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Review Article

Effects of Glutamine, Growth Hormone and Modified Diet in Short Bowel Syndrome: A Systematic Review

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ABSTRACT

Rehabilitation therapy for short bowel syndrome (SBS) may improve patients' nutritional status and promote intestinal adaptation. In this systematic review, we assessed the efficacy of growth hormone (GH) and glutamine (GLN) with a modified diet (high-carbohydrate-low-fat, HCLF) in patients with SBS. Electronic searches were performed to identify all publications describing clinical trials on the use of GH, GLN and diet for the treatment of patients with SBS, from the following databases: PubMed, Embase and Cochrane until December 2018, without any time and design restriction. Also, a manual search was performed to find extra relevant articles. Our research included sixteen trials involving 323 patients. These trials evaluated improvement of SBS through intervention by using GH, GLN and modified diet with different outcomes such as body weight (BW), lean body mass (LBM), fat mass, stool output, absorption of carbohydrates, fat, energy, nitrogen, and D-xylose and off total parenteral nutrition (TPN). It was shown that in all studies that were performed with a combination of GH, GLN and HCLF diet, there was a positive treatment effect on body weight, lean body mass, stool output, absorption of carbohydrates, nitrogen, and D-xylose and off TPN, but there were no improvements in absorption of fat, and energy and fat mass. Based on this s review, treatment with a combination of GH, GLN and modified diet can be more effective in improvement of adaptation of the small intestine than when they are used alone. Finally, further trials suggested the combination of these three factors.

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Introduction

Short-bowel syndrome (SBS) is considered a rare disease and the estimated population prevalence is approximately 1 per million (1), also The Canadian Collaborative Study Group-39 estimated the incidence of SBS across Canada as 4.8/million population/year (2). Short bowel syndrome (SBS) results from resection of unviable intestine secondary to vascular insufficiency, Crohn's disease, malignancy or radiation in adults. In the pediatric population, congenital intestinal anomalies such as gastroschisis or atresia, or necrotizing enterocolitis lead to insufficient intestinal length to maintain nutrition (2). Thus SBS is characterized by the inability to maintain protein, energy, fluid, electrolyte, or micronutrient balances and causes

symptoms such as chronic diarrhea, dehydration, fluid and electrolyte imbalances (3).

There are several therapies for SBS. The patients often require long-term parenteral nutrition (PN) to maintain daily nutritional requirements, but the use of long-term PN is expensive and is associated with certain complications, including venous occlusions, catheter sepsis, and liver failure (3). In patients who can no longer receive parenteral support, small bowel transplantation has been performed. The results of transplantation have improved, but still remain disappointing. The long-term survival rate of intestinal transplantation is not high enough to be accepted as a routine procedure for some patients (4). Since a program of intestinal rehabilitation, which included growth hormone (GH), glutamine, and a modified diet, was proposed by Byrne et al. (5) to enhance intestinal compensation and attenuate intestinal failure.

GH is a protein-based peptide hormone that promotes somatic growth, stimulates protein synthesis, and regulates carbohydrate and lipid metabolism (3). GH has been shown to increase small bowel growth after resection. Glutamine (GLN) is a conditional essential nutrient and most abundant free amino acid in the body (6). Among the various tissues using glutamine at high rates, the intestine utilizes about 30% of total glutamine, indicating that it is a key nutrient for the intestine. Supplemental glutamine was shown to enhance the absorption of sodium and glucose and to prevent intestinal atrophy in humans who received PN therapy (3).

A modified diet may be useful for clinically defining functional SBS. For example, one recommendation is to maintain patients with SBS with residual colon on a HCLF diet, which provides about 60% of calories as complex carbohydrates, 20% as protein, and the remainder as fat. Such a diet results in greater caloric absorption than a high-fat, low-carbohydrate diet because malabsorbed carbohydrates are salvaged in the colon, whereas malabsorbed fatty acids are not (6). According to controversial results of the effects of GH, GLN and modified diet on the treatment of SBS, in some articles, in this review, our aim was to assess the efficacy of GH, GLN and modified diet in patients with short bowel syndrome.

Materials and Methods

We searched PubMed, EMBASE and Cochrane databases up to December 2018 to find clinical trials examining the effect of GH, GLN and modified diet in patients with SBS. We did not apply any restriction on the study design and the time. A group of search terms were used including: ("growth hormone" or "GH" or "pituitary growth hormone" or "somatotropin" or "recombinant growth hormone") and ("L-glutamine" or "D-glutamine") and ("diet" or "modified diet") and ("short bowel syndrome" or "SBS") in search protocol.

Studies that met all of the following criteria were included in this review: Clinical trial studies, patients of all ages with SBS, the different agents and doses of GH, GLN and modified diet, main outcome such as body weight (BW), lean body mass (LBM), fat mass, stool output, absorption of carbohydrates, fat, energy, nitrogen, and D-xylose and the number of patients off TPN. PICOS criteria was used to define the research question for the systematic review (Table 1). Studies were excluded from the review for meeting any of the following criteria: Patients with clinically active inflammatory bowel disease and patients that were supported with pharmacologic treatment; no original articles or case report; animal studies and review articles (Table 1).

Results

We identified 61 articles after the search of the 3 databases and 17 duplicate records were excluded. Then 4 records were excluded based on assessing the title and abstract. The remaining 40 articles in addition to 2 records identified through hand searching, were assessed for eligibility. Then 26 articles were removed as follows: 16 review articles

Table 1: PICOS criteria for inclusion and exclusion of studies

Criteria	Inclusion criteria	Exclusion criteria
Population	Male and female patients of any ages with short bowel syndrome	Patients with clinically active inflammatory bowel disease (IBD)
Intervention	Treatment with glutamine, growth hormone, Modified diet	Pharmacological treatment
Comparison	Compared with placebo	
Outcomes	Body weight (BW), Lean body mass (LBM), Fat mass, Stool output, Absorption of carbohydrates, Absorption of fat, Absorption of energy, Absorption of nitrogen, Absorption of D-xylose and the number of patients off TPN	
Study design	Any clinical trial	No original articles or case report; Animal studies and review articles

and 1 meta-analysis article and 6 animal studies, 2 studies were not available and one of them did not have English full text. Finally, 16 articles were included in this systematic review, as summarized in Figure 1. Characteristics of studies included of GH, GLN and diet on short bowel syndrome was presented in Figure 1.

The dose of GH used in these trials ranged from 0.024 to 0.14 mg/kg/day and the dose of GLN ranged from 0.45-0.63 (oral) and 0.3-0.56 (parenteral). The length of interventions range was from 3 weeks to 4 weeks. Characteristics of studies included of GH, GLN and diet on short bowel syndrome were presented in Table 2. In 13 studies, body weight was reported. Weight gain was reported in all of the three studies (7-9) that were conducted with growth GH intervention. One study (10) including treatment with GH and GLN, had reported weight gain ($P<0.05$). Also in 9 studies (4, 5, 11-17) following GH and GLN and HCLF diet consumption, increase in body weight was identified. One study (18) following GLN and HCLF diet, reported no change in body weight ($P=0.570$).

Regarding the effect on lean body mass, in all of the three studies (7-9) that were conducted with GH intervention, lean body mass increased compared to placebo group. A study (10) including treatment with GH and GLN, had reported increase in LBM. Also in 3 studies (4, 13, 16) following GH and GLN and HCLF diet consumption, increase in LBM was reported. Considering the effect on fat mass, in two studies (7, 8) following GH consumption and one study (18) following GLN and HCLF diet consumption, no change in fat mass was reported. In a study (10) that involved intervention with GH and GLN, fat mass decreased ($P<0.001$).

Also in two studies (4, 13) of treatment with GH, GLN and HCLF diet, one of them reported a decrease in fat mass ($P<0.001$), and in the other, no change was reported ($P=0.244$). Regarding the effect on stool output, seven studies (4, 5, 11, 14, 16, 17, 19) evaluated the effect of GH and GLN and HCLF diet consumption on stool output. There was a decrease compared to placebo group. One study (15) reported no change in stool output. Considering the effect on absorption, the absorption of energy in one study (8) that conducted with GH, was increased ($P<0.002$) and in the other study (20) following GH and GLN consumption, no change was reported ($P>0.05$). One

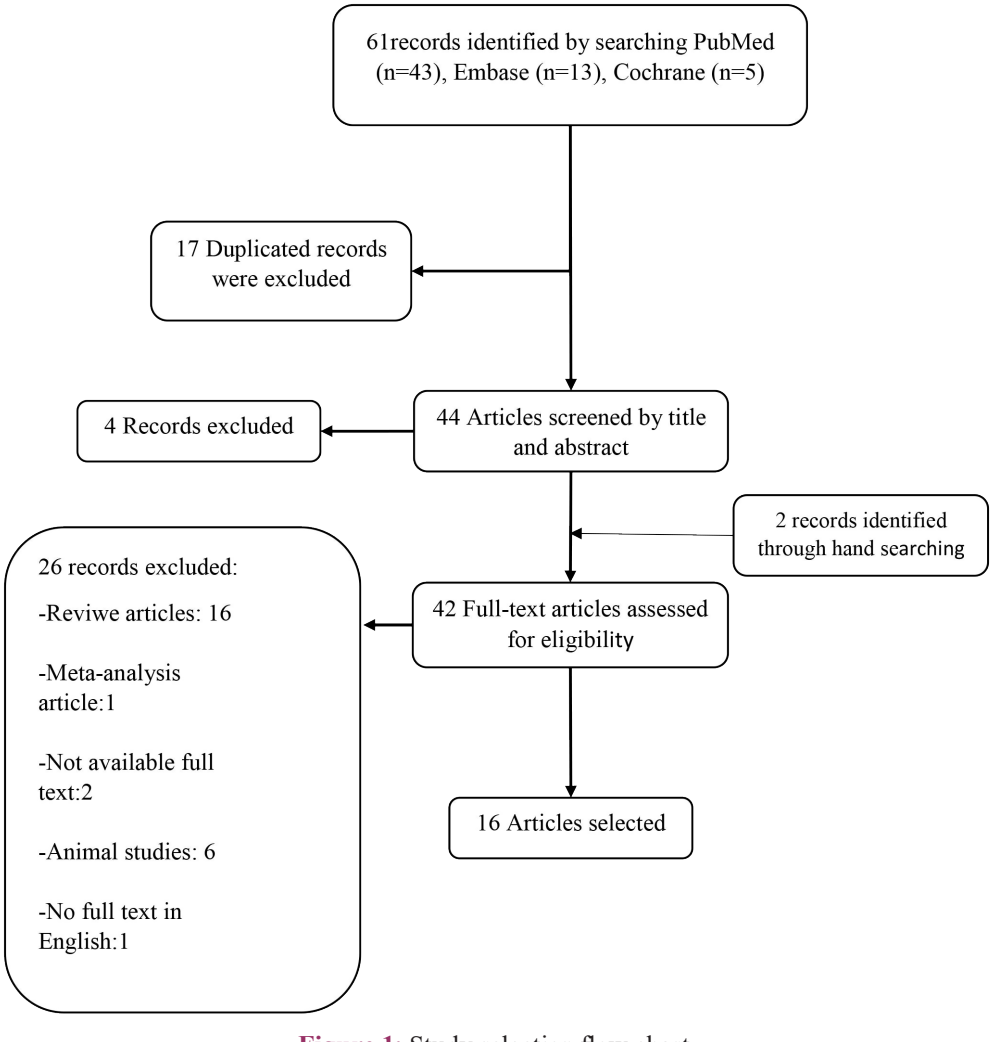

Figure 1: Study selection flow chart.

Table 2: Characteristics of studies included growth hormone, glutamine and a modified diet for short bowel syndrome

Author, Year	Participant and sex	Age (year)	Study design	Duration	Growth hormone (mg/kg/d	Glutamine (g/kg/d)	Diet	Outcome
Byrne (1995)	10 (5M/5F)	Range,28-68 Mean,43	Clinical trial	28 Days	0.14	OR:0.63 PE:0.42	HCLF	Increase in BW (P≤0.0001), Increase in absorption of calories (P≤0.003) and carbohydrate (P≤0.02), decrease in stool output (P≤0.05)
Byrne (1995)	47 (25M/22F)	Range,19-76 Mean,46	Clinical trial	4 Weeks	0.14	OR/PE:0.6	HCLF	Increase in BW (P≤0.0001), decrease in stool output (P<0.05), Off TPN
Ellegard (1997)	10 (7M/3F)	Range,30-72 Mean,49	Double-blind RCT	8 Weeks	0.024	None	HCLF	Increase in BW (P=0.005) and LBM (P=0.005), No change in fat mass
Scolapio (1997)	8 (6M/2F)	Range,39-69 Mean,48.4	Double-blind RCT	6 Weeks	0.14	OR:0.63	HCLF	Increase in BW
Scolapio (1999)	8 (6M/2F)	Range,39-69 Mean,48.4	Double-blind RCT	6 Weeks	0.14	OR:0.63	HCLF	Increase in BW (P<0.05) and LBM (P<0.001) and fat mass (P<0.001)
Szkud-larek (2000)	8 (1M/7F)	Rnge,32-74 Mean,47	Double-blind RCT	28 Days	0.12	OR/PE:0.56	No change	No change in absorption of calories and carbohydrate and fat and nitrogen (P>0.05)
Jeppesen (2001)	8 (1M/7F)	Rnge,32-74 Mean,47	Double-blind RCT	28 Days	0.12	OR/PE:0.56	No change	Increase in BW (P<0.05) and LBM (P<0.001), Decrease in fat mass (P<0.001), No change in absorption of fat
Scolapio (2001)	8 (3M/5F)	Range,42-73 Mean,65.5	Double-blind RCT	8 Weeks	None	OR:0.45	HCLF	No change in absorption of fat (P>0.05) and D-xylose (P=0.109) and BW (P=0.570)
Seguy (2003)	12 (8M/4F)	Range,19-51 Mean, 35	Double-blind RCT	3 Weeks	0.05	None	No change	Increase in absorption of energy (P<0.002), carbohydrate (P<0.04), D-xylose (P<0.02), No change in fat mass, Increase in BW (P<0.003), LBM (P<0.002)
Wu GH (2003)	38 (28M/10F	Range,7-68 Mean, 38	Clinical trial	3 Weeks	0.14	PE:0.3	HCLF	Increase in absorption of D-xylose (P<0.05), Off TPN, Increase in BW, Decrease in stool output

Weiming (2004)	37 (27M/10F	Range,9-74 Mean,36.3	Clinical trial	4 Weeks	0.05	OR:0.6	HCLF	Increase in absorption of D-xylose, Off TPN, Decrease in stool output (P=0.002)
Byrne (2005)	41 (12M/29F	Range,18-75	RCT	6 Weeks	0.1	OR:30 g/d	HCLF	Increase n BW (P=0.0024), No change in stool output, Decrease in PN requirement (P<0.02)
Gong (2009)	61(46M/15F	Range,18-74 Mean,37.56	Clinical trial	3 Weeks	0.05	OR:30 g/d	HCLF	Increase in BW (P=0.015) LBM (P=0.012), Increase in absorption of D-xylose (P=0.028), Decrease in stool output (P=0.004), Off TPN
Guo (2012)	7 Pediatric (4M/3F)	Range,21-90 Month Mean 55	Clinical trial	3 Weeks	0.05	OR:0.45	HCLF	Increase in absorption of nitrogen (P=0.038), and D-xylose (P=0.043), Increase in BW, Decrease in stool output (P<0.05)
Guo (2013)	12(9M/3F)	Range,8-61 Mean, 33	Clinical trial	4 Weeks	0.05	OR:30 g/d	HCLF	Increase BW (P=0.007), and LBM (P=0.03), No change in fat mass (P=0.244), Increase in absorption of nitrogen (P=0.000), Decrease in stool output (P<0.05), Off PN
Seguy (2014)	8 (6M/2F)	Range,19-51 Mean, 32	Double-blind RCT	7 Weeks	0.05	None	None	Increase in BW (P=0.012), No change in fat free mass (P=0.17)

study (5) reported that absorption of carbohydrate and energy increased by intervention with GH and GL and HCLF diet (P≤0.02).

The absorption of fat was reported by two studies (10, 20), which did not change in both of them (P>0.05). For absorption of nitrogen, one study (20) following treatment with GH and GLN, no change was reported (P>0.05) and three studies (4, 17, 19) following GH and GLN and HCLF diet consumption, reported increase in absorption of nitrogen. Absorption of D-xylose was reported as increase in one study (8) following GH consumption (P<0.02), and also increased in three studies (14, 16, 17) by consumption of GH and GLN and HCLF diet. One study (18) reported no change in absorption of D-xylose, following GLN and HCLF diet consumption (P=0.109).

Regarding the effect on off TPN, off TPN was reported in 6 studies (4, 5, 14, 16, 17, 19), during GH, GLN, and HCLF diet consumption. One study reported 27 of the 47 patients (57%) not to require TPN and 14 patients (30%) showed reduction in TPN requirements after intervention by GH and GLN and HCLF diet. Another study reported 3 of 38 patients (7.9%) to wean from TPN completely, and 3 patients (7.9%) demonstrated a reduction in TPN requirements, and 2 patients failed the therapy after the treatment by GH. Another one more study reported that among 23 patients, 18 weaned off TPN (78%). Another study revealed that 85.5% weaned off TPN in patients during GH and GLN and HCLF diet consumption. In one study (17) that was conducted in the pediatric population, 6 of 7 patients weaned off TPN by GH and GLN and HCLF diet consumption and reported among 11 patients, 5 were weaned off TPN (45.45%).

Discussion

Post-resection intestinal adaptation is complex and influenced by several factors, and management of patients with SBS is challenging and requires

vigorous attention to every detail. Studies showed that rehabilitation therapy for short bowel syndrome can improve patient nutritional status effectively and promote intestinal adaptation, providing a new hope for these patients. The rehabilitation therapy included enteral or parenteral nutrition, glutamine, recombinant human growth hormone and rehabilitative diet (3).

Both animal and human studies have demonstrated that GH stimulates intestinal growth and enhances transport of nutrients across the small bowel (6). Although opinions differ, GH is supposed to vigorously stimulate intestinal adaptation. It is suggested that GH takes part in the maintenance of the structure and function of the intestinal mucosa (21). Additionally, GH induces IGF1 synthesis in the liver, which is thought to be the primary source of circulating IGF-1, and in many tissues with GH receptors including intestinal tissues (22). IGF-1is an important peptide growth factor and leads to an increase in crypt cell production rate, with a consequent increase in villus height and nutrient absorptive capability (23).

The efficacy of glutamine supplementation has been tested in humans and animal models with intestinal diseases. Its functions include maintaining nucleotide metabolism and intestinal barrier function, modulation of inflammation, and regulating stress responses and apoptosis. Moreover glutamine influences a number of signaling pathways that regulate cell cycle regulation and proliferation. When proliferation is activated by these signals, crypt-residing intestinal stem cells differentiate into specialized epithelial cell types, including enterocytes, goblet cells, paneth cells, and enterocytes, which enables the maintenance of normal intestinal tissue integrity (24).

All three studies that were assess the efficacy of GH on SBS, shown that a positive effects on body weight and lean body mass and also increased energy and carbohydrate absorption. There are few studies about the effect of GLN on SBS and as suggested by Scolapio (2001), glutamine and diet has no significant effect on small bowel morphology, absorption and transit in patients with short bowel syndrome. Many studies have shown that treatment with GH and GLN is more anabolic than administration of either GH or GLN alone in the remnant small intestine (22). Moreover, studies suggested that when GH and GLN are administered in combination, GLN supply could be maintained and adaptation of the small intestine would be further improved (21).

Butin this systematic review, the results showed that when a HCLF diet is added to combination of GH and GLN, they can affect more factors that contribute to the improvement of the short bowel syndrome and be more effective in the adaptation of small intestine. A meta-analysis on this issue was also conducted by Zhou et al. in 2005, and we achieved similar results by adding newer papers in this study. We also investigated the effects of GLN and GH separately in this study.

Conclusion

The treatment with a combination of GH, GLN and HCLF diet can be positive treatment effect on body weight, lean body mass, stool output, absorption of carbohydrate, energy, nitrogen, and D-xylose and off TPN; but there was no improvement in fat mass and absorption of fat.

Conflict of Interest

None declared.

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