Intestinal adaptation in short bowel syndrome. What is new?

Adaptación intestinal en el síndrome de intestino corto: ¿qué hay de nuevo?

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Abstract

Short bowel syndrome (SBS) is a well-known cause of intestinal failure (IF) (1). SBS occurs after extensive resection of the small bowel (RSB) resulting in a bowel length of less than 150/200 cm. The colon may have been partially or completely removed. SBS patients experience severe water and nutrient malabsorption, so that they are often managed with parenteral nutrition (PN) to supplement their oral intake (2–4). A complete understanding of the pathophysiology of SBS and postoperative adaptations may allow identifying the spontaneous processes that compensate for the reduction in absorptive surface. A better knowledge of these adaptive mechanisms may help to improve the management of patient nutrition, to reduce the need for PN and to prevent D-encephalopathy episodes. This review focuses on the overall adaptations described in adult SBS patients but does not review pediatric cases.
INTRODUCTION

Short bowel syndrome (SBS) is a well-known cause of intestinal failure (IF) (1). SBS occurs after extensive resection of the small bowel (RSB) resulting in a bowel length of less than 150/200 cm. The colon may have been partially or completely removed. SBS patients experience severe water and nutrient malabsorption, so that they are often managed with parenteral nutrition (PN) to supplement their oral intake (2-4). A complete understanding of the pathophysiology of SBS and postoperative adaptations may allow identifying the spontaneous processes that compensate for the reduction in absorptive surface. A better knowledge of these adaptive mechanisms may help to improve the management of patient nutrition, to reduce the need for PN and to prevent D-encephalopathy episodes. This review focuses on the overall adaptations described in adult SBS patients but does not review pediatric cases.

INTESTINAL FAILURE AND SHORT BOWEL SYNDROME

Intestinal failure (IF) occurs in various gastrointestinal diseases such as gut motility disorders, mechanical obstruction, intestinal fistula, extensive small bowel mucosal disease, volvulus or systemic conditions such as mesenteric infarction and post-radiation enteritis. IF is defined as a reduction in gut function below the minimum needed for the absorption of macronutrients and/or water and electrolytes, resulting in intravenous (IV) supplementation to maintain health and/or growth (1).

Three different types of IF have been described based on duration: a) acute, short-term and usually self-limiting conditions; b) prolonged acute conditions, often in metabolically unstable patients, requiring complex multi-disciplinary care and IV supplementation over long periods; and c) chronic reversible or irreversible conditions in metabolically stable patients, requiring long-term intravenous supplementation. In adults, SBS appears after massive intestinal resection leaving patients with less than 200 cm of small bowel defines SBS, and a small bowel length of < 100 cm is highly predictive of permanent IF (5-7). While the actual prevalence of SBS in adults is unknown, the estimated prevalence is 1.4 cases per million people in Europe. It varies depending on the region, from 0.4 to approximately 30 cases per million in Poland and Denmark, respectively (8). The prevalence of SBS is lower in regions where there are no major intestinal rehabilitation centers and efficient home PN (HPN) or IV programs, likely because of under-reporting and the inability to adequately treat these patients.

Adaptive changes following resection explain why some patients can be weaned off PN. The degree of intestinal adaptation depends on the underlying pathology for which resection is needed, the unresected anatomic sections of the intestine and the length of the remaining bowel (6,9). Resection of the small bowel results in three different anatomic anastomoses: a) enterostomy; b) jejuno-colonic; and c) jejuno-ileo-colonic. In most cases, intestinal adaptation in adults is supposed to occur 1-2 years after resection, but no objective, clinically practical markers have been identified to determine the time course or extent of adaptation in humans (10). Preserving the colon is essential for reducing the need for PN in SBS patients (6,11). The probability of PN-independence is of 47% five years after surgery and is significantly associated with a remnant small bowel length greater than 75 cm, a large portion of remaining colon and a postoperative citrulline concentration greater than 20 µmol/l (12). The post-absorptive concentration has been shown to correlate with the small bowel length and to be a prognostic factor for HPN dependency (11,12).

ROLE OF THE COLON IN FLUID AND ELECTROLYTE ABSORPTION

The large intestine or colon measures about 1.5 m in length in adults and consists of four parts: the ascending colon, the transverse colon, the descending colon, and the sigmoid colon. Once the chyme has reached the colon, almost all nutrients and 80-90% of the water have been absorbed in the small intestine. At this point, some electrolytes such as sodium, magnesium and chloride are left as well as indigestible carbohydrates known as dietary fibers. Bacteria, by metabolizing dietary fibers, play a crucial role in the nourishment of the colon and in calorie sparing. Thus, the colon is involved in some clinical disorders such as SBS. Immediately after extended ileal intestinal resection, gastric hypersecretion associated with hypergastrinemia may be observed (13). Both H2 antagonists and proton pump inhibitors aim to reduce gastric fluid secretion, and therefore, fluid losses (13-15). Intravenous delivery is usually needed. In patients without colon in continuity or who have a short residual jejunum or duodenum, fluid losses are especially high and a chronic control with antimitoty agents such as loperamide or codeine sulphate may be needed. Therefore, in SBS patients, the rapid restoration of intestinal continuity not only helps to control fluid and electrolyte losses but also provides the metabolic benefits of the colon.

IMPORTANT ROLE OF THE COLON IN SBS PATIENTS

Metabolic role of the colon

Medium chain triglycerides (MCTs) (C8-C10) contain 8.3 kcal/g, are water-soluble and may be absorbed by the colon. Diets containing MCTs, long chain triglycerides (LCTs) and 50% of MCTs/50% of LCTs have been assessed in a randomized cross-over study comparing ten SBS patients with colon in continuity to nine SBS patients without residual colon (16). Patients with intact colon absorbed 96% of C8 and 87% of C10 from the mixed LCT/MCT diet, while energy absorption was significantly increased (500 kcal/day). Patients without residual colon absorbed 63% of C8 and 57% of C10 (p = 0.007 for C8 and p = 0.004 for C10). The LCT/MCT diet did not increase energy absorption in patients who underwent end-jejunosotmy or ileostomy.

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Some starches and soluble non-starch polysaccharides are not digested by the small intestine. They are fermented later in the colon by colonic bacteria into hydrogen, methane and short chain fatty acids (SCFAs) such as propionate, butyrate and acetate. In the colon, some SCFAs such as butyrate are metabolized and used as a source of fuel by colonic epithelial cells (17-20). It has been estimated that up to 1,000 kcal may be absorbed daily by the adult human colon in the form of SCFAs (21). In SBS animal models, adaptation of the small and large intestines may be improved by adding an elemental diet with pectin, which is also fermented into SCFAs in the colon (22). Supplementing PN with SCFAs or their intracecal administration reduces mucosal atrophy and intestinal immune dysfunction (23-25).

Animal studies have shown that systemic SCFAs may, in addition to their local effects, affect the motility of the stomach and the ileum through neuroendocrine mechanisms, probably by acting on intestinal secretion of proglucagon-derived peptides (GLP-1) and peptide YY (PYY). Systemic and enteral SCFAs exert trophic effects on the jejunal mucosa (17).

In patients with SBS, the colon becomes an important organ for energy salvage (26). About 75 mmol of SCFAs are produced from 10 g of unabsorbed carbohydrates. In SBS patients with intact colon in continuity, the fecal energy loss has been shown to be decreased by 310-740 kcal when they were fed with a diet consisting of 60% carbohydrates (19) and the colonic metabolism of unabsorbed carbohydrates was confirmed by a decrease in fecal carbohydrate losses in patients with colon in continuity. An intact colon may absorb up to 525-1,170 kcal daily from dietary fibers (19,27,28). Colonic energy absorption may also slightly increase during the post-resection adaptation phase, due to an increase in colonic bacterial carbohydrate fermentation (29). This may be due to changes in colonic microbiota in SBS patients as well as an increased concentration or activity of various enzymes such as galactosidase over time during the adaptation phase (29). Since bacterial metabolites such as SCFAs stimulate sodium and water absorption, patients are likely to experience a decrease in fecal fluid and sodium loss (19).

Morphological adaptation occurs in the colon of SBS patients. Both hyperphagia and adaptation of the remaining colon improve patient outcome. A study has assessed the morphology, proliferation status, and expression level of transporters in the epithelium of the remaining colon of SBS adult patients compared to controls (30). The authors have demonstrated the appearance of colonic hyperplasia with an increase in crypt depth compared to a control group. This increase in crypt depth and colonic epithelial cell number could participate in the decrease in PN dependency within two years after restoration of intestinal continuity in SBS patients. Based on clinician experience, the presence of a colon in continuity in SBS patients may help to improve residual intestinal absorption capacity and to decrease PN. Nowadays, the time needed to achieve this physiological process of intestinal adaptation is not yet completely known. After two or three years, the proportion of patients with a decrease in or weaning off PN remains very low. We can assume that the adaptive processes of physiological intestinal adaptation take time after surgery. Oral/enteral feeding is essential to promote adaptation. Even in cases with very short bowel syndrome, oral feeding should be encouraged, especially when SBS is associated with jejunocolonic anastomosis.

TRANSPORTER ADAPTATION IN ADULT SBS PATIENTS

Functional absorptive adaptation of the gut has also been reported in SBS patients through the induction of glucose absorption by the intestinal mucosa, net protein intake (31) and calcium absorption (32,33). There are some discrepancies in the literature regarding colonic transporters. An increase in H+-coupled oligopeptide (PepT1) transporter and Na+/H+ exchanger (NHE2 and NHE3) mRNA levels has been reported in the colon of SBS patients (34) and in rodents (35). But these data have not been confirmed as part of a SBS human study since similar levels of NHE2, NHE3 and PepT1 have been found compared to controls (30). These differences may be due to various nutritional statuses of patients, the use of different animal models and different times between the surgery and the study. The use of the overexpression of some transporters as an indicator of intestinal adaptation is not yet validated.

ENDOCRINE FUNCTIONS IN ADULT SBS PATIENTS

In SBS patients, intestinal absorption depends on the intestinal resection site and transit time (36). The accelerated transit time observed in jejunostomy and ileum-resected SBS patients promotes nutrient malabsorption since a precise control of the transit time is required to maintain equilibrium of hydroelectric and energetic balances. Hormones play a key role in gastric emptying and small bowel transit time. The endocrine functional adaptation should be assessed in SBS patients. Elevated fasting plasma levels of GLP1 and GLP2 have been reported in extensive gut resection patients with preserved colon and they further increased after breakfast (37). These two hormones are produced by entero-endocrine L cells located in the ileum and colon. GLP2 increases the absorptive surface via its trophic action on mucosal epithelial cells and GLP1 slows down gastric emptying and intestinal transit (38,39). These effects (increased contact time and surface of nutrients) may potentially improve intestinal absorption (38,40).

HYPERPHAGIA IN ADULT SBS PATIENTS

Dietary intervention is essential to improve the outcome and reduce PN dependency in SBS patients. Post-surgery, continuous tube feeding (exclusively or in conjunction with oral feeding) significantly increases the net absorption of lipids, proteins and energy compared to oral feeding (2). When oral feeding is possible, oral dietary intake and hyperphagia should be recommended. Specific dietary recommendations should be made depending on
intake > 1.5 times patient resting energy expenditure (REE) (41). Hyperphagia remains an essential mechanism to reduce the need for PN (42).

In hyperphagic patients, enterohormones play a key role. Increased secretions of glucagon-like peptide-1 (GLP-1) and GLP-2 have been reported in preclinical models and in SBS patients with colon in continuity. They orchestrate gastrointestinal functions, including intestinal trophicity, expression of intestinal nutrient transporters and gastro-intestinal motility. Ghrelin, an orexigenic gut hormone, increases food intake through the activation of orexigenic hypothalamic neurons (co-expressing neuropeptide Y and agouti-related peptide). Recently, a study has been conducted to better understand the hormonal mechanisms involved in the development of hyperphagia in an animal model of SBS and in SBS patients (59). An increase in plasma ghrelin concentrations, major changes in hypothalamic neuropeptide levels, and a greater induction of PYY have been shown in SBS rats with jejunocolonic anastomosis. As hyperphagia leads to an increased amount of nutrients passing through the gastrointestinal tract, this adaptive mechanism may indirectly contribute to the structural and functional adaptations of the mucosa observed in the remaining gut (31, 42).

**COLONIC MICROBIOTA COMPOSITION AND METABOLIC FUNCTIONS IN ADULT SBS PATIENTS**

The composition of the microbiota of SBS patients highly differs from the common profile observed in healthy humans with intact gastrointestinal tract. The fecal microbiota of healthy humans is mainly composed of a phylogenetic core containing Firmicutes, Bacteroidetes and Actinobacteria. The human gastrointestinal tract is colonized by a dense complex community of microorganisms, mainly composed of anaerobic bacteria in adults, and the dominant groups are *Clostridium leptum*, *Clostridium coccoides* and *Bacteroides-prevotella*. Gut microbiota composition and metabolic functions in SBS patients and healthy controls have been compared (44). The overall bacterial diversity is reduced in SBS patients. The composition of the fecal and colonic mucosa microbiota is unbalanced in SBS: *Lactobacillus* dominates and anaerobic bacteria (*C. leptum, C. coccoides* and *Bacteroides*) are under-represented (41, 44). Lactobacillus overload should be considered massive, since this group contributes little (< 1%) to the complex microbiota population in healthy humans. For this reason, we proposed that the microbiota of SBS patients could be referred to as lactobiota. The essential role of the colon in SBS patients is related to its own absorptive capacity, the metabolic capacity of its specific lactobiota and the reciprocal cross-talk between the lactobiota and the colonic mucosa (43). After resection, the substrates that arrive in the colon are abundant and poorly digested. The fermentation of substrates by gut bacteria helps to maintain gut ecosystem diversity and to recover energy from nutrients in SBS patients (27). The bioconversion of macromolecules by the gut microbiota into metabolites is carried out by bacteria belonging to various functional groups (sharing similar and complementary activities) resulting in metabolic trophic chains and homeostasis with the colonic epithelium. In SBS, the trophic chains and fermentative end-products are produced by the lactobiota and are different from those produced by a healthy microbiota (44).

Fecal microbiota transfer from SBS rats to recipient germ-free (GF) rats triggers colonic changes through crypt deepening (45) and humanized SBS rats (SBS-H) had higher levels of some hormones than rats carrying a conventional microbiota. The microbiota from SBS rats may promote energy recovery since its transfer to GF rats is associated with high plasma levels of leptin. In summary, the microbiota from SBS rats seems to be a reservoir of multiple and complex signals that could modify the postresection adaptation. Several studies have described an increase in fasting plasma GLP1 in the presence of the microbiota from SBS rats might promote energy recovery.

**FECAL D- AND L-LACTATE AND CLINICAL RISK FOR D-ENCEPHALOPATHY IN ADULT SBS PATIENTS WITH COLON IN CONTINUITY**

D-lactic acidosis is very rare in humans. This disease is mainly observed in SBS patients who have a part of or an intact colon in continuity (47). Metabolic acidosis seems to be due to D-lactic acid accumulation but the mechanisms involved in its toxicity are not well understood. D-lactic acid predominantly affects the central nervous system. As D-lactate is converted into pyruvate and the cerebellar level of pyruvate dehydrogenase (the enzyme required to convert pyruvate into acetyl co-A) is limited, the cerebellum may...
been successfully treated with fecal transplantation (49). Under-
with SBS and recurrent, debilitating D-lactic acidosis has recently
taking the substrates responsible for D-lactate production. A child
controlled. The long-term management should focus on avoiding
future occurrences must be implemented once the acute phase is
antibiotics (clindamycin, vancomycin, neomycin and kanamycin)
D-lactate-producing bacteria in the colon. Poorly absorbed oral
The therapeutic strategy is based on the decrease of the offend-
ing agent (carbohydrates) and treatment to decrease the level of
D-lactate-producing bacteria in the colon. Poorly absorbed oral
antibiotics (clindamycin, vancomycin, neomycin and kanamycin)
are the most effective and may be used. Strategies for preventing
future occurrences must be implemented once the acute phase is
controlled. The long-term management should focus on avoiding
taking the substrates responsible for D-lactate production. A child
with SBS and recurrent, debilitating D-lactic acidosis has recently
been successfully treated with fecal transplantation (49). Under-
standing the pathophysiological mechanisms for the effects of
D-lactate should help physicians to identify D-lactate acidosis and
to improve preventive and therapeutic strategies (48). We have
proposed that HCO32 amount in blood, total fecal lactate and the
fecal D/L lactate ratio may become useful tools for identifying SBS
patients at risk for D-encephalopathy (Mayeur 2013). However,
进一步 investigations are needed to diagnose patients with high
risk of D-lactic encephalopathy using the most relevant combina-
tion of specific biomarker(s) and to propose a specific microbiota
modulation in order to prevent acute episodes.

A PLACE FOR PHARMACOLOGICAL
ADAPTATION

Some recombinant hormones are produced and used as a spe-
cific therapy in SBS patients. In controlled clinical trials, the admin-
istration of teduglutide, a GLP-2 analog, has reduced by more than
20% the intravenous needs in 63% of patients after a 6-month
treatment (50). Teduglutide has been shown to significantly reduce
stool wet weight and fecal energy excretion (51). It also signifi-
cantly increased villus height, crypt depth and the mitotic index in
the jejunum of SBS patients with end jejunostomy, whereas crypt
depth and the mitotic index did not change in colonic biopsies
of SBS patients with an intact colon (51). The purpose of these
novel approaches using GLP-2 analogs is to enhance the natu-
ral adaptation process, and to reduce intravenous calorie needs.
While some patients were weaned off PN, a greater number of
patients were able to reduce the frequency of infusions. Patients
who received teduglutide showed significant increases in plasma
citrulline levels compared to patients receiving a placebo in two
phase III studies (52).

While teduglutide is currently marketed and used in some coun-
tries with very good results in terms of efficacy in SBS patients,
other hormones or combinations will probably be assessed in SBS
in the future. In 2013, an open-label, sequential, placebo-con-
trolled study assessing the acute effects of continuous infusions
of GLP-1, GLP-2 and their combination (GLP-1 + GLP-2) on intest-
al absorption in SBS patients has shown that GLP-1 decreased
diarrhea and fecal excretions. Although GLP-1 reduced fecal weight,
and sodium and potassium excretions, the absolute absorption was not significantly improved.

Recently, liraglutide (a GLP-1 analog) has been given subcuta-
nearously once daily to eight end-jejunostomy patients in the context
of an eight-week, open-label pilot study (53). Liraglutide reduced
ostomy wet weight output by 474 ± 563 g/d from 3,249 ± 1,352
to 2,775 ± 1,187 g/d (p = 0.049).

In the last two decades, a hormonal treatment paradigm focusing
on intestinal rehabilitation by promoting intestinal “hyperlada-
tion” has been proposed in patients with SBS who require PN.
But, if we consider all aspects of physiological intestinal adapta-
tion in SBS patients, especially in SBS patients with jejunocolonic
anastomosis and a physiological increase of hormone levels such
glucagon-like peptide 1 (GLP1), glucagon-like peptide 2 (GLP2), peptide YY (PYY) in the absence of treatment, conducting
further studies assessing the response of new drugs and taking
into account the levels of native hormones will be of interest.

CONCLUSIONS

The morphological and functional alterations described in SBS
may contribute to improve nutrient and fluid absorption in the
remnant bowel. A better understanding of the cellular, molecular
and microbiological mechanisms involved in functional adaptation
of the remnant bowel in SBS could help clinicians to optimize the
overall nutritional absorption, and thus to reduce or wean patients
off PN and to prevent D encephalopathy episodes. It would now be
informative to identify molecular and functional links between the
three levels of signal integration: control of food intake, remodeling
of the intestinal mucosa and balancing of the microbiota. Important
issues should be addressed in the future: a) study nutritional
peripheral hormones and central hypothalamic neuropeptides that
control food intake in SBS patients; b) determine whether mucosal
adaptation of the remnant gut is involved in hyperphagia in SBS
patients; c) investigate whether the lactobiota of SBS patients con-
tributes to hyperphagia and mucosal hyperplasia; and d) assess the
real impact of new drugs such as GLP2 agonist on intestinal
adaptation and the specific benefits of these trophic agents in
SBS treatment.

REFERENCES

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