Carol Rees Parrish, R.D., M.S., Series Editor

Growth Hormone, Glutamine and Glucagon-like Peptide 2 in Short Bowel Syndrome

Palle Bekker Jeppesen

By definition, intestinal failure prevails when oral compensation is no longer feasible and parenteral support is necessary to maintain nutritional equilibrium. In the past, research has mainly focused on "making the most of what the short bowel syndrome patient still has" by optimizing remnant intestinal function through dietary interventions, anti-diarrheals and anti-secretory agents. However, in recent years, pharmacological hormonal therapy has been introduced aiming to enhance the spontaneous morphological and functional changes seen after intestinal resection, the so-called, "adaptive processes." This review describes selected factors responsible for these changes in the adaptive process and presents results of clinical trials that employ growth hormone, glutamine or glucagon-like peptide (GLP)–2 in order to facilitate a condition of hyperadaptation in patients with short bowel.

INTRODUCTION

Rapid gastric emptying, gastric hypersecretion and intestinal malabsorption are key findings in patients with short bowel syndrome (SBS) (1–2). Fecal losses of fluids, electrolytes, and nutrients will, if not compensated for by increased oral intake (hyperphagia), lead to diminished body stores, subclinical and eventually clinical nutritional deficiencies. By definition, intestinal failure prevails when oral compensation is no longer feasible and parenteral nutrition (PN) support is necessary to maintain nutritional equilibrium (3) (Figure 1). Large fecal losses and the need for PN impair the quality of life in SBS patients (4). In addition, PN is associated with complications such as recurrent infections, increased risk of venous thrombosis and parenteral nutrition (PN) associated liver failure (4–6). In the past, research has mainly focused on "making the most of what the short bowel syndrome (SBS) patient still has" by optimizing remnant intestinal function through dietary interventions (7), anti-

Palle Bekker Jeppesen, M.D., Ph.D., Department of Medical Gastroenterology CA-2121, Rigshospitalet, Blegdamsvej, Copenhagen, Denmark.

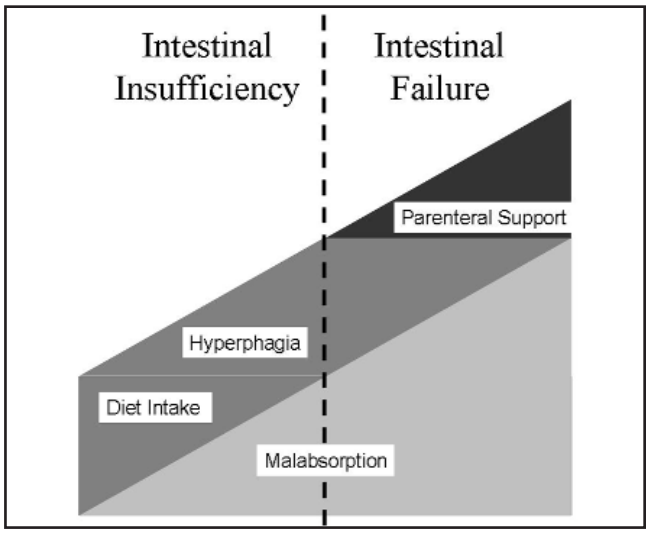

Figure 1. The spectrum of short bowel syndrome.

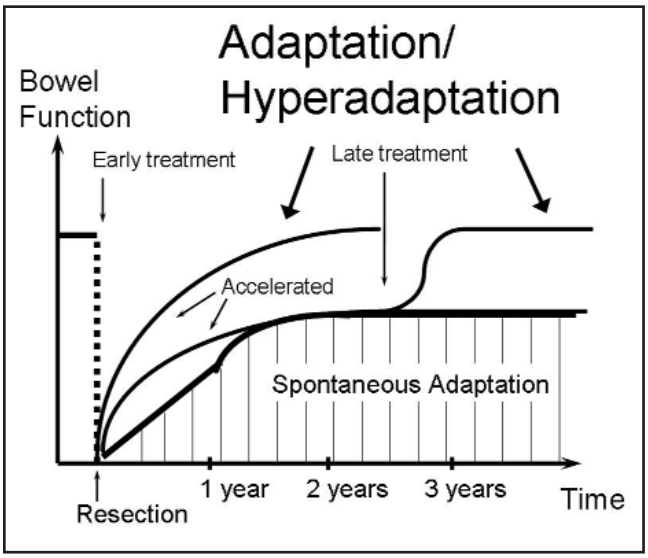

Figure 2. Schematic presentation of intestinal adaptation. SA ~Spontaneous Adaptation, AA ~ Accelerated Adaptation, HA ~ Hyperadaptation, AHA ~ Accelerated Hyperadaptation.

diarrheals and anti-secretory agents (8). However, in recent years pharmacological hormonal therapy has been introduced aiming to enhance the spontaneous morphological and functional changes seen after intestinal resection, the so-called adaptive processes. This review describes selected factors responsible for the morphological and functional changes in adaption and presents results of clinical trials that employ growth hormone, glutamine or glucagon-like peptide (GLP)–2 in order to facilitate a condition of hyperadaptation in short bowel patients (Figure 2).

INTESTINAL ADAPTATION

The term "intestinal adaptation" may be applied to the progressive recovery from intestinal insufficiency or failure that follows a loss of intestinal length. Morphological, biochemical, hormonal, and neural systems appear to be involved in intestinal adaptation. Data supporting this are mainly derived from animal studies in which the process of compensatory hyperplasia is extraordinary in some species. Thus, it is important to realize that an overall translation of this data to humans cannot be presumed. In the rat, the ileal villi grow to their fully adapted height within weeks. In humans, this process has been demonstrated in patients with jejunoileal bypass operations after which villous heights increased 80% and reached a plateau in one-year (9). However, in other studies intestinal hypertrophy has not been found in humans (10,11). At most, animal and human resection studies describe jejunal changes in those having short bowel with colon-in-continuity. Thus, conclusions drawn may not hold for patients left with only a jejunostomy.

There are only a few longitudinal studies that have been performed in humans with respect to functional changes following intestinal resection. However, it is the clinical experience that short bowel patients with an intact colon show improved absorption with time, whereas patients with jejunostomy do not (1). Althausen, et al described diminished fecal water losses and increased absorption of glucose, galactose, amino acids, and fats during the time after extensive small bowel resection in two patients with preserved colon (12). The jejunal absorptive capacity of short bowel patients has also been examined by segmental perfusion techniques, and the absorption of glucose, water, and sodium was increased per unit of length compared to that of control subjects (13). Ileostomy adaptation does occur within a period of six months; however, this response is lacking in "ostomates" who have had an ileal resection (14). Thus, the preservation of the terminal ileum and the colon seems to be of sig-

(continued on page 40)

(continued from page 38)

Table 1
Summary of Studies and Results

Citation	*Drug/ dose (mg/kg/d)*	*Days*	*Diet*	*Glutamine i.v./p.o*	*ORS*	*Pts with CD (n/total)*
Byrne (22), (28)	GH/0.14	21	HCLF	.42 g/kg/d or .62 g/kg/d	Yes	1/8
Scolapio (24), (32)	GH/0.14	21	HCLF	0 g/d and .63 g/kg/d	No	7/8
Szkudlarek (25), Jeppesen (33)	GH/0.12	28 (+5)	Habitual	5.2 ± 2.2 g/d and 28 ± 2 g/d	No	6/8
Byrne (28)	a) Placebo	28	HCLF	0 g/d and 30 g/d	Yes	1/9
"	b) GH/0.10	28	HCLF	0 g/d and 30 g/d	Yes	2/16
"	c) GH/0.10	28	HCLF	0 g/d and 30 g/d	Yes	5/16
"	a) vs. c)	—	—	—	—	—
Seguy (27)	GH//0.05	21	Habitual	0 g/d and 0 g/d	No	3/12
Ellegaard (26)	GH/0.024	56	Habitual	0 g/d and 0 g/d	No	8/8
Jeppesen (30)	GLP-2/0.013	35	Habitual	No	No	6/8
Jeppesen (31)	Teduglutide/ 0.03-0.15	21	Habitual	No	No	11/16

GH ~ Growth Hormone. HCLF ~ High Carbohydrate Low Fat. ORS ~ Oral Rehydration Solutions, CD ~ Crohn's Disease, Δ ~ compared to baseline. NM ~ Not Measured. NR ~Not Reported. n.s. ~not significant.

nificant importance in the adaptive response following intestinal resection. The time required to maximum adaptation is not certain. Studies of calcium absorption have suggested that it may continue for more than two years (15), although the main adaptive response seems to take place within a few months.

It seems that the increase in intestinal function with time following intestinal resection may simply be related to the morphologically demonstrated villous hyperplasia, because only minor changes in the activity of specific intestinal disaccharidases, hydrolases, enterokinase, and sodium-potassium-ATPase have been demonstrated (16). However, the demonstration of an up-regulation of colonic PepT1 independent of changes in mucosal surface area also suggests a functional adaptation (11). Functional adaptation may also involve a trend towards normalization of gastric hypersecretion, gastric emptying, and rapid intestinal transit reported in the SBS (17).

The signals and precise mechanisms that trigger the hyperplastic adaptive response after small bowel resection are not completely understood. The main factors thought to influence intestinal adaptation are exposure of the remaining mucosa to luminal nutrients and non-nutritive components of the diet (such as non-digestible starch), various factors related to the provision of enteral feedings (e.g., pancreatic-biliary secretions and enteric hormones), and possibly various growth factors and hormones not secreted from the intestine.

HORMONAL STIMULATION OF INTESTINAL ADAPTATION

Two major hormonal candidates—growth hormone and GLP-2—have been employed in the treatment of patients with SBS. The studies described in this review are presented in Table 1. Actually, the FDA in the United States has approved both growth hormone and

Remnant small bowel (cm)	*Colon in continuity (n/total)*	*Δ PN volume (kg/d)*	*Δ Wet weight Abs (kg/d)*	*Δ PN energy (kcal/d)*	*Δ Energy Abs (kcal/d)*	*Δ Body weight (kg)*	*Edema*
37 ± 27	8/8	Fixed	0.7	Fixed	141	5.4	NR
71 ± 23	2/8	Fixed	NR, n.s.	Fixed	NM	3.0	100%
104 ± 37	4/8	Fixed	–0.3, n.s.	Fixed	–72 n.s.	1.0	100%
62 ± 31	8/9	–0.54	NM	–376	NM	–0.7	44%
84 ± 50	15/16	–0.84	NM	–620	NM	1.2	94%
68 ± 33	13/16	–1.10	NM	–822	NM	1.8	94%
—	—	–0.56, $p < 0.05$	NM	-445, $p<0.001$	NM	2.5, n.s.	—
48 ± 11	9/12	Fixed	NR, n.s.	NM	102	2.4	0%
125 ± 29	5/10	Fixed	NR, n.s.	Fixed	NR, n.s.	2.3	0%
30 – 180	0/8	Fixed	0.42, $p < 0.05$	Fixed	105, $p = 0.09$	1.2, $p = 0.01$	0%
25 – 150	6/16	Fixed	0.74, $p < 0.05$	Fixed	189, n.s.	0.9, $p = 0.12$	44%

glutamine as drugs to be used for this indication. However, currently, hormonal therapy in short bowel patients should be considered experimental and is only recommended in research settings.

A wide spectrum of considerations should be taken into consideration when introducing or evaluating studies using exogenous adaptive agents. Some of these are presented in Table 2.

The overall aim of any given treatment in short bowel patients is to improve their quality of life. Quality of life may be estimated by the use of standardized questionnaires; however, at present, it is difficult to establish which numerical improvement on the disease-specific inflammatory bowel disease questionnaire or non-disease specific sickness impact profile scales that would justify the introduction of a new treatment.

The main focus of research performed in short bowel has been to increase absolute intestinal absorption. However, in most studies assessing the effects of pharmacological interventions, the dietary intake has been fixated during balance studies. Therefore, in contrast to these "physiological studies," the effect on dietary intake of these interventions, and thereby on the true spontaneous absolute absorption, has not been established in vivo in the everyday settings of the individual patient. For instance, pharmacological agents could (i.e., due to an effect on gastric emptying) induce a sensation of satiety, thereby also reducing the overall dietary intake. Alternatively, pharmacological agents could promote appetite and increase overall absorption merely by increasing oral intake.

Even in studies in which a true increase in intestinal absorption has been established, the outcomes may differ in individual patients. It is possible that an improved energy and macronutrient balance in some patients may lead to changes in body weight and composition and, in others, to a change in basal metabolic

Table 2
Considerations When Evaluating Studies Using Exogenous Adaptive Agents

- Which type of SBS patients were selected for the study (colon vs. no colon, time from last resection, time on HPN, cause of SBS e.g. Crohn's disease vs. mesenteric infarction, previous use of exogenous adaptive agents)?
- Were dietary modifications or oral rehydration solutions part of the intervention?
- Were anti-diarrhea and anti-secretory agents maximized?
- If tapering of parenteral support is considered as an endpoint, was there supportive evidence that the patients studied demonstrated a need for parenteral support in the first place?
- Were nutritional and fluid balance studies performed before and after the intervention?
- Was the hydrational status of the patients evaluated by reporting changes in oral intake, parenteral support, urine production, and presence of edema?
- Did the intervention change renal function evaluated by e.g. creatinine clearance?
- Did the intervention change dietary intake?
- Did the intervention change body composition?
- Was the nutritional status of the patients evaluated?
- Was muscle function evaluated (exercise test, hand grip, etc.)?
- Did the study include direct or indirect measurements of changes in bowel morphology (biopsies, plasma citrulline, etc.)?
- Did the study include other measurements of intestinal absorption (d-Xylose absorption, measurements of mannitol/lactulose absorption, etc.)?
- Did the study include measurements of changes in quality of life?
- Did the study include measurements of treatment satisfaction?
- Did the study consider financial issues in relation to introduction of the new treatment?
- Did the study register adverse events in relation to treatment and disclose potential risks involved in the treatment?

rate, whereas some may increase their physical activity. Improved fluid and electrolyte balance may allow for increased perspiration and production of urine and sweat. Thus, to get a more precise picture of the individual short bowel patient, each of these parameters ideally should be measured in long-term experiments.

Because of the vast requirements and efforts to conduct such experiments, the ability to wean patients from PN has been used as a surrogate marker of an effect of given treatments. However, unless the pretreatment need for PN has been verified, such an endpoint is invalid. Most home PN patients can be reduced in PN for shorter or longer periods, especially patients with colon-in-continuity. They may even compensate for these changes in energy, macronutrient, fluid, and electrolyte balances.

Citrulline has a unique metabolism that has prompted suggestion that plasma citrulline level could be a reliable marker of gut function (18). Several studies have found a strong and significant correlation between postabsorptive plasma or serum citrulline concentration and remnant small bowel length (19,20). A threshold plasma citrulline of 19 umol/l has even been suggested as a reliable biomarker of the probability of PN weaning (18). However, results concerning the relationship between citrulline and intestinal absorptive function are less impressive (21). Thus, citrulline may reflect remnant intestinal mucosal mass, but it may not necessarily demonstrate how well the patient will utilize this mass. Furthermore, it is unlikely that citrulline concentration reflects the various aspects of gut absorption since it not only involves small bowel mucosa, but also the trophic effects of pancreatic-biliary secretions, gut motility and colonic absorption. Finally, given the alternative, making every effort to free a patient of PN should always be attempted vs relying on a lab value that might suggest a patient might not be able to successfully wean off of PN.

In spite of these difficulties, the search for factors to enhance bowel adaptation and increase the assimilation of macronutrients and absorption of wet weight, thereby decreasing the need for PN, is intensive. Although, the evidence is weak, a comparison of the results obtained in short-term clinical trials employing growth hormone and GLP-2 is presented.

(continued from page 42)

EFFECTS OF GROWTH HORMONE, GLUTAMINE, AND GLUCAGON-LIKE PEPTIDE 2 IN CLINICAL STUDIES

Wet-weight Absorption

Byrne and Wilmore were the first to introduce the concept of "bowel rehabilitation" with the introduction of high dose (0.14 mg/kg/day) growth hormone, glutamine, and a high complex carbohydrate diet in the treatment of short bowel patients (22). The wet-weight absorption increased ~0.7 kg/d (from 1.7 to 2.4 kg/day), and sodium absorption increased ~40 mmol/d (from 74 to 113 mmol/day) over four weeks of treatment. From the baseline absorptive parameters, the actual need for parenteral fluid and sodium could be questioned in the majority of the patients in that study, according to the borderlines of intestinal failure defined by Jeppesen, et al (23). All eight patients in the Byrne and Wilmore study had a colon-in-continuity, and, in addition to dietary changes toward a high-carbohydrate diet, they were also given oral rehydration solutions as a part of the "rehabilitation." Therefore, the effects may be related to dietary changes and rehydration solutions, rather than growth hormone and glutamine. Although significant, the effect of growth hormone (0.13 mg/kg/day) and oral glutamine on intestinal sodium and potassium absorption was less than 5 mmol/day in the placebo-controlled, double blind study by Scolapio, et al (24). No effect was described on wet-weight absorption. In contrast, growth hormone (0.11 mg/kg/day) and glutamine, both orally and parenterally administered, tended to decrease wet-weight absorption and increase fecal excretion of sodium and potassium, which reached significance ($p < 0.05$) in comparison with baseline values from the study of Szkudlarek, et al (25). However, this was contrasted by clinical findings of generalized edema, increased body weight, a need for diuretics, and a reduction in parenteral saline during treatment. The patients were probably in the process of excreting water and sodium accumulated during the treatment at the time of the post-treatment balance studies five days after termination of treatment. In the lower dose studies from Ellegaard (growth hormone 0.024 mg/kg/day) (26) and Seguy (0.05 mg/kg/day) (27), no significant positive effects on either wet-weight or sodium absorption were seen. The efficacy data of somatotropin (0.1 mg/kg/day for 4 weeks) in a randomized, double-blind parallel group study of 41 patients with SBS (mainly with a preserved colon and stool volume less than 3 L/day) who were PN-dependent have recently been published by Byrne, et al (28). The protocol for weaning from PN was based on pre-established weaning criteria, mainly based on body weight, measurement of total body water by bioimpedance analysis (BIA) and measurements of serum sodium, potassium and bicarbonate. A significantly greater reduction from baseline in total parenteral volume occurred in recipients of somatropin (Zorptive™) plus glutamine or somatropin (Zorptive™) alone than in placebo plus glutamine recipients (–7.7 and –5.9 vs –3.8 L/week). Thus, the effect of somatropin (Zorptive™) and glutamine averages 0.5-0.6 L/day compared to the placebo group. However, in all groups, the oral fluid intake was approximately 0.5 L/day higher in relation to treatment at week six compared to baseline values at week two. Balance studies on intestinal absorption were not performed and the results on urinary excretion were not given.

The effects of growth hormone are global and not specific for the intestine. It has recently been reported that growth hormone increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis (29). Therefore, when employing BIA in the weaning from parenteral support, it should be considered that the effects of growth hormone on fluid balance in short bowel patients may be related to effects on the kidneys and the extracellular space rather than on the intestine.

In a study with native GLP-2 by Jeppesen, et al, eight patients were treated with 400 mcg of GLP-2 twice a day, given subcutaneously for 35 days in an open label study (corresponding to 0.013 + 0.002 mg/kg/day, a range of 0.011–0.017 mg/kg/day) (30). Four patients with a mean residual jejunal length of 83 cm required home PN; 4 patients with a mean ileal resection of 106 cm did not. None of the patients had colon-in-continuity. Their average wet-weight absorption was 1.2 ± 1.7 kg/day at baseline and the wet-weight absorption increased by ~0.4 ± 0.5 kg/day ($p = 0.04$).

In a subsequent open label pilot study with 16 short bowel patients (six with remnant parts of the colon) employing a dipeptidyl peptidase IV resistant GLP-2 analog, Teduglutide, in doses of 0.03 to 0.15 mg/kg/day,

wet-weight absorption increased by ~0.7 ± 0.5 kg/day ($p < 0.001$), thereby significantly increasing urine weight by ~0.6 ± 0.5 kg/day ($p < 0.001$) and sodium excretion by ~50 ± 40 mmol/day ($p < 0.001$) (31).

Energy Absorption

In the initial study by Byrne and Wilmore, the baseline dietary energy intake was 2,692 kcal/day, 1,618 kcal/day (60%) of which was absorbed (22). Thus, according to the borderlines that define intestinal failure suggested by Jeppesen, et al (23), the majority of these patients did not need parenteral energy. After three weeks of treatment, the intake and absorption were 2,367 and 1,759 kcal/day (74%), respectively, which was a significant improvement ($p < 0.003$), but only an increase of 141 kcal/day in absolute amounts. In this study by Byrne and Wilmore, all eight short bowel patients had a colon-in-continuity. As stated, the "rehabilitation" included a high-carbohydrate, low-fat diet, which in itself is known to increase the energy absorption in this segment of short bowel patients. Supporting the hypothesis that diet alone resulted in this effect, intestinal fat absorption did not improve. In the study by Scolapio, et al, where only two of eight patients had colon-in-continuity, high-carbohydrate diets were provided in both the placebo and treatment arms (24). Energy absorption was not measured, but no changes were observed regarding nitrogen or fat absorption. In the studies by Ellegaard, et al (26) and Szkudlarek, et al (25), no changes were found in intestinal energy, fat or nitrogen absorption. In the study by Seguy, et al, growth hormone (0.05 mg/kg/day, nine of 12 patients with colon-in-continuity) and an unrestricted hyperphagic diet increased intestinal absorption of nitrogen by 14 ± 6% ($p < 0.040$), carbohydrates by 10 ± 4% ($p < 0.040$), and energy by 15 ± 5% ($p < 0.002$), which in absolute terms was ~400 kcal/day (27). Fat absorption was unaffected by the treatment. During growth hormone treatment the mean dietary energy intake was ~200 kcal/day higher.

In a study using somatropin (Zorptive™), the mean reductions from baseline in total PN calories were significantly greater in recipients of somatropin (Zorptive™) plus glutamine or somatropin (Zorptive™) alone than in recipients of placebo plus glutamine (5,751 and 4,338 versus 2,633 kcal/week) ($p < 0.001$ and $p < 0.01$, respectively) (28). Thus, the effect of the combined therapy of somatropin (Zorptive™) plus glutamine would correspond to an effect of ~400–500 kcal/day. However, although not statistically significant, the diet energy intake was 200 kcal/day higher during treatment with somatropin (Zorptive™) plus glutamine compared to baseline.

In the study with native GLP-2, the absolute energy absorption tended to increase by ~100 kcal/day, $p = 0.09$. The trend towards improvement in the absolute amount of energy absorbed was obtained in spite of a non-significant decrease in energy intake of ~50 kcal/day, which means that the reduction in the energy malabsorbed (equal to the stomal excretion) was proportionally larger ~150 kcal/day.

In the study employing 16 short bowel patients (six with remnant colonic segments), the dipeptidyl peptidase IV resistant GLP-2 analog, Teduglutide, in doses 0.03 to 0.15 mg/kg/day, reduced fecal energy excretion by ~200 kcal/day ($p = 0.04$), but this only translated into a significant increase in intestinal absorption of ~250 kcal/day in a post-hoc defined subset of patients with high dietary compliance during balance studies. No significant changes were seen in the absorption of individual macronutrients (31).

Body Weight, Composition, and Urine Creatinine Excretion

In the growth-hormone study by Byrne, et al, a weight gain of 5.4 ± 1.2 kg was described in all eight patients after 21 days of treatment (22). Occurrences of edema were not reported, but increases in body weight of this size are difficult to explain considering the magnitude of the summarized effect of approximately 3000 kcal (or ~150 kcal/day) on the energy balance over the 21 days of treatment. In the study by Byrne, et al, neither body composition nor urine creatinine excretion was measured. In the eight-week growth-hormone (0.024 mg/kg/day) study by Ellegård, et al, an increase in lean body mass of 2.5 kg and a decrease in fat mass of 0.1 kg were found (26). Total body potassium increased 4.7%, equivalent to 1.1 ± 0.4 kg of body cell mass, which was parallel to the 5.6% increase in lean body

(continued on page 49)

(continued from page 46)

mass measured by dual energy x-ray absorptiometry (DXA). Ellegård, et al concluded that the increase in lean body mass was derived from both increased body cell mass and extracellular water. Using DXA measurements, Scolapio, et al found an increase in lean body mass of 3.96 ± 0.5 kg and a decrease in percent body fat of 2.51± 0.4%, which corresponded to approximately 1.0 kg compared to placebo (32). Scolapio, et al concluded that the increased body weight during treatment with high doses of growth hormone was mainly caused by the increase in extracellular water and the presence of peripheral edema, which was encountered in all eight patients treated. In the study by Szkudlarek, et al, a weight gain of 1.0 ± 0.3 kg ($p < 0.050$) was measured daily for five days after four weeks of treatment. DXA evaluation indicated that lean body mass increased 2.9 kg ($p < 0.001$) and fat mass decreased 2.4 kg ($p < 0.001$) compared with baseline, whereas the changes were not significant in comparison to placebo. No changes were seen in urinary creatinine excretion (33). The most likely explanation of the rather modest weight gain and increase in lean body mass in the high dose study of Szkudlarek, et al could be the timing of measurements. The patients had been off growth hormone and glutamine for five days, when the DXA-scan measurements were performed. At this time, generalized edema, which occurred in all eight patients, were on the decline. In the other studies, lean body mass was measured while patients were still receiving treatment. In the study by Seguy, et al, body weight increased 2.0 kg ($p < 0.003$) and lean body mass, measured by bioimpedance, increased 2.2 kg ($p < 0.006$) (27). No adverse events to the growth hormone treatment were encountered.

In the study on somatropin (Zorptive™), a weight loss of 5.2 kg of body weight was observed from week two (pre-treatment) to week 18 (12 weeks post-treatment) in patients treated with the combined therapy of somatropin (Zorptive™) plus glutamine. This weight loss closely reflects the anticipated weight loss derived by calculation of the energy deficit obtained by reduction of the parenteral energy support of ~450 kcal/day (28).

In the 35-day study with native GLP-2 treatment, the overall increase in energy absorption of 4,500 kcal translated into a significant increase in body weight of 1.2 ± 1.0 kg ($p = 0.010$) (30). Lean body mass improved by 2.9 ± 1.9 kg ($p = 0.004$), and fat mass decreased by 1.8 ± 1.3 kg ($p = 0.007$). The study demonstrated positive findings on urine creatinine excretion (0.7 ± 0.7 mmol/day, $p = 0.02$), which could suggest an increase in muscle mass in relation to GLP-2 treatment. An alternative hypothesis is that GLP-2 improves hydrational status and thereby renal function and creatinine clearance in these patients, who often suffer from reversible renal impairment due to intermittent dehydration (34).

In the three-week study of the GLP-2 analog, Teduglutide, no changes were seen in body weight (0.9 ± 2.1 kg, 0.12) (31).

CONCLUSION

Since none of the studies employing hormonal therapy thus far have demonstrated ongoing effects after termination of treatment, there is a need for sustained treatment. However, side effects such as swelling, fluid retentions symptoms, hyperglycemia, myalgia, arthralgia, gynecomastia, carpal tunnel syndrome, nightmares, and insomnia reported in the high-dose growth-hormone studies in short bowel patients may jeopardize the long-tem use of the drug. Abdominal pain is described in patients treated with GLP-2. In addition, long-term treatment with any growth factor could be questioned due to a theoretical risk of stimulating tumor growth (35). At present, it is therefore recommended that treatment of short bowel patients with intestinal growth factors should be initiated in research settings only, and that close surveillance and monitoring of long-term effects is a necessary part of the protocol.

It is believed that a host of growth factors, such as insulin-like growth factor (IGF-I/II), peptide YY, glucagon-like peptide 1 (GLP-1), neurotensin, keratinocyte growth factor (KGF), transforming growth factor (TGF alfa and beta), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), control the integrity and growth of the intestinal mucosa. In order to understand the complexity of these processes, the key players need to be identified, and subsequently the degree of regulation, crosstalk and transactivation between these factors needs to be understood. In this respect, GH and GLP-2 are just the first candidates identified.

For now, when treating short bowel patients, maximizing effects of less costly dietary interventions, oral rehydration solutions and medications known to have a positive effect on intestinal function (anti-diarrhea and anti-secretory agents) is the prudent first step. ■

References

1. Nightingale JM, Lennard Jones JE. The short bowel syndrome: what's new and old? *Dig Dis,* 1993; 11:12-31.
2. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology*, 2003; 124:1111-1134.
3. Fleming CR, Remington M. Intestinal failure. In: Hill GL, editor. *Nutrition and the Surgical Patient.* New York: Churchill Livingstone, 1981: 219-235.
4. Jeppesen PB, Langholz E, Mortensen PB. Quality of life in patients receiving home parenteral nutrition. *Gut*, 1999; 44:844-852.
5. Jeppesen PB, Staun M, Mortensen PB. Adult patients receiving home parenteral nutrition in Denmark from 1991 to 1996: who will benefit from intestinal transplantation? *Scand J Gastroenterol,* 1998; 33:839-846.
6. Ugur A, Marashdeh BH, Gottschalck I, et al. Home parenteral nutrition in Denmark in the period from 1996 to 2001. *Scand J Gastroenterol,* 2006; 41:401-407.
7. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel [see comments]. *Lancet*, 1994; 343:373-376.
8. Jeppesen PB, Staun M, Tjellesen L, et al. Effect of intravenous ranitidine and omeprazole on intestinal absorption of water, sodium, and macronutrients in patients with intestinal resection. *Gut*, 1998; 43:763-769.
9. Friedman HI, Chandler JG, Peck CC, et al. Alterations in intestinal structure, fat absorption and body weight after intestinal bypass for morbid obesity. *Surg Gynecol Obstet,* 1978; 146:757-767.
10. O'Keefe SJ, Haymond MW, Bennet WM, et al. Long-acting somatostatin analogue therapy and protein metabolism in patients with jejunostomies. *Gastroenterology*, 1994; 107:379-388.
11. Ziegler TR, Fernandez-Estivariz C, Gu LH, et al. Distribution of the H+/peptide transporter PepT1 in human intestine: up-regulated expression in the colonic mucosa of patients with short-bowel syndrome. *Am J Clin Nutr,* 2002; 75:922-930.
12. Althausen TL, Doig RK, Uyeyama K, et al. Digestion and absorption after massive resection of the small intestine. II. Recovery of the absorptive function as shown by intestinal absorption tests in two patients and a consideration of compensatory mechanisms. *Gastroenterology*, 1950; 16:126-134.
13. Dowling RH, Booth CC. Functional compensation after small-bowel resection in man. Demonstration by direct measurement. *Lancet*, 1966; 2:146-147.
14. Hill GL, Mair WS, Goligher JC. Impairment of "ileostomy adaptation" in patients after ileal resection. *Gut*, 1974; 15:982-987.
15. Gouttebel MC, Saint Aubert B, Colette C, et al. Intestinal adaptation in patients with short bowel syndrome. Measurement by calcium absorption. *Dig Dis Sci,* 1989; 34:709-715.
16. Weser E, Hernandez MH. Studies of small bowel adaptation after intestinal resection in the rat. *Gastroenterology*, 1971; 60:69-75.
17. Remington M, Malagelada JR, Zinsmeister A, et al. Abnormalities in gastrointestinal motor activity in patients with short bowels: effect of a synthetic opiate. *Gastroenterology*, 1983; 85:629-636.
18. Crenn P, Coudray LC, Cynober L, et al. Post-absorptive plasma citrulline concentration: a marker of intestinal failure in humans. *Transplant Proc,* 1998; 30:2528.
19. Rhoads JM, Plunkett E, Galanko J, et al. Serum citrulline levels correlate with enteral tolerance and bowel length in infants with short bowel syndrome. *J Pediatr,* 2005; 146:542-547.
20. Papadia C, Sherwood RA, Kalantzis C, et al. Plasma citrulline concentration: a reliable marker of small bowel absorptive capacity independent of intestinal inflammation. *Am J Gastroenterol,* 2007; 102:1474-1482.
21. Peters JH, Wierdsma NJ, Teerlink T, et al. Poor diagnostic accuracy of a single fasting plasma citrulline concentration to assess intestinal energy absorption capacity. *Am J Gastroenterol,* 2007; 102:2814-2819.
22. Byrne TA, Morrissey TB, Nattakom TV, et al. Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. *JPEN*, 1995; 19:296-302.
23. Jeppesen PB, Mortensen PB. Intestinal failure defined by measurements of intestinal energy and wet weight absorption. *Gut*, 2000; 46:701-706.
24. Scolapio JS, Camilleri M, Fleming CR, et al. Effect of growth hormone, glutamine, and diet on adaptation in short-bowel syndrome: A randomized, controlled study. *Gastroenterology*, 1997; 113:1074-1081.
25. Szkudlarek J, Jeppesen PB, Mortensen PB. Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover, placebo controlled study. *Gut*, 2000; 47:199-205.
26. Ellegard L, Bosaeus I, Nordgren S, et al. Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. *Ann Surg,* 1997;225:88-96.
27. Seguy D, Vahedi K, Kapel N, et al. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. *Gastroenterology*, 2003; 124:293-302.
28. Byrne TA, Wilmore DW, Iyer K, et al. Growth hormone, glutamine, and an optimal diet reduces parenteral nutrition in patients with short bowel syndrome: a prospective, randomized, placebo-controlled, double-blind clinical trial. *Ann Surg,* 2005; 242:655-661.
29. Johannsson G, Sverrisdottir YB, Ellegard L, et al. GH increases extracellular volume by stimulating sodium reabsorption in the distal nephron and preventing pressure natriuresis. *J Clin Endocrinol Metab,* 2002; 87:1743-1749.
30. 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.
31. 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.
32. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. JPEN, 1999; 23:309-313.
33. Jeppesen PB, Szkudlarek J, Hoy CE, et al. Effect of high-dose growth hormone and glutamine on body composition, urine creatinine excretion, fatty acid absorption, and essential fatty acids status in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. *Scand J Gastroenterol,* 2001; 36:48-54.
34. Lauverjat M, Hadj AA, Vanhems P, et al. Chronic dehydration may impair renal function in patients with chronic intestinal failure on long-term parenteral nutrition. *Clin Nutr,* 2006; 25:75-81.
35. Thulesen J, Hartmann B, Hare KJ, et al. Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice. *Gut*, 2004; 53(8):1145-1150.