Somatropin in short bowel syndrome: opening the door to trophic factor use

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The management of short bowel syndrome is complex and frequently requires parenteral nutrition support to ensure the sufficient administration of nutrients and fluids. Despite advances in the provision of parenteral nutrition, this mode of nutritional support carries with it significant risks to the patient, impairs quality of life and is very costly. Since intestinal adaptation plays a key role in the successful management of patients with short bowel syndrome, recent investigations have focused on the use of trophic substances to enhance intestinal adaptation and increase the absorptive function of the remaining gut. Published reports from a number of studies conducted in animal models and humans with short bowel syndrome evaluating the efficacy of recombinant human growth hormone (i.e., somatropin) in this regard have demonstrated conflicting findings. However, substantial methodologic differences among the studies limit definitive conclusions regarding the benefit of this therapy on intestinal adaptation. Subsequent studies in short bowel syndrome patients have focused on the ability of recombinant human growth hormone to allow reduction in parenteral nutrition requirements. In a recent randomized, controlled trial of recombinant human growth hormone, glutamine and a specialized oral diet, treatment with recombinant human growth hormone 0.1 mg/kg/day for 4 weeks resulted in significant reductions in parenteral nutrition requirements compared with the control group. These results led to the approval of somatropin by the US Food and Drug Administration for use in patients with short bowel syndrome receiving specialized nutrition support. Somatropin appears to be well tolerated with generally manageable side effects. Fluid retention, gastrointestinal symptoms and injection site reactions occur commonly; however, serious adverse effects are uncommon. Optimal clinical benefits appear to be achieved when somatropin is administered in combination with a specialized oral diet and, if possible, oral glutamine. It should be used under the guidance of clinicians experienced in the management of short bowel syndrome, with the expectation that these patients need to be monitored closely during and after its use. Further study is needed regarding the persistence of effect after treatment, optimal dose and length of administration for subsequent courses of treatment with somatropin as well as its safety, long-term benefit and use in the pediatric and geriatric populations.

Short bowel syndrome (SBS) occurs following massive resection of the small bowel and results in inadequate digestion and/or absorption of nutrients and fluids. SBS can be either congenital or acquired. Necrotizing enterocolitis and congenital intestinal abnormalities are often the cause in infants. In adults, resections for inflammatory bowel disease (primarily Crohn's disease), catastrophic mesenteric vascular events (e.g., thrombosis, trauma and volvulus), carcinoma and radiation enteritis are typical causes of SBS [1]. These patients commonly experience chronic diarrhea, dehydration and macro- and micronutrient deficiencies.

The prevalence of SBS is difficult to estimate. A 1997 European survey indicated a point prevalence of home parenteral nutrition (PN) use of approximately four/million, of whom nearly 35% had SBS [2]. In the USA, the annual prevalence of home PN use was estimated at approximately 120/million, of whom nearly 25% had SBS [3]. While SBS is clearly uncommon, it remains an important clinical problem due to the significant morbidity, mortality and high associated costs.

Intestinal adaptation plays an important role in the successful management of patients with SBS. Adaptation is the process by which the bowel, in response to a variety of internal and external stimuli, attempts to increase fluid and nutrient absorption to that occurring before resection. Both morphologic and functional intestinal adaptive changes can occur depending upon the extent and site of the intestine removed

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and the nutrient components of the diet. Functional adaptive changes include modifications of the brush border membrane fluidity and permeability and up- or downregulation of carrier-mediated transport [4]. Most adaptation occurs during the first year following resection.

The management of SBS is complex and frequently necessitates long-term use of PN to ensure the sufficient administration of nutrients and fluids [5]. It has been demonstrated using nutrient absorption (i.e., balance) studies that patients who absorb less than 1.4 kg/day of wet weight or less than 84% of their calculated energy needs will likely require parenteral fluid and/or nutrition support [6]. While factors other than bowel length are also important, this typically translates into a patient with less than 50 to 70 cm of small bowel when the colon is intact, or less than 100 to 150 cm of small bowel when the colon is absent [7].

Approximately 50% of SBS patients will be unable to be weaned from PN within a year of resection using conventional treatment strategies [7]. Despite advances in the provision of PN, this mode of nutritional support carries with it significant risks to the patient such as catheter sepsis, venous thrombosis and liver disease, impairs quality of life and is very costly. As a consequence, there has been intense investigation, particularly over the past decade, to identify treatments that maximize intestinal absorption/adaptation with the goal of eliminating or at least minimizing the need for PN support. Recent investigations in humans have focused on the use of trophic substances such as growth factors (e.g., growth hormone [GH] and glucagon-like peptide-2) and nutrients (e.g., glutamine) to increase the absorptive function of the remaining gut.

Somatropin is a highly purified human (h)GH preparation produced by recombinant DNA technology that has recently been approved for use in adults with SBS who require PN support. In the pages that follow, the efficacy of GH in both animal models and humans with SBS will be reviewed and the role of this therapy in the current management of SBS will be discussed.

Pharmacodynamics

In order to better understand the potential role of trophic substances on the gut adaptive process following massive intestinal resection, an appreciation of the differences in human versus animal intestinal adaptation is needed. However, rodents are commonly used as models of intestinal adaptation and importantly, few studies have confirmed these adaptive responses in humans. Therefore, the clinical adequacy of the rat as a model of human intestinal adaptation remains to be determined. Furthermore, while animal intestinal adaptation is characterized by epithelial hyperplasia (increase in crypt cell depth, villus height and enterocyte number), human intestinal adaptation appears to be primarily associated with an increase in the absorptive function of the enterocyte irrespective of morphologic changes [8,9]. This is supported by a recent study in humans with SBS treated with recombinant (r)-hGH in which postabsorptive plasma citrulline levels, an indirect biomarker of enterocyte mass [10], increased nonsignificantly compared with placebo, despite an enhancement in intestinal absorption [11].

Somatropin produces its intestinal physiologic effects by binding to specific receptors on the intestinal epithelium. Many of its effects are also mediated by insulin-like growth factor (IGF)-1, which results in an inhibition of apoptosis and stimulation of crypt cell proliferation [12]. Furthermore, exogenous GH administration has been shown to increase serum and tissue (small intestine) IGF-1 concentrations and, in rodents, administration of GH and IGF-1 increases small bowel growth after resection [13].

Evidence of r-hGH efficacy in animal models of SBS

A number of studies conducted in animal models of SBS have investigated the effect of GH, either alone or combined with glutamine, on intestinal adaptation. Glutamine is a highly abundant amino acid and the major energy source of the enterocyte that becomes conditionally essential in states of severe physiologic stress [14,15]. In such conditions, without adequate glutamine supplementation, gut atrophy may occur. Although a variety of GH preparations, doses and animals have been used, the exogenous administration of GH has generally been shown to enhance mucosal hyperplasia and to result in an increase in body weight, small bowel length, colonic mass and biomechanic strength [16–20]. Furthermore, it has been demonstrated in the hypophysectomized rat that intestinal atrophy and reduced absorptive capacity develop and these changes can be restored by GH [21]. Intestinal hypertrophy has been shown to occur in transgenic mice over expressing GH [22]. In addition to its effects on structural

adaptation, GH has been shown to exert specific functional effects. In particular, GH resulted in an increase in water, sodium, glucose, palmitic acid and amino acid absorption in several studies conducted in animals [23–25]. Nevertheless, it is important to remember that other reports have not supported an effect of GH on stimulating intestinal adaptation [26–28].

In humans, the administration of GH has been shown to inhibit the liberation of glutamine from muscle during catabolic states [29], suggesting a role for combined GH and glutamine in enhancing intestinal adaptation. Indeed, the combination of GH and glutamine has been shown to synergistically increase IGF-1 plasma levels, intestinal DNA and villus growth in rodent models of SBS [25,30–32]. However, once again, not all studies have demonstrated positive effects of this combination on intestinal adaptation [33].

Evidence of r-hGH efficacy in humans with SBS

In the last 10 years, several clinical studies have been conducted using r-hGH in humans with SBS (Table 1). The following sections review the specifics of the studies in humans with SBS, focusing first on the effects of r-hGH on nutrient and fluid absorption and then on a reduction in parenteral support (i.e., PN weaning).

Table 1. Principal studies investigating the efficacy of r-hGH on intestinal absorption and parenteral nutrition weaning in short bowel syndrome patients.

n	Study design	Mean remnant small bowel length (cm) (range)	Colon present (n)	Mean time on PN (years)	Treatment (duration)	Results	Ref.
12	RCCT	48 (0–120)	9	7.5	r-hGH (0.05 mg/kg/d), hyperphagic diet (3 weeks)	Improved nitrogen, energy and carbohydrate absorption; increased body weight and lean body mass; no change in plasma citrulline	[11]
10	Open	37 (8–90)	10	6	r-hGH (0.14 mg/kg/d), glutamine, HCLF diet (3–4 weeks)	Improved nutrient and water absorption; decreased stool output	[34]
10	RCCT	130 (90–170)	4	Only 1 patient on PN	r-hGH (0.024 mg/kg/d) (8 weeks)	Increased body weight, lean body mass, total body potassium, bone mineral content; no change in energy or fluid absorption	[37]
8	RCCT	71 (55–120)	2	12.9	r-hGH (014 mg/kg/d), glutamine (3 weeks)	Transient increase in body weight and lean body mass; increased sodium and potassium absorption	[38]
8	RCCT	104 (30–150)	4	7	r-hGH (0.14 mg/kg/d), glutamine (4 weeks)	No improvement in intestinal absorption; increased body weight	[39]
61 (49 on PN)	Open	61 (0–183)	37	4	r-hGH (0.09 mg/kg/d), glutamine, individualized diet (4 weeks)	41% off PN, 51% on reduced amount of PN, 8% no change in PN after 1 year	[45]
41	RCPGT	73 (NR)	36	4	r-hGH (0.1 mg/kg/d), glutamine, individualized diet (4 weeks)	Reduced PN requirements (9 off PN); stable body weight	[48]

d: Daily; HCLF: High carbohydrate, low fat; NR: Not reported; PN: Parenteral nutrition; RCPGT: Randomized, controlled, parallel-group trial; r-hGH: Recombinant human growth hormone; RCCT: Randomized, controlled, crossover trial.

Effect on nutrient & fluid absorption

In the first published report on the use of r-hGH in humans with SBS, Byrne and colleagues analyzed the effects of the combination of r-hGH, glutamine and a modified diet on nutrient and fluid absorption [34]. In this open-label study, following a 1-week control period, ten patients received a high-carbohydrate, low-fat diet either alone (n = 2) or in combination with r-hGH (0.14 mg/kg/day) and supplemental enteral or parenteral glutamine (n = 8) for an additional 3 weeks. A third group of patients (n = 5) received either r-hGH alone or glutamine alone for 3 to 4 weeks while on a standardized diet. All patients received an oral rehydration solution and antimotility medications according to their clinical need. Sodium and protein absorption were unaffected by diet modification alone or when combined with glutamine. In contrast, while treatment with r-hGH and diet resulted in minor improvements in sodium and protein absorption, treatment with r-hGH, glutamine and the modified diet enhanced overall energy (from 60 to 74%) and wet weight (from 51 to 68%) absorption. Carbohydrate (from 60 to 82%) and protein (from 49 to 63%) absorption also increased. Fat absorption was unaltered. A nonsignificant increase (37%) in sodium absorption was also shown. Although stool output increased slightly with dietary modification alone and was unaffected by glutamine plus diet, it decreased nonsignificantly (16%) with r-hGH plus diet and decreased significantly with r-hGH, glutamine and diet (32%).

A more recent open-label study using similar methodology demonstrated improvements in body weight, D-xylose absorption, stool nitrogen loss and stool frequency in nine PN-dependent SBS patients [35]. Similarly, Wu and colleagues found that a 3-week course of r-hGH combined with oral glutamine and an individualized diet led to improvements in macronutrient absorption; however, the effects were not sustained beyond the treatment period [36].

Ellegard and colleagues reported results of the first randomized, controlled, crossover study of the efficacy of a lower dose of r-hGH without glutamine in ten patients, nine of whom were not PN-dependent, with SBS due to Crohn's disease [37]. Patients were treated with 0.024 mg/kg daily of r-hGH and placebo for two 8-week periods, separated by a washout period of at least 12 weeks. Patients remained on their usual diets, with the exception that during the metabolic balance studies (before treatment and at the end of each 8-week treatment period), patients received a low-fat, high-carbohydrate diet. Nonsignificant increases in the absorptive capacity of water, energy and protein were observed following r-hGH administration. Compared with baseline, r-hGH significantly increased body weight (2.3 kg). Using dual-energy x-ray absorptiometry (DXA), an increase in lean body mass (2.5 kg), decrease in fat mass (0.1 kg) and increase in total body potassium (5%) after r-hGH was demonstrated. Fat-free mass and total body water increased by 6%. Treatment with r-hGH also increased total bone calcium and bone mineral content by an average of 1%. Only total body water increased with placebo treatment.

A further two randomized and controlled crossover studies failed to confirm the benefits of the combination of r-hGH and oral glutamine on intestinal absorption in SBS patients [38,39]. In the study by Scolapio and colleagues, eight SBS patients were treated for a 3-week period during which they consumed a standardized 1500 kcal/day high-carbohydrate, low-fat diet [38]. The use of antimotility medications was not allowed. Balance studies were performed at the end of each treatment period. In the study by Szkudlarek and colleagues, eight SBS patients were treated for 4 weeks and consumed an unrestricted diet [39]. Balance studies were performed 5 days after discontinuing treatment. Neither study demonstrated significant improvements in macronutrient or water absorption. Significant reductions in stool sodium and potassium were noted in patients who received r-hGH plus glutamine in one study [38]. Further analysis of body composition in patients from both studies using DXA revealed significant increases in body weight and lean body mass with r-hGH plus glutamine compared with placebo; however, the development of edema while receiving active treatment was common and the effects on body composition were not maintained after discontinuing treatment [40,41]. This has led to the suggestion that the increased body weight seen during these studies after active treatment may be due to increased extracellular water and the presence of edema. Jeppesen and colleagues found no differences in 24 h urinary creatinine excretion (an index of muscle mass) after active treatment [41]. The study of Scolapio was the only one to assess intestinal morphologic and transit changes after treatment. No significant increase in villus height or crypt cell proliferation was identified; however, a significant decrease in gastric emptying was noted [38].

In the most recent randomized, double-blind, placebo-controlled crossover study of the effects of r-hGH without glutamine, 12 patients with SBS were treated with a medium dose of r-hGH (0.05 mg/kg/day) and placebo for two 3-week periods separated by a 1-week washout period [11]. No changes were made to the patients' usual hyperphagic, hypercaloric diets. Treatment with r-hGH significantly increased intestinal absorption of energy (54 vs 39%; p < 0.002), nitrogen (39 vs 25%; p < 0.04) and carbohydrate (75 vs 66%; p < 0.04) compared with placebo (Figure 1). A nonsignificant increase in fat absorption was observed (12 ± 8%). The increases in nutrient absorption corresponded to an increase in mean net intestinal absorption of 427 ± 87 kcal/day during treatment with r-hGH compared with placebo. Body weight and lean body mass increased by 4% with r-hGH compared with less than 1% with placebo (p < 0.01); however, the effects on body composition were not maintained during the washout period.
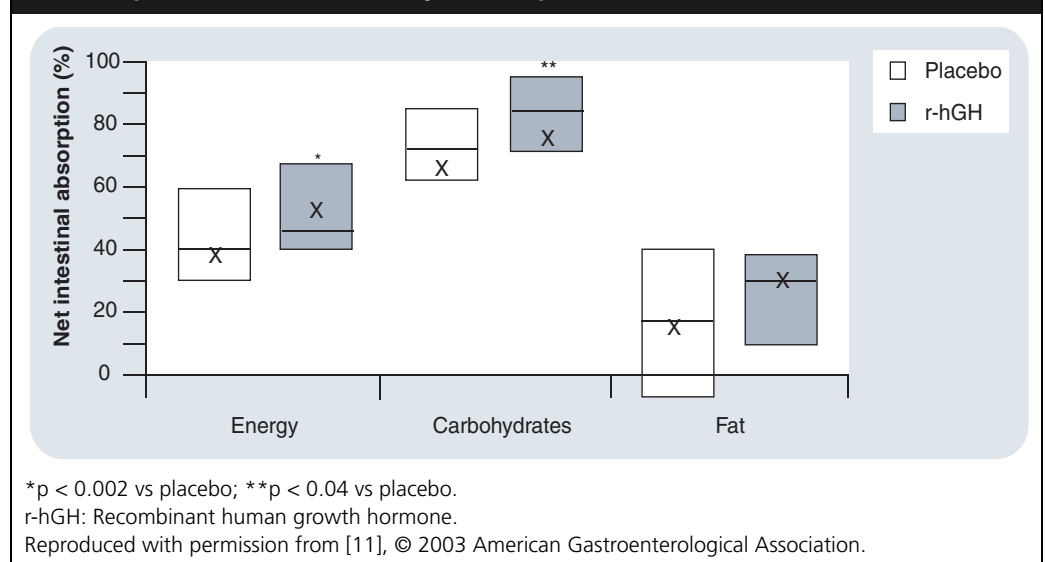
The discrepant findings from the above studies have contributed to the continuing controversy regarding the benefit of r-hGH with or without glutamine and has led some to conclude that the beneficial effects demonstrated may be related to the dietary modification rather than from the addition of GH and glutamine [42]. Nevertheless, it is also likely that the mixed results are, at least partly, attributable to differences in study design and patient characteristics (see Expert commentary). Indeed, methodologic

differences among the studies prevent definitive conclusions regarding the benefit (or lack thereof) of this therapy on intestinal absorption.

Effect on parenteral nutrition weaning

On the basis of the encouraging early results from animal models and humans with SBS, Byrne and colleagues conducted an open-label study in which 47 SBS patients received r-hGH (mean daily dose, 0.11 mg/kg; range: 0.03–0.14) with oral glutamine (30 g/day) and a high-carbohydrate, low-fat diet for 4 weeks while admitted to a clinical research facility [43]. The primary end point of this study was on PN weaning not intestinal absorption or body composition. Following treatment, patients were discharged and instructed to continue with oral glutamine and the modified diet. Patients were allowed to continue the use of other standard treatments used in SBS such as antimotility and antisecretory medications and oral rehydration solution. Follow-up data were reported for 1 year. Most patients (n = 39) were dependent on PN, while several patients (n = 8) were referred due to the lack of central venous access and progressive malnutrition in order to prevent the need to initiate PN. After 4 weeks of treatment, 27 patients (57%) had eliminated PN use, 14 (30%) were able to reduce their PN requirements and six (13%) experienced no change in PN requirements. Inability to make any reduction in PN requirements was only seen in end-jejunostomy patients. A year later, 19 patients (40%) remained off PN while 19 (40%) others

Figure 1. Intestinal absorption of energy, carbohydrates and fat after treatment with r-hGH or placebo in short bowel syndrome patients.

*p < 0.002 vs placebo; **p < 0.04 vs placebo.
r-hGH: Recombinant human growth hormone.
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were on reduced PN and nine (19%) were receiving PN at levels similar to their initial pretreatment requirements.

The same group of investigators then evaluated the SBS patients who were able to eliminate or reduce PN and compared them with those who were unable to reduce their parenteral support after 4 weeks of treatment [44]. They found that the patients who were unable to be weaned from PN were slightly older (p = 0.02) and had Crohn's disease as the underlying cause for resection (p = 0.04). In addition, patients who had no change in their PN requirements tended to have larger stool output (p < 0.002). The most discriminating predictor of successful PN elimination was a bowel length–body weight ratio of 0.5 cm/kg or more. Interestingly, no significant difference among the three groups based on remaining bowel length was observed.

In follow-up to this study, these investigators conducted a larger open-label study involving 61 SBS patients who were treated daily with a mean r-hGH dose of 0.09 mg/kg plus oral glutamine 30 g in combination with an individualized diet based upon their remaining bowel anatomy [45]. This treatment continued for 4 to 6 weeks, once again while admitted to a clinical facility for intense monitoring and education, afterwards patients were discharged with instructions to continue on the glutamine and modified diet. PN status after 1 year of follow-up was the primary end point. Of the 61

enrolled patients, 49 were PN-dependent and 12 were treated to prevent initiation or resumption of PN. Of the 49 patients infusing PN at study entry, 20 (41%) were completely weaned from PN and remained off PN at 1 year, 25 (51%) had a reduction in PN requirements and four (8%) had no change in PN requirements (Figure 2). In patients without a colon, elimination of PN occurred only in those patients who had 100 cm or less of remaining small bowel. Of the 12 patients not on PN at study entry, 75% remained PN-free at 1 year.

These results have recently been confirmed in open-label case series published by other investigators. Zhu and colleagues treated 27 SBS patients with r-hGH, glutamine and modified diet [46]. Interestingly, these patients were treated much earlier in relation to the onset of SBS compared with the other studies (mean: 86 ± 105 days). Of 13 patients followed for more than 1 year, ten (77%) were weaned completely from PN prompting the investigators to conclude that early initiation of this therapy promotes intestinal adaptation and increases patients' ability to wean from PN. More recently, Weiming and colleagues treated 37 SBS patients with r-hGH and oral glutamine for 4 weeks in addition to a high-carbohydrate, low-fat diet and supplemental enteral nutrition support via a feeding tube [47]. Most were treated within 2 years of the onset of SBS. Of the 23 patients followed for more than 2 years, 21 were weaned completely

Figure 2. Parenteral nutrition use 1 year after treatment.
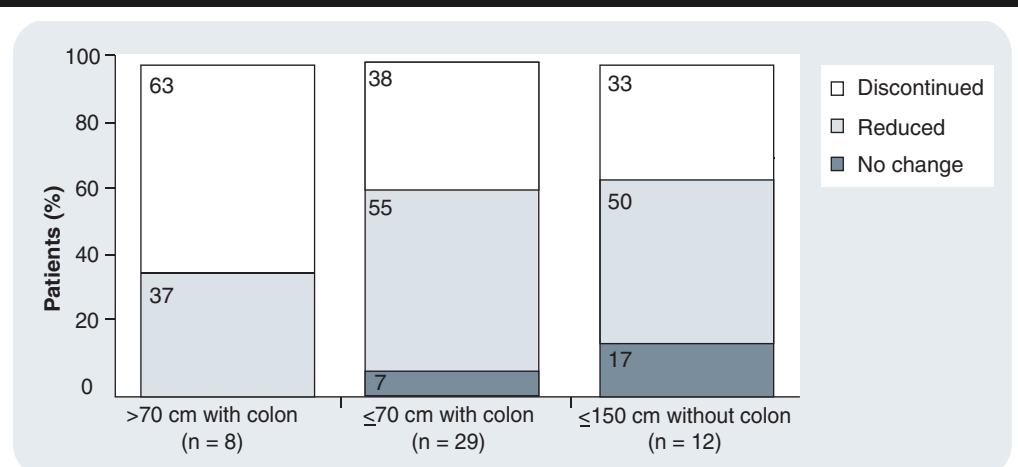
Treatment with r-hGH + glutamine + individualized diet in short bowel syndrome patients with a small bowel larger than 70 cm and a portion of colon, 70 cm small bowel with a portion of colon or 150 cm small bowel without a colon.

r-hGH: Recombinant human growth hormone.

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from PN – 18 of these were maintained on an oral diet supplemented with enteral nutrition, while the other three were on oral diet alone.

While encouraging, these studies are clearly limited by their uncontrolled design, making it difficult to determine the relative importance of the individual components of this bowel rehabilitation regimen (i.e., diet/education, oral rehydration solution and glutamine or r-hGH) in helping to wean patients from PN. The conflicting findings from the randomized, controlled trials on intestinal absorption also contribute to the lack of certainty on the clinical utility of this treatment program. To address some of these concerns, Byrne and colleagues recently completed a randomized, double-blind, controlled trial of r-hGH combined with an individualized specialized oral diet (SOD) and oral glutamine in 41 patients with PN-dependent SBS requiring 3000 calories/week or more [48]. These patients were admitted to a clinical facility and were stabilized for 2 weeks on a SOD, antimotility medications, oral rehydration solution and the PN formula they were receiving at home. Following the stabilization period, they randomly received one of three treatments:

- Oral glutamine (30 g/day) + r-hGH placebo (control group [n = 9])

- Glutamine placebo + r-hGH (0.1 mg/kg/day) (n = 16)

- Glutamine + r-hGH (n = 16)

Treatment continued 'in-house' for 4 additional weeks. After this period, the patients were discharged with instructions to continue on the SOD and glutamine or glutamine placebo for 12 additional weeks. The primary end point was the change from baseline in the weekly total PN volume (PN + lipids + supplemental intravenous fluids). Secondary end points included the reduction from baseline in weekly PN calories and frequency of PN administration. Intestinal absorption studies were not performed in this study, nor were morphologic assessments of the small intestine.

After 4 weeks of treatment, patients receiving r-hGH and SOD with or without glutamine showed significantly greater reductions in total PN volume, calories and frequency compared with patients receiving glutamine and SOD (i.e., the control group) (Figure 3). Importantly, the patients receiving all three interventions (i.e., r-hGH, glutamine and SOD) achieved the greatest reductions in these parameters with a mean reduction in PN volume (r-hGH + glutamine + SOD: -7.7;

vs r-hGH + SOD: -5.9; vs glutamine + SOD: -3.8 l/week), PN calories (-5751 vs -4338 vs -2633 kcal/week), and PN infusions (-4.2 v. -3.0 vs. -2.0 days/week) compared with baseline. After 12 additional weeks, only patients who had received r-hGH with glutamine and SOD maintained statistically significant reductions in PN (Figure 3), and nine patients eliminated PN use. Despite these PN reductions, the patients who received r-hGH with glutamine and SOD were able to maintain body weight, body water and adequate urine output suggesting stability of their nutritional and fluid status. These most recent data suggest:

- While treatment with r-hGH and a SOD is effective in reducing PN requirements in SBS patients, glutamine is of additional benefit

- The effects of r-hGH treatment with glutamine and a SOD persist after discontinuation of r-hGH

A 2-year retrospective follow-up of 55% of the original cohort found that 78% of patients (seven out of nine) who were weaned entirely from PN at week 18 remained PN-free [48]. Of the two patients who did not remain PN-free, one resumed PN temporarily and the other resumed PN at a reduced level.

Pharmacokinetics, dose & administration

Data concerning the pharmacokinetics of somatropin were obtained from the manufacturer's prescribing information [49]. Somatropin has a bioavailability of 70 to 90% following subcutaneous injection with a maximal serum concentration achieved in 5 h and a mean elimination half-life ($t_{1/2}$) of 4 h. No significant accumulation of somatropin occurred after repeat administration for 6 weeks. Somatropin primarily undergoes proteolysis in the kidneys, although some hepatic metabolism also occurs. It is degraded into peptides and amino acids, which are then returned to the systemic circulation. The recommended daily dose is 0.1 mg/kg (maximum 8 mg/day), administered subcutaneously once daily for 4 weeks. The somatropin dose may need to be reduced by half temporarily, stopped temporarily or discontinued altogether if adverse events occur. Somatropin should be used in conjunction with a specialized nutrition program with constituents depending upon the patient's bowel anatomy and caloric needs, as well as optimal conventional medical management of SBS.

Figure 3. Changes from baseline in parenteral nutrition requirements after 4 weeks of treatment.
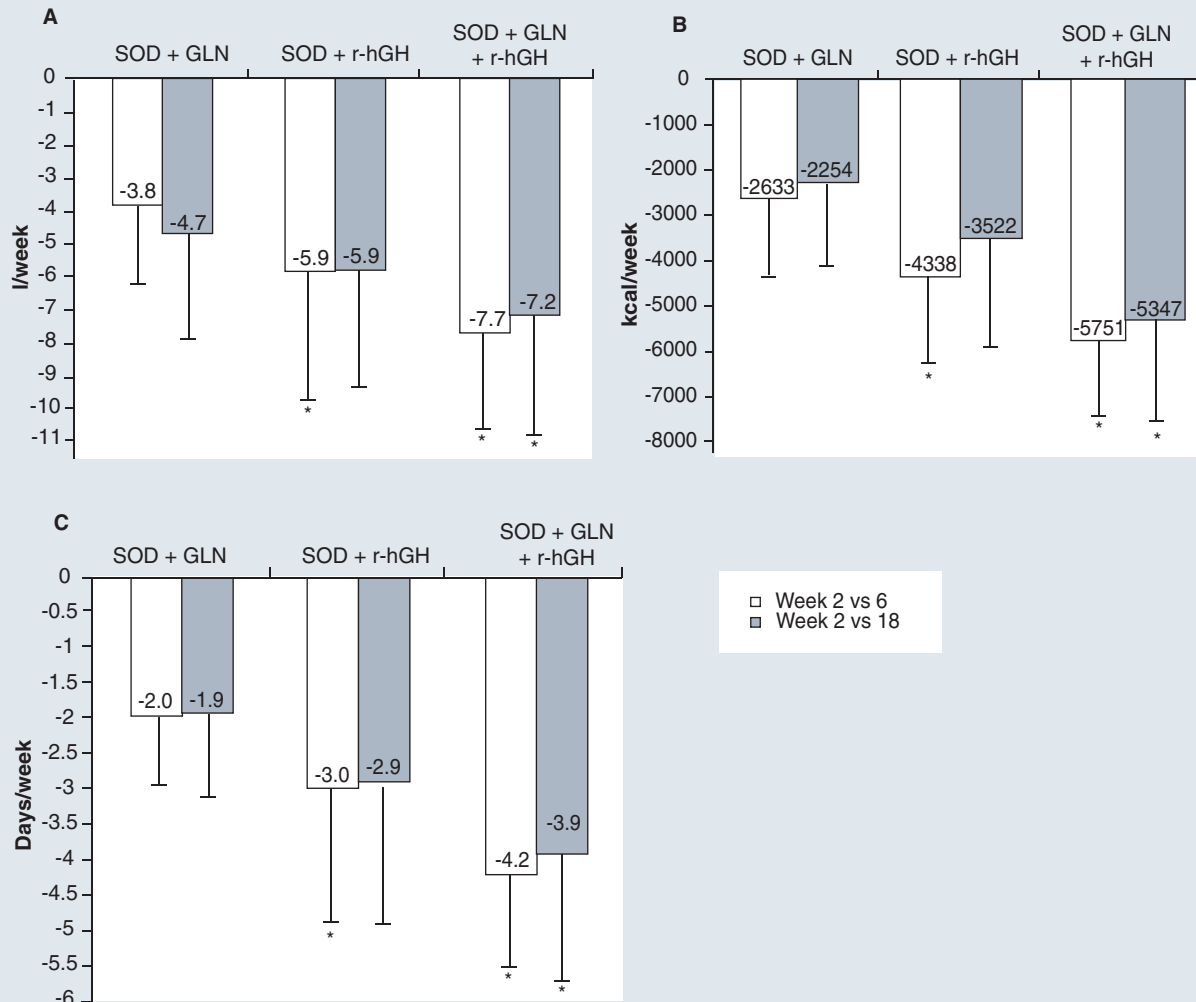
Treatment with r-hGH + SOD, GLN + SOD or r-hGH + GLN + SOD (week 6) and after a 12-week follow-up during which patients continued to receive GLN only or the GLN placebo along with the SOD (week 18).
(A) Reduction in parenteral nutrition volume per week, **(B)** Reduction in parenteral nutrition calories per week and **(C)** Reduction in parenteral nutrition frequency per week.
*p < 0.05 vs diet + glutamine control.
GLN: Glutamine; r-hGH: Recombinant human growth hormone; SOD: Specialized oral diet.
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Safety & tolerability

It is not uncommon to observe adverse events with the dose of somatropin used for SBS. In the study of Byrne and colleagues, the most commonly reported adverse event was fluid retention, manifested as peripheral edema and arthralgia [34]. Reducing the r-hGH dose, limiting fluid intake or administering diuretics were reported to minimize these effects. In the study of Ellegard and colleagues, in which a lower dose of r-hGH was used, no serious adverse events relating to r-hGH

occurred; however, five patients reported slight stiffness of muscles or joints, two experienced gynecomastia, one reported hand paresthesias and one experienced nightmares, nasal obstruction and an exanthema during the first week of treatment [37]. No patients developed clinical edema or arthralgia. In the study of Seguy and colleagues, in which a dose between those of Byrne and Ellegard was used, the most commonly reported adverse events were arthralgia and myalgia [11]. No serious adverse events relating to

r-hGH occurred. There were no occurrences of edema or glycosuria during active treatment. Clinically significant peripheral edema, sometimes requiring diuretic administration or a reduction in parenteral fluid administration, was encountered commonly in the studies reported by Scolapio and Szkudlarek [38,39]. In fact, all patients in the Szkudlarek trial experienced adverse events including one with gynecomastia requiring a lumpectomy and one who underwent surgery for carpal tunnel syndrome. Sleep disturbance, headache, nausea, fatigue and low-grade fever were also reported by patients in the Scolapio study. Finally, in the study of Byrne and colleagues, all of the patients who received r-hGH reported at least one adverse event [48,49]. Peripheral and facial edema, arthralgias, gastrointestinal symptoms, rhinitis and injection site reactions were the most commonly reported adverse events. While edema and arthralgias were more common in patients receiving r-hGH ± glutamine compared with glutamine alone, the incidence of gastrointestinal disturbances was not significantly different for r-hGH ± glutamine compared with glutamine alone. Serious adverse events reported during treatment included chest pain, purpura, fungal infection and pharyngitis in recipients of r-hGH. All drug-related symptoms resolved with dose reduction or drug discontinuation.

In summary, it is not uncommon to observe adverse events with the relatively high dose of somatropin used for SBS. The most common adverse events include peripheral/facial edema, nausea, flatulence, arthralgias and injection site reactions. Serious adverse events appear to occur infrequently. Importantly, many adverse events may be attributable to these patients' underlying condition or to a complication of PN.

Expert commentary

The optimal management of the SBS is based on balancing a minimal dependence on parenteral support with maximal dietary and pharmacologic modification. In order to ensure compliance, the diet should be individualized based upon the individual's bowel anatomy and personal taste [50]; however, perhaps the most important element of the diet is for it to be a high-calorie, hyperphagic diet [11,51]. Pharmacologic treatments mainly consist of antisecretory and antimotility agents together with micronutrient supplementation and antibiotics as necessary [5]. Recently, somatropin has been added to the SBS pharmacologic armamentarium. The primary objective of somatropin is to enhance intestinal

adaptation, thereby allowing a reduction of PN support. Despite encouraging results on PN weaning, the role of r-hGH remains controversial, mainly due to conflicting results obtained from the studies investigating its effects on nutrient absorption.

It is difficult to reconcile the modest benefits of the intestinal absorption studies with the dramatic findings from the PN weaning studies. Part of the difference may be related to one or more of a number of factors including numerous study methodologic differences, such as:

- Small number of patients studied
- Dose of r-hGH used (from 0.024 to 0.14 mg/kg/day)
- Length of treatment (3–8 weeks)
- Use of a modified diet (none, hyperphagic, high-carbohydrate, low-fat, individualized and based on bowel anatomy)
- Patient characteristics (presence of colon, etiology of SBS and length of time on PN)
- Addition of glutamine

The difficulty in performing high-quality, reliable balance studies may also be a factor. Certainly, it should be recognized that the contribution from an optimized diet can be substantial, particularly with patients with colon-in-continuity, and in the studies described previously, these patients were most likely to be successfully weaned from PN.

The explanation for the difference in durability of the treatment effect on nutrient absorption [11,37–39] compared with PN weaning [43,45–48] also remains unclear. Clearly, the use of PN weaning as the primary (clinically relevant) end point is taking into account not only alterations in nutrient and fluid absorption but also other effects, known or unknown, that may relate to other aspects of SBS patient care, such as conventional SBS dietary and medication optimization and compliance. Nevertheless, despite the difficulties of performing balance studies, it has been suggested that the use of PN weaning as the sole clinical end point after introduction of new treatments in the SBS patient is inappropriate and not to be recommended [52].

Appropriate patient selection appears to be critical for the successful use of r-hGH as an adjunct to PN weaning in SBS patients [53]. In particular, while not absolute, those SBS patients with at least a portion of colon remaining, those without underlying mucosal disease in the remaining bowel (e.g., Crohn's disease and radiation enteritis) and those without evidence

of malnutrition at the onset of r-hGH therapy appear to be the best candidates for this therapy [11,54].

Another factor that may have played an important role in the successful outcomes of the studies of Byrne and colleagues [43–45,48] is their conduct in a controlled in-patient-like setting that allowed close monitoring of the patient status and intensive dietary, education and behavior modifications. This likely enhanced compliance with the program both during and after completion of the r-hGH administration period. Despite the administration of somatropin in an in-patient-like setting in the Wilmore study, there is no US Food and Drug Administration (FDA) restriction on out-patient somatropin administration. It remains to be seen whether similar results can be achieved in an out-patient setting.

The study by Byrne and colleagues suggests that the combination of glutamine with r-hGH and a specialized diet is more effective than r-hGH and diet alone [48]. Although it remains controversial whether glutamine coadministration is necessary, given evidence of a potential synergistic role of glutamine and r-hGH in animals and humans, at the present time, the use of glutamine as was used in the clinical trial (i.e., 30 g/day from the first day of r-hGH administration to at least 12 weeks following the end of r-hGH therapy) should be considered.

The gain of approximately 300 to 550 ml/day in fluid and 250 to 450 kcal/day in energy versus the control group in the Byrne study [48] is consistent with the gain observed in the study by Seguy and colleagues (427 kcal/day), in which balance studies were performed [11]. On the basis of these findings, it can be extrapolated that PN may be able to be reduced by one or two infusions per week with this treatment. Therefore, this approach seems best suited for the 'borderline' PN-dependent patients. The ability to wean patients completely from seven infusions per week with this therapy in some of the studies suggests that factors other than r-hGH ± glutamine are playing a role in those patients' success [42].

While findings from the initial studies of Byrne and colleagues suggest that r-hGH can be used to prevent the need for PN in SBS patients [43–45], further studies are needed before this preventative approach can be recommended as r-hGH resistance (and a lower likelihood of response) may be seen in patients with baseline protein calorie malnutrition [11,54]. At this time,

r-hGH should only be used in SBS patients on PN who are unable to eliminate PN use despite an optimized diet and conventional medical management program.

Somatropin appears to be tolerable when used in the doses and duration described in the studies presented. Fluid retention, gastrointestinal symptoms and injection site reactions occur commonly; however, serious adverse effects appear to be uncommon. How long the benefit of somatropin will last remains unknown. Although the FDA approval of somatropin is based on a 4-week administration period, the balance studies indicate that the duration of effect is limited to the treatment period and the safety of long-term continuous treatment or intermittent 4-week treatment with GH needs to be considered. In particular, the potential for promoting the development of colon cancer with long-term r-hGH needs to be considered [55]. In this regard, it should be noted that patients receiving r-hGH replacement therapy (in which the IGF-1 levels are maintained in the normal range) do not have an increased rate of colon cancer [56]. Moreover, mice with transgenic overexpression of GH do not develop colon cancer [57]. This may be related to GH-dependent upregulation of suppressor of cytokine signaling (SOCS)-2, with subsequent inhibition of the proliferative effects of IGF-1 [58].

Outlook

Somatropin is the first pharmacologic treatment for the treatment of PN-dependent SBS patients approved by the FDA. While conflicting data regarding its benefits exist, r-hGH has been shown to enhance intestinal absorption of nutrients in SBS patients and seems to play a role in allowing many of these patients to be weaned from PN completely or to reduce their PN requirements [59–61]. It appears that the optimal clinical benefits are achieved when patients are treated with r-hGH in combination with glutamine and a SOD. Whether these results can be reproduced when patients are not treated in an in-patient-like facility and by less experienced practitioners remains to be seen.

Given the findings from the intestinal absorption studies, somatropin would appear to be a useful adjunct, along with dietary modifications and other standard pharmacologic therapies in the borderline SBS patient on PN. At this time, somatropin is only approved for adults with SBS who require PN support. It

should be used under the guidance of a physician, and preferably a dietitian also experienced in the management of SBS, with an expectation that these patients need to be monitored closely during and after its use. Further study is needed regarding the persistence of effect after treatment and the need for optimal dosage and length of administration for subsequent courses of somatropin as well as its safety, long-term benefit and use in the pediatric and geriatric populations. Despite many unanswered questions, the FDA approval of somatropin in the USA has opened the door to the clinical use of trophic gut factors in SBS.

Highlights

- The management of short bowel syndrome is complex and frequently requires parenteral nutrition support to ensure the sufficient administration of nutrients and fluids. Despite advances in the provision of parenteral nutrition, this mode of nutritional support carries with it significant risks to the patient, impairs quality of life and is costly.
- Intestinal adaptation plays a key role in the successful management of patients with short bowel syndrome. Recent investigations have focused on the use of trophic substances to increase the absorptive function of the remaining gut.
- Published reports from a number of studies using animal models and humans with short bowel syndrome have demonstrated conflicting findings regarding the efficacy of recombinant human growth hormone (r-hGH) to stimulate intestinal absorption. Substantial methodologic differences among the studies prevent definitive conclusions regarding the benefit of this therapy on intestinal adaptation.
- In a recent randomized, controlled trial of somatropin (i.e., r-hGH), glutamine and a specialized oral diet in patients with parenteral nutrition-dependent short bowel syndrome, treatment with somatropin resulted in significant reductions in parenteral nutrition requirements compared with the control group.
- Somatropin appears to be well tolerated with generally manageable side effects. Fluid retention, gastrointestinal symptoms and injection site reactions occur commonly; however, serious adverse effects appear to be uncommon.
- Optimal clinical benefits appear to be achieved when somatropin is administered in combination with glutamine and a specialized oral diet. It should be used under the guidance of clinicians experienced in the management of short bowel syndrome, with the expectation that these patients need to be monitored closely during and after its use.
- Further study is needed regarding the persistence of effect after treatment and the optimal dosage and length of administration for subsequent courses of somatropin as well as its safety, long-term benefit and use in the pediatric and geriatric populations.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology* 124, 1111–1134 (2003).
•• Review of SBS management including intestinal transplantation.

2. Bakker H, Bozzetti F, Staun M *et al*. Home parenteral nutrition in adults: a European multicentre survey in 1997. ESPEN – Home Artificial Nutrition Working Group. *Clin. Nutr.* 18, 135–40 (1999).

3. Howard L, Ament M, Fleming CR *et al*. Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology* 109, 355–65 (1995).

4. Thiesen A, Drozdowski L, Iordache C *et al*. Adaptation following intestinal resection: mechanisms and signals. *Best Pract. Res. Clin. Gastroenterol.* 17, 981–995 (2003).

5. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 2. *Am. J. Gastroenterol.* 99, 1823–1832 (2004).

6. Jeppesen PB, Mortensen PB. Intestinal failure defined by measurements of intestinal energy and wet weight absorption. *Gut* 46, 701–706 (2000).

7. Messing B, Crenn P, Beau P *et al*. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology* 117, 1043–1050 (1999).

8. Crenn P, Morin MC, Joly F *et al*. Net digestive absorption and adaptive hyperphagia in adult short bowel patients. *Gut* 53, 1279–1286 (2004).

9. Dowling FH, Booth CC. Functional compensation after small bowel resection in man: demonstration by direct measurement. *Lancet* 2, 146–147 (1966).

10. Crenn P, Coudray-Lucas C, Thuillier F, Cynober L, Messing B. Postabsorptive plasma citrulline concentration is a marker of absorptive enterocyte mass and intestinal failure in humans. *Gastroenterology* 119, 1496–1505 (2000).

11. Seguy D, Vahedi K, Kapel N, Souberbielle JC, Messing B. Low-dose growth hormone in adult home parenteral nutrition-dependent short bowel syndrome patients: a positive study. *Gastroenterology* 124, 293–302 (2003).
• Demonstrates a beneficial effect on nutrient absorption.

12. Tritos NA, Mantzoros CS. Recombinant human growth hormone: old and novel uses. *Am J Med.* 105, 44–57 (1998).

13. Lund PK. Molecular basis of intestinal adaptation: the role of the insulin-like growth factor system. *Ann. NY Acad. Sci.* 859, 18–36 (1998).

14. Kovacevic Z, McGivan JD. Mitochondrial metabolism of glutamine and glutamate and its physiological significance. *Physiol. Rev.* 63, 547–605 (1983).

15. Askanazi J, Carpentier YA, Michelsen CB *et al*. Muscle and plasma amino acids following injury. Influence of intercurrent infection. *Ann. Surg.* 192, 78–85 (1980).

16. Shulman DI, Hu CS, Duckett G, Lavallee-Grey M. Effects of short-term growth hormone therapy in rats undergoing 75% small intestinal resection. *J. Pediatr. Gastroenterol. Nutr.* 14, 3–11 (1992).

17. Hart MH, Phares CK, Erdman SH, Grandjean CJ, Park JHY, Vanderhoof JA. Augmentation of post-resection mucosal hyperplasia by pleceroid growth factor (PGF) – analog of human growth hormone. *Dig. Dis. Sci.* 32, 1275–1280 (1987).

18. Christensen H, Jorgensen PH, Oxlund H. Growth hormone increases the mass, the collagenous proteins and the strength of rat colon. *Scand. J. Gastroenterol.* 25, 1137–114 (1990).

19. Verhage AH, Aghdassi E, Allard JP. Effects of growth hormone in rats with 80% small bowel resection fed totally by parenteral nutrition. *Nutr. Res.* 18, 823–832 (1998).

20. Benhamou PH, Canarelli JP, Richard S *et al*. Human recombinant growth hormone increases small bowel lengthening after massive small bowel resection in piglets. *J. Pediatr. Surg.* 32, 1332–1336 (1997).

21. Taylor B, Murphy GM, Dowling RH. Pituitary hormones and the small bowel: effect of hypophysectomy on intestinal adaptation to small bowel resection in the rat. *Eur. J. Clin. Invest.* 9, 115–127 (1979).

22. Ulshen MH, Dowling RH, Fuller CR *et al*. Enhanced growth of small bowel in transgenic mice overexpressing bovine growth hormone. *Gastroenterology* 104, 973–980 (1993).

23. Mainoya JR. Effects of bovine growth hormone, human placental lactogen and ovine prolactin on intestinal fluid and ion transport in the rat. *Endocrinology* 96, 1165–1170 (1975).

24. Mainoya JR. Influence of bovine growth hormone on water and NaCl absorption by the rat proximal jejunum and distal ileum. *Comp. Biochem. Physiol.* 71, 477–479 (1982).

25. Zhou X, Li YX, Li N, Li JS. Glutamine enhances the gut trophic effect of growth hormone in rat after massive small bowel resection. *J. Surg. Res.* 99, 47–52 (2001).

26. Park JH, Vanderhoof JA. Growth hormone did not enhance mucosal hyperplasia after small-bowel resection. *Scand. J. Gastroenterol.* 31, 349–355 (1996).

27. Iannoli P, Miller JH, Ryan CK, Gu LH, Ziegler TR, Sax HC. Epidermal growth factor and human growth hormone accelerate adaptation after massive enterectomy in an additive nutrient-dependent and site-specific fashion. *Surgery* 112, 721–729 (1997).

28. Ljungmann K, Grofte T, Kissmeyer-Nielsen P *et al*. GH decreases hepatic amino acid degradation after small bowel resection in rats without enhancing bowel adaptation. *Am. J. Physiol. Gastrointest. Liver Physiol.* 279, G700–706 (2000).

29. Biolo G, Iscra F, Bosutti A *et al*. Growth hormone decreases muscle glutamine production and stimulates protein syntheses in hypercatabolic patients. *Am. J. Physiol.* 279, E323–E332 (2000).

30. Ziegler TR, Mantell MP, Chow JC, Rombeau JL, Smith RJ. Gut adaptation and the insulin-like growth factor system: regulation by glutamine and IGF-1 administration. *Am. J. Physiol.* 271:G866–875 (1996).

31. Gu Y, Wu Z-H, Xie JX, Jim DY, Zhuo HC. Effects of growth hormone and glutamine supplemented parenteral nutrition on intestinal adaptation in short bowel rats. *Clin. Nutr.* 20, 159–166 (2001).

32. Waitzberg DL, Cukier C, Mucerino DR, Logulo AF, Torrinhas RS, de Castro I. Small bowel adaptation with growth hormone and glutamine after massive resection of rat's small bowel. *Nutr. Hosp.* 14, 81–90 (1999).

33. Vanderhoof JA, Kollman KA, Griffin S, Adrian TE. Growth hormone and glutamine do not stimulate intestinal adaptation following massive small bowel resection in the rat. *J. Pediatr. Gastroenterol. Nutr.* 25, 327–331 (1997).

34. Byrne TA, Morrisey TB, Nattakom TV, Ziegler TR, Wilmore DW. Growth hormone, glutamine and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. *J. Parenter. Enter. Nutr.* 222, 296–302 (1995).
   • **Suggests benefit of r-hGH combined with glutamine and a modified diet.**

35. Zhu W, Li N, Ren J *et al*. Rehabilitation therapy for short bowel syndrome: experimental study and clinical trial. *Chin. Med. J. (Engl.)* 115, 776–778 (2002).

36. Wu GH, Wu ZH, Wu ZG. Effects of bowel rehabilitation and combined trophic therapy on intestinal adaptation in short bowel patients. *World J. Gastroenterol.* 9, 2601–2604 (2003).

37. Ellegard L, Bosaeus I, Nordgren S, Bengtsson BA. Low-dose recombinant growth hormone increases body weight and lean body mass in patients with short bowel syndrome. *Ann. Surg.* 22, 88–96 (1997).

38. Scolapio JS, Camilleri M, Fleming CR *et a*l. Effect of growth hormone, glutamine, and diet on adaptation in short bowel syndrome: a randomized, controlled study. *Gastroenterology* 113, 1074–1081 (1997).
   • **Demonstrates lack of r-hGH effect combined with glutamine and modified diet on nutrient absorption in SBS patients.**

39. Skudlarek 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 randomized, double-blind, crossover, placebo-controlled study. *Gut* 47, 199–205 (2000).
   • **Demonstrates lack of r-hGH effect combined with glutamine, without a modified diet.**

40. Scolapio JS. Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: a randomized, controlled study. *J. Parenter. Enter. Nutr.*23, 309–312 (1999).

41. Jeppesen PB, Szkudlarek J, Hoy CE, Mortensen PB. Effect of high-dose growth hormone and glutamine on body composition, urine creatinine excretion, fatty acid absorption, and essential fatty acid status in short bowel patients: a randomized, double-blind, crossover, placebo-controlled study. *Scand. J. Gastroenterol.* 36, 48–54 (2001).

42. Scolapio JS. Tales from the crypt. *Gastroenterology.* 124, 561–564 (2003).

43. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A new treatment for patients with short-bowel syndrome: growth hormone, glutamine, and a modified diet. *Ann. Surg.* 222, 243–254 (1995).
   • **Suggests benefit of r-hGH with glutamine and a modified diet.**

44. Wilmore DW, Lacey JM, Soultanakis RP, Bosch RL, Byrne TA. Factors predicting a successful outcome after pharmacologic bowel compensation. *Ann. Surg.* 226, 288–293 (1997).

45. Byrne TA, Cox S, Karimbakas M *et al*. Bowel rehabilitation: an alternative to long-term parenteral nutrition and intestinal transplantation for some patients with short bowel syndrome. *Transplant Proc.* 34, 887–890 (2002).

46. Zhu W, Li N, Ren J, Gu J, Jiang J, Li J. Rehabilitation therapy for short bowel syndrome. *Chin. Med. J. (Engl.)* 115, 776–778 (2002).

47. Weiming Z, Ning L, Jieshou L. Effect of recombinant human growth hormone and enteral nutrition on short bowel syndrome. *J. Parenter. Enter. Nutr.* 28, 377–281 (2004).

48. 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.* 242, 655–661 (2005).
   •• **Demonstrates the beneficial effect of r-hGH with glutamine and a modified diet.**

49. Zorbtive™ (somatropin [rDNA origin] for injection), Serono, Inc., MA, USA.

50. Byrne TA, Veglia L, Camelio M *et al.* Beyond the prescription: optimizing the diet of patients with short bowel syndrome. *Nutr. Clin. Pract.* 15, 306–311 (2000).

51. Jeejeebhoy KN. Short bowel syndrome: a nutritional and medical approach. *CMAJ* 166, 1297–1302 (2002).

52. Jeppesen PB, Mortensen PB. Experimental approaches: dietary and hormone therapy. *Best Pract. Res. Clin. Gastroenterol.* 17, 1041–1054 (2003).

53. Byrne T, Wilmore D. Does growth hormone and glutamine enhance bowel absorption? *Gastroenterology* 114, 1110–1112 (1998).

54. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endo. Rev.* 15(1), 80–101 (1994).

55. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J. Nutr.* 131(Suppl.), 3109S–3120S (1994).

56. Beentjes JA, van Gorkom BA, Sluiter WJ, de Vries EG, Kleibeuker JH, Dullaart RP. One year growth hormone replacement therapy does not alter colonic epithelial proliferation in growth hormone deficient adults. *Clin. Endocrinol. (Oxf.)* 52, 457–462 (2000).

57. Williams KL, Fuller CR, Dieleman *et al.* Enhanced survival and mucosal repair after dextran sodium sulfate-induced colitis in transgenic mice that overexpress growth hormone. *Gastroenterology* 120, 925–937 (2001).

58. Theiss AL, Fruchtman S, Lund PK. Growth factors in inflammatory bowel disease: the actions and interactions of growth hormone and insulin-like growth factor-1. *Inflamm. Bowel Dis.* 10, 871–880 (2004).

59. Ling L, Irving M. The effectiveness of growth hormone, glutamine and a low-fat diet containing high-carbohydrate on the enhancement of the function of remnant intestine among patients with short bowel syndrome: a review of published trials. *Clin. Nutr.* 20, 199–204 (2001).

60. Matarese LE, Seidner DL, Steiger E. Growth hormone, glutamine, and modified diet for intestinal adaptation. *J. Am. Diet Assoc.* 104, 1265–1272 (2004).

61. Zhou Y, Wu XT, Yang G, Zhuang W, Wei ML. Clinical evidence of growth hormone, glutamine and a modified diet for short bowel syndrome: meta-analysis of clinical trials. *Asia Pac. J. Clin. Nutr.* 14, 98–102 (2005).

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