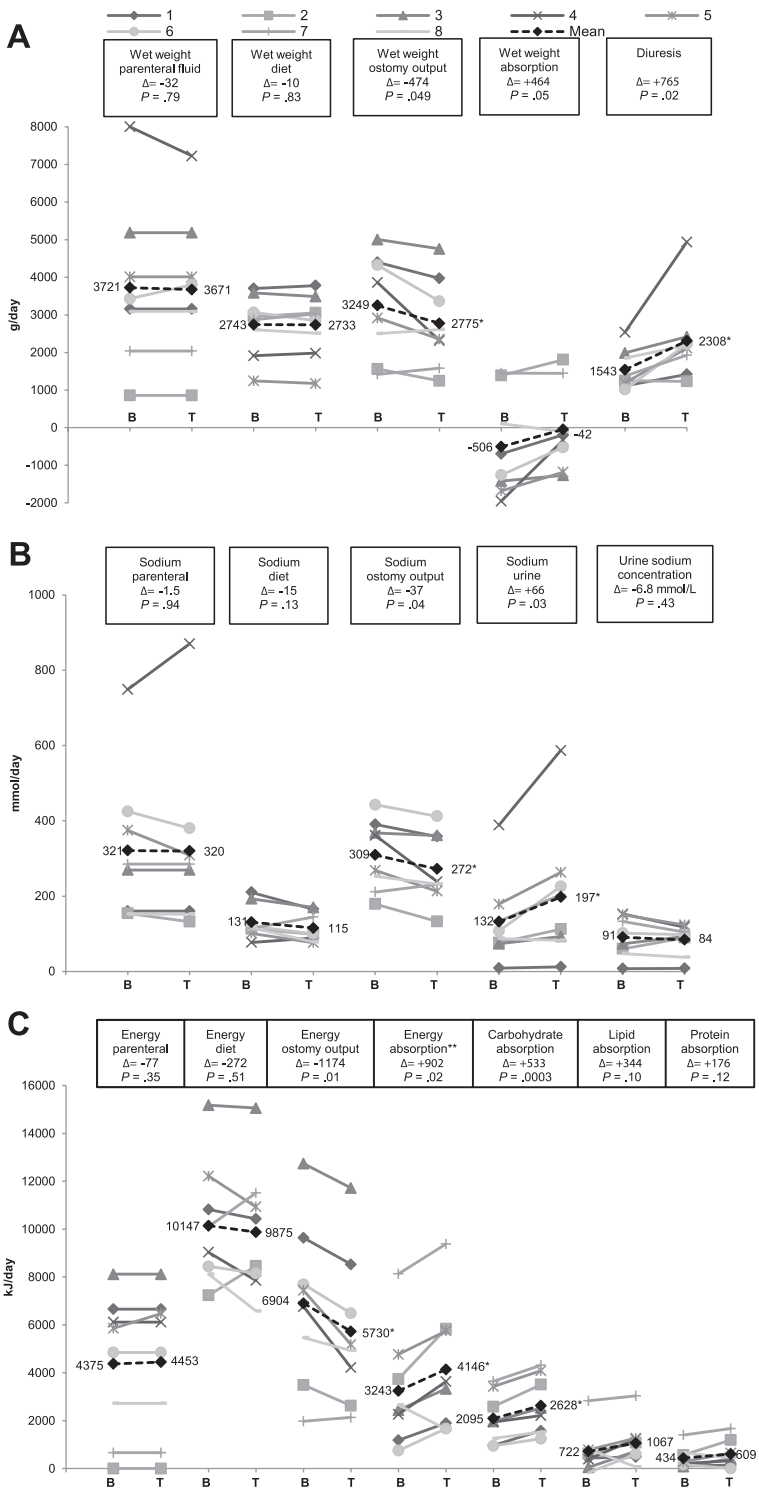

Figure 2. The 72-hour metabolic balance study results for each patient. (A) Changes in wet weight parenteral fluid, wet weight diet, wet weight ostomy output, and wet weight absorption and diuresis before and after liraglutide treatment. (B) Changes in sodium in parenteral energy, dietary intake, ostomy output, and urine and urine sodium concentration before and after liraglutide treatment. (C) Changes in parenteral energy, dietary energy intake, ostomy energy output, intestinal energy absorption, carbohydrate absorption, lipid absorption, and protein absorption before and after liraglutide treatment. Dashed line = mean. B, baseline; T, treatment. *$P < .05$ (Student *t* test). **Energy measured by bomb calorimetry.

Downloaded from pen.sagepub.com by guest on October 4, 2016

Accordingly, this resulted in adjustment in PS volume by −5%, −15%, and −14%. The dietary fluid intake was constant during urine measurement periods.

Electrolytes

The oral sodium intake tended to be 15 ± 25 mmol/d lower in relation to liraglutide treatment (P = .13). After treatment, the total amount of sodium excreted in the ostomy output decreased by 37 ± 42 mmol/d (P = .04; from 309 ± 94 mmol/d to 272 ± 94 mmol/d). No significant changes in the absolute (22 ± 50 mmol/d; P = .26) or the relative (7% ± 85%; P = .81) absorption of sodium were seen in relation to liraglutide treatment. The effects on absorption of potassium, calcium, and magnesium in relation to liraglutide were minor (Supplemental Table S3). However, the increase in urinary excretion of sodium (66 ± 68 mmol/d; P = .03) and magnesium (1 ± 1 mmol/d; P = .01) was significant in relation to liraglutide treatment, whereas the potassium (10 ± 15 mmol/d; P = .12) and calcium excretion (1 ± 1 mmol/d; P = .22) did not reach statistical significance. Thus, since the urinary sodium concentration was constant (Figure 2B), the increased urinary sodium excretion was a consequence of an increased urine volume.

Creatinine

Serum creatinine remained unchanged when comparing before and after liraglutide treatment (113 ± 64 µmol/L and 119 ± 83 µmol/L, respectively; P = .49). The 24-hour urinary creatinine excretion increased by 1.0 ± 1.1 mmol/d from 10.9 ± 3.1 mmol/d to 11.9 ± 3.3 mmol/d after liraglutide treatment (P = .03). However, creatinine clearance (($creatinine_{urine}$/$creatinine_{serum}$) × ($volume_{urine}$/time (h) × 60 min/h)) did not change (87 ± 39 mL/min at baseline and 93 ± 44 mL/min after liraglutide treatment; P = .37).

Energy and Macronutrients

The unrestricted oral energy intake remained constant during both metabolic balance studies (10,147 ± 2584 kJ/d and 9875 ± 2694 kJ/d at baseline and after liraglutide treatment, respectively; P = .51). The energy content in the ostomy output was reduced by 1174 ± 877 kJ/d (P = .01), from 6904 ± 3390 kJ/d to 5730 ± 3165 kJ/d. Thus, the absolute energy absorption increased by 902 ± 882 kJ/d (P = .02), corresponding to a relative increase in intestinal energy absorption of 9% ± 9% (P = .03). The distribution of the unrestricted dietary macronutrient intake did not differ during the metabolic balance studies. The relative absorption of carbohydrate increased from 53% ± 23% to 62% ± 21% (P = .002), lipid absorption tended to increase from 20% ± 24% to 30% ± 24% (P = .09), and the relative protein absorption tended to increase from 24% ± 25% to 31% ± 28% (P = .15). Due to financial limitations in a nonsponsored, investigator-initiated study, plasma glucose or insulin was not measured. HbA1c did not change following liraglutide treatment with a baseline value of 6.0 ± 0.6 mmol/L and 5.9 ± 0.8 mmol/L after treatment (P = .32).

Body Composition, Bone Mineral Content, and Body Weight

The small numerical reduction in body weight of 0.62 ± 1.8 kg was not significant (P = .36). No significant changes in body composition evaluated by DEXA measurements were detected (Supplemental Table S4).

Postprandial Hormone Profile

The AUC of the postprandial hormone profile of GLP-1, GLP-2, glucagon, GIP, CCK, and gastrin was not changed by liraglutide treatment (Supplemental Tables S5–S10; Supplemental Figure S1). Unfortunately, funds were not obtained for measurements of pharmacokinetics or antibodies to liraglutide in this investigator-initiated, non-company-sponsored study.

Gastric Emptying and Absorption of Paracetamol

The $AUC_{0\text{-}180\ min}$ of plasma-paracetamol did not change in relation to liraglutide treatment (12.9 ± 5.7 min·mmol/L vs 12.9 ± 5.2 min·mmol/L; P = .94). No significant changes in the paracetamol C_{max} (0.098 ± 0.039 mmol/L vs 0.104 ± 0.045 mmol/L; P = .31) or T_{max} (44 ± 34 minutes vs 47 ± 36 minutes; P = .63) were seen comparing the baseline and liraglutide treatment period (Supplemental Table S11 and Supplemental Figure S2).

Assessment of Mucosal Growth

Plasma citrulline concentrations were unchanged when comparing baseline with liraglutide treatment values (33.5 ± 30.9 µmol/L vs 34.5 ± 25.2 µmol/L; P = .82).

Quality of Life

No significant changes in the overall QoL were seen in relation to liraglutide treatment. Detailed results from the SF-36 and the SBS-QoL questionnaire can be found in Supplemental Table S12 and Supplemental Table S13, respectively.

Discussion

Over the past decade, clinical research has confirmed the role of exogenous treatment with ileo-colonic brake hormones in the intestinal rehabilitation of patients with SBS. Because GLP-2 showed the most significant effects on growth of the intestinal mucosa in preclinical studies, the initial focus from the pharmaceutical industry was directed toward this peptide.[30]

Downloaded from pen.sagepub.com by guest on October 4, 2016

Following U.S. Food and Drug Administration and European Medicines Agency approval, teduglutide has become commercially available for the treatment of patients with SBS. However, the pathophysiological features contributing to the lack of structural and functional adaptation following intestinal resection in patients with SBS may involve not only the reduction in intestinal surface area but also changes in GI secretions and motility. In this respect, exogenous provision of other ileocolonic brake hormones could contribute by restoring a feedback adaptation, which favors a delaying of the accelerated GI motility and diminishing proximal GI hypersecretion, thereby improving conditions for intestinal absorption in patients with SBS. Positive effects on the "gut-liver axis" and enterohepatic circulation, which is disturbed in these patients, could also be speculated.[31–33]

By employing complementary strategies to target GI motility, secretion, and adaptation,[34] we have previously shown, in short-term, 72-hour metabolic infusion studies, that both native GLP-1 and GLP-2, as monotherapy and as a combination, reduce ostomy losses in patients with SBS.[14] Apart from promoting insulin secretion, GLP-1 and liraglutide inhibit gastric acid secretion, reduce gut motility, and decrease appetite.[35] By expanding the half-life from <2 minutes in the native peptide to 13 hours in the dipeptidyl peptidase-4–resistant GLP-1 analogue, liraglutide is suitable for once-daily subcutaneous treatment. Plasma half-lives of peptide hormones are currently a "hot topic" when developing new therapeutic pharmaceuticals for treatment within the SBS indication. No one thus far probably knows if a GLP-1 spike is preferable or if a large AUC (obtained from prolonging half-life) is more potent regarding treatment effects.

This open-label, 8-week pilot study indeed suggests that liraglutide, like teduglutide, has a place in the limited treatment armamentarium available for these patients with SBS-IF, who have a significantly impaired QoL.[36] Liraglutide significantly reduced the ostomy wet weight output by 474 ± 563 g/d (P = .049), which was the primary end point of the study. The onset of the effect was immediate, and in 3 patients, the increased intestinal wet weight absorption mandated an early reduction in PS volume within days to reduce fluid retention. Two of 8 patients (patients 5 and 7; Table 1) had participated in a native GLP-1 infusion study conducted by our research team.[14] However, patient 7 in this study was in fact a nonrespondent to liraglutide with regard to the primary and secondary end points; therefore, these 2 patients do not seem to be the main drivers of the positive results.

When performing an analysis of covariance (ANCOVA) with the 2 balance study periods as groups, fecal wet weight output (the primary end point) as the dependent variable, and the small bowel length as the covariate, we found that reduction in ostomy output could not be predicted by the small bowel length (P = .849).

Although a direct comparison between studies is difficult because of a significant patient and effect heterogeneity in patients with SBS and the low number of patients in these studies, the proabsorptive effect of liraglutide seems to be lower than the effect of teduglutide (788 ± 551 g/d) on wet weight absorption demonstrated in a similar phase 2 metabolic study performed in our department.[7] However, the effects of liraglutide on wet weight absorption translated into a significant improvement in fluid balance, resulting in an increase in urine production of 765 ± 759 mL/d, which was on the same order of magnitude (680 ± 535 mL/d) as the changes demonstrated in the phase 2 teduglutide study. A significant correlation between the reduction in wet weight excretion and an increase in urine production was seen. In contrast to the findings in relation to teduglutide treatment, liraglutide treatment induced a significant increase in the absolute intestinal energy absorption of 902 ± 882 kJ/d (P = .02). The physiological cause of this beneficial effect on intestinal macronutrient absorption is currently unknown, but we recommend that larger future studies with a more robust study design and more elaborate methods should characterize the effects of GLP-1 and GLP-2 analogues on mucosal growth as well as GI motility, secretion, blood flow, intestinal barrier function, and the effects of these hormones on the gut-liver axis and the enterohepatic circulation. No significant changes were observed in body weight, body composition, or the measured BMR over the 8 weeks of liraglutide treatment. Although no significant decreases in body weight were found in relation to liraglutide treatment in this rather short-term study, it will be of paramount importance to monitor potential changes body weight in long-term studies. A tendency toward a reduction in the sense of appetite was indeed demonstrated in the VAS, but the spontaneous oral energy and macronutrient intake were unaffected by liraglutide. Actually, 3 patients perceived it beneficial that liraglutide diminished their constant, insatiable, and unpleasant sensation of thirst and hunger. Whether these sensations of reduced hunger and the regulation of appetite are mediated directly by central effects of liraglutide or possibly mediated indirectly through effects on gastric emptying, intestinal motility, or GI secretions is unknown. Patient interviews suggests that constant hunger may be an unpleasant sensation in selected patients with SBS-IF (unpublished data), which may be as bothersome as pain and nausea. For these patients, liraglutide seems effective to relieve them from this feeling, which in these patients seems to be perceived just as unpleasant as the experience of a high ostomy output.

Plasma citrulline has been suggested to represent a biomarker of enterocyte mass.[37] Liraglutide has previously been shown to increase mucosal mass and the wet weight of the intestine in mice.[38] Plasma citrulline was unaffected in patients with SBS-IF who were treated with liraglutide in this study. No biopsies were obtained in this explorative pilot study to investigate effects on mucosal growth. The potentially limited effect of liraglutide treatment on intestinal mucosal growth may actually be desirable, if a link between the development of intestinal neoplasia and hyperplasia should exist.[39] Moreover, the

Downloaded from pen.sagepub.com by guest on October 4, 2016

acceptable safety profile of liraglutide has been proven in the postmarketing surveillance in a high number of patients with diabetes in contrast to the more limited safety data existing in the lower numbers of patients treated with teduglutide. Although based on findings in these few patients in an open-label pilot-study, it was noticeable that liraglutide treatment was rarely associated with abdominal distention, pain, or signs of bowel obstruction.

No significant differences in gastric emptying were demonstrated by the paracetamol absorption test. C_{max} and T_{max} remained unchanged by liraglutide treatment. This is in contrast to the narratives from most patients who noticed that the time from oral intake to the appearance of ostomy output was prolonged. Three patients independently described in their study diary that liraglutide allowed them to participate in a full dinner sequence without having to interrupt the meal and go to the bathroom to empty their stoma bag. The paracetamol absorption method has been criticized as a suitable test for gastric emptying when a mixed meal of both fluid and solid is ingested, illustrating rather the food-drug interaction on absorption.[40] Appropriate scintigraphy measurements should be employed in future studies to address effects of liraglutide on gastric emptying in patients with SBS.

No changes in the postprandial hormone secretions could be detected in relation to liraglutide treatment. As anticipated, the endogenous secretion of GLP-1 and GLP-2 was low in these patients with an end-jejunostomy.[14] Again, in a small pilot study, caution should be taken to exclude the possibility that effects of liraglutide still could be mediated through an interaction with other secretory hormones of the GI tract, such as gastrin. However, in this particular respect, all patients with SBS in this study received proton pump inhibitors, since long-term proton pump inhibitor treatment is common practice in Denmark.

Teduglutide has been demonstrated to be efficacious, but the current high cost may be prohibitive for its use in many countries. Furthermore, safety concerns have been raised regarding the potential long-term, detrimental effects of the growth-promoting effects of teduglutide. Current evidence in this respect relies on findings in a limited number of patients with SBS. In contrast, liraglutide is a novel, low-cost, readily available drug with a proven acceptable safety profile in patients with diabetes. Given the noncontrolled, open-label nature of this liraglutide study in patients with SBS, a placebo effect cannot be excluded. We also acknowledge that, given the limited study size, a comparison with teduglutide in patients with SBS may be inappropriate. However, because of the low cost and profit on GLP-1 receptor agonists, the limited size of the orphan SBS patient population, and the high cost of phase 2 and 3 development programs, it is a huge challenge to conduct larger trials to consolidate the efficacy of liraglutide or other GLP-1 analogues and achieve regulatory approval for treatment of this indication. However, our results suggest that more ileo-colonic brake hormones should be considered for future treatments of patients with SBS, and development of "dual-agonist peptides"[41] could be the next appropriate step forward in this respect.

Acknowledgment

We thank Jette Christiansen, Dorte Christensen, Birgitte Schou, and Andreas Haltorp for technical assistance.

Statement of Authorship

M. Hvistendahl, C. F. Brandt, S. Tribler, J. R. Andersen, P. Brøbech Mortensen, and P. B. Jeppesen contributed to the conception/design of the research; M. Hvistendahl, C. F. Brandt, S. Tribler, R. M. Naimi, B. Hartmann, J. J. Holst, J. F. Rehfeld, M. Hornum, J. R. Andersen, B. M. Henriksen, P. Brøbech Mortensen, and P. B. Jeppesen contributed to acquisition, analysis, or interpretation of the data; M. Hvistendahl and P. B. Jeppesen drafted the manuscript; and M. Hvistendahl, C. F. Brandt, S. Tribler, R. M. Naimi, B. Hartmann, J. J. Holst, J. F. Rehfeld, M. Hornum, J. R. Andersen, B. M. Henriksen, P. Brøbech Mortensen, and P. B. Jeppesen critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work and read and approved the final manuscript.

Supplementary Material

Tables S1–S13 and Figures S1 and S2 are available online at http://jpen.sagepub.com/supplemental.

References

1. Nightingale JM, Kamm M, van der Sijp JR, et al. Disturbed gastric emptying in the short bowel syndrome: evidence for a "colonic brake." *Gut*. 1993;34:1171-1176.
2. Buxton B. Small bowel resection and gastric acid hypersecretion. *Gut*. 1974;15:229-238.
3. Nightingale JM, Lennard-Jones JE, Gertner DJ, Wood SR, Bartram CI. Colonic preservation reduces need for parenteral therapy, increases incidence of renal stones, but does not change high prevalence of gall stones in patients with a short bowel. *Gut*. 1992;33:1493-1497.
4. Jeppesen PB, Hartmann B, Hansen BS, Thulesen J, Holst JJ, Mortensen PB. Impaired meal stimulated glucagon-like peptide 2 response in ileal resected short bowel patients with intestinal failure. *Gut*. 1999;45:559-563.
5. Jeppesen PB, Hartmann B, Thulesen J, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. *Gastroenterology*. 2001;120:806-815.
6. Jeppesen PB, Lund P, Gottschalck IB, et al. Short bowel patients treated for two years with glucagon-like peptide 2 (GLP-2): compliance, safety, and effects on quality of life. *Gastroenterol Res Pract*. 2009;2009:425759.
7. Jeppesen PB, Sanguinetti EL, Buchman A, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut*. 2005;54:1224-1231.
8. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut*. 2011;60:902-914.
9. Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology*. 2012;143:1473-1481.
10. O'Keefe SJD, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in

Downloaded from pen.sagepub.com by guest on October 4, 2016

patients with short bowel intestinal failure. *Clin Gastroenterol Hepatol*. 2013;11:815-823.
11. Schirra J, Goke B. The physiological role of GLP-1 in human: incretin, ileal brake or more? *Regul Pept*. 2005;128:109-115.
12. Schirra J, Nicolaus M, Roggel R, et al. Endogenous glucagon-like peptide 1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. *Gut*. 2006;55:243-251.
13. Wettergren A, Maina P, Boesby S, Holst JJ. Glucagon-like peptide-1 7-36 amide and peptide YY have additive inhibitory effect on gastric acid secretion in man. *Scand J Gastroenterol*. 1997;32:552-555.
14. Madsen KB, Askov-Hansen C, Naimi RM, et al. Acute effects of continuous infusions of glucagon-like peptide (GLP)-1, GLP-2 and the combination (GLP-1+GLP-2) on intestinal absorption in short bowel syndrome (SBS) patients: a placebo-controlled study. *Regul Pept*. 2013;184:30-39.
15. Kunkel D, Basseri B, Low K, et al. Efficacy of the glucagon-like peptide-1 agonist exenatide in the treatment of short bowel syndrome. *Neurogastroenterol Motil*. 2011;23:739-e328.
16. Herper M. Inside the pricing of a $300,000-a-year drug. *Forbes*. http://www.forbes.com/sites#/sites/matthewherper/2013/01/03/inside-the-pricing-of-a-300000-a-year-drug/#29d24ce13c28. Accessed August 8, 2016.
17. Brandt C, Tribler S, Hvistendahl M, Staun M, Brøbech P, Jeppesen P. A single-center, adult chronic intestinal failure cohort analyzed according to the ESPEN endorsed recommendations, definitions and classifications [published online October 20, 2015]. *JPEN J Parenter Enteral Nutr*.
18. Amgros. Sygehusmedicin 2015. Reg Laegemiddelorganisation. 2015:1-12. http://www.amgros.dk/media/45580/sygehusmedicin-2015.pdf. Accessed October 29, 2015.
19. Ladenheim EE. Liraglutide and obesity : a review of the data so far. *Drug Des Dev Ther*. 2015;9:1867-1875.
20. Jeppesen PB. Intestinal insufficiency and failure. *Dan Med Bull*. 2003;50:238-261.
21. Orskov C, Rabenhoj L, Wettergren A, Kofod H, Holst JJ. Tissue and plasma-concentrations of amidated and glycine-extended glucagon-like peptide I in humans. *Diabetes*. 1994;43:535-539.
22. Hartmann B, Johnsen AH, Orskov C, Adelhorst K, Thim L, Holst JJ. Structure, measurement, and secretion of human glucagon-like peptide-2. *Peptides*. 2000;21:73-80.
23. Holst JJ. Evidence that glicentin contains the entire sequence of glucagon. *Biochem J*. 1980;187:337-343.
24. Kuhre RE, Wewer Albrechtsen NJ, Hartmann B, Deacon CF, Holst JJ. Measurement of the incretin hormones: glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. *J Diabetes Complications*. 2015;29:445-450.
25. Stadil F, Rehfeld JF. Determination of gastrin in serum. *Scand J Gastroenterol*. 1973;8:101-112.
26. Rehfeld JF. Accurate measurement of cholecystokinin in plasma. *Clin Chem*. 1998;44:991-1001.
27. Medhus AW, Lofthus CM, Bredesen J, Husebye E. Gastric emptying: the validity of the paracetamol absorption test adjusted for individual pharmacokinetics. *Neurogastroenterol Motil*. 2001;13:179-185.
28. Demacker PNM, Beijers AM, van Daal H, Donnelly JP, Blijlevens NMA, van den Ouweland JMW. Plasma citrulline measurement using UPLC tandem mass-spectrometry to determine small intestinal enterocyte pathology. *J Chromatogr B Anal Technol Biomed Life Sci*. 2009;877:387-392.
29. Raben A, Tagliabue A, Astrup A. The reproducibility of subjective appetite scores. *Br J Nutr*. 1995;73:517-530.
30. Drucker DJ, Ehrlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci U S A*. 1996;93:7911-7916.
31. Visschers RGJ, Luyer MD, Schaap FG, Olde Damink SWM, Soeters PB. The gut-liver axis. *Curr Opin Clin Nutr Metab Care*. 2013;16:576-581.
32. Pereira-Fantini PM, Lapthorne S, Joyce SA, et al. Altered FXR signaling is associated with bile acid dysmetabolism in short bowel syndrome-associated liver disease. *J Hepatol*. 2014;61:1115-1125.
33. Erpecum KJ, Van Schaap FG. Intestinal failure to produce FGF19: a culprit in intestinal failure–associated liver disease? *J Hepatol*. 2015;62:1231-1233.
34. Jeppesen PB. Pharmacologic options for intestinal rehabilitation in patients with short bowel syndrome. *JPEN J Parenter Enteral Nutr*. 2014;38:45S-52S.
35. Rotondo A, Janssen P, Mulè F, Tack J. Effect of the GLP-1 analog liraglutide on satiation and gastric sensorimotor function during nutrient-drink ingestion. *Int J Obes*. 2013;37:693-698.
36. Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. *Gut*. 1999;44:844-852.
37. Crenn P, Lucas CC, Thuiller F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. *Gastroenterology*. 2000;119:1496-1505.
38. Kissow H, Hartmann B, Holst JJ, et al. Glucagon-like peptide-1 (GLP-1) receptor agonism or DPP-4 inhibition does not accelerate neoplasia in carcinogen treated mice. *Regul Pept*. 2012;179:91-100.
39. Koehler JA, Baggio LL, Yusta B, et al. GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. *Cell Metab*. 2015;21:379-391.
40. Bartholomé R, Salden B, Vrolijk MF, et al. Paracetamol as a post prandial marker for gastric emptying, a food-drug interaction on absorption. *PLoS One*. 2015;10(9):1-9.
41. Dalbøge LS, Almholt DLC, Neerup TSR, Vrang N, Jelsing J, Fosgerau K. The novel GLP-1-gastrin dual agonist ZP3022 improves glucose homeostasis and increases β-cell mass without affecting islet number in db/db mice. *J Pharmacol Exp Ther*. 2014;350:353-360.

Downloaded from pen.sagepub.com by guest on October 4, 2016