SHORT BOWEL SYNDROME

PATHOPHYSIOLOGY, MANAGEMENT AND ADAPTION

Internal Medicine Grand Rounds

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The small intestine maintains our nutritional balance by a number of specialized transport mechanisms that ensure adequate absorption of nutrients, water, electrolytes, minerals and vitamins. It is also an important endocrine organ in that a number of gastrointestinal hormones involved in the regulation of secretory and absorptive processes and in the modulation of gastrointestinal motility are synthesized at various locations in the bowel (1). In addition, the small intestine is an important immune organ engaged in the defense against pathogens introduced into the gut (2). The defense is mediated by secretion of secretory IgA and by lymphocytes in the epithelium and lamina propria. It is not surprising then that extensive intestinal resections may have catastrophic consequences and lead to serious disturbances in gastrointestinal function. Because of advances in surgical techniques and postoperative care an increasing number of infants and adults will survive extensive bowel resections but are left with a short bowel syndrome. It is the purpose of this grand rounds to review the pathophysiology and current management of patients with short bowel syndrome with an emphasis on adaptive responses in the remaining intestine.

The long-term severity of symptoms after intestinal resection depends on the extent of resection, the location of resection (jejunal, ileal and/or colonic), the presence or absence of the ileo-cecal valve, the sequential adaptation of the remaining intestine and residual disease of preserved bowel (3). The disease processes that lead to extensive intestinal resections differ according to age. Congenital abnormalities such as gastroschisis, atresia and volvulus are the leading causes in infancy (4). Abdominal trauma with damage of the intestinal vascular supply and Crohn's disease are the main causes in young adults. Ischemic injury (SMA thrombosis, embolus, etc.), radiation injury and Crohn's disease dominate in older age. The extent of resection in any of these presentations is determined by the primary lesion and the estimated viability of

the residual intestine which may require a second look operation in patients with ischemic insults. It is important to stress that every effort should be made during surgery to preserve as much intestine as possible. In general, these patients may require one of the following types of resection: 1. isolated small bowel resection (jejunal, ileal or both) with preservation of the ileo-cecal valve and colon; 2. combined small intestinal and partial colonic resection and 3. extensive small intestinal resection and total colectomy. The result of any of these types of resection is a loss of absorptive surface area which may compromise nutrient, electrolyte, water, mineral and vitamin absorption to a variable extent depending on the length and area of resection. The short bowel syndrome may simply be defined as a malabsorption syndrome resulting from intestinal resection.

Normal digestion and absorption

The digestive and absorptive processes of the small intestine are compromised to a variable extent in patients with the short bowel syndrome. In this section a brief overview of normal digestion and absorption is presented to facilitate an understanding of the underlying pathophysiology and to indicate possible interventions in the management of these patients.

a. Nutrients:

A normal adult person consumes roughly 400 g of carbohydrates, 100 g of proteins and 150 g of fat per day, i.e., about 3350 kcal/day, to cover the caloric needs and the obligatory requirement for essential amino acids. The digestive process starts in the stomach where the food is mixed with acid, salivary amylase, pepsin and lipase (lingual or gastric). The extent of digestion in the stomach depends on the time the nutrients remain during the mixing and grinding of the food particles by stomach contractions. Liquids are emptied from the stomach at a faster rate than solid particles which must be broken down to a certain size (< 0.5 mm) before they are

propelled into the proximal duodenum. The rate of gastric emptying is regulated by at least three factors in gastric contents: osmolality, long-chain fatty acids and the acidity. A high osmolality, the generation of long-chain fatty acids by gastric lipolysis and a low pH retard gastric emptying. Long-chain fatty acids and a high [H^+] are also potent signals for the release of cholecystokinin (CCK) and secretin which are synthesized and stored in endocrine cells in the proximal small intestine. The release of these two hormones in turn cause gallbladder contraction and stimulate pancreatic enzyme and bicarbonate secretion. The result of these processes is that pH increases to about 6-7 in the distal duodenum and that the food particles are bathed in a solution with a high bile acid concentration and high concentration of pancreatic enzymes (amylase, lipase, trypsin, chymotrypsin) that generates a favorable condition for continued digestion which proceeds at a rapid rate in the proximal jejunum. Carbohydrates are broken down to disaccharides (lactose, maltose and sucrose), proteins to

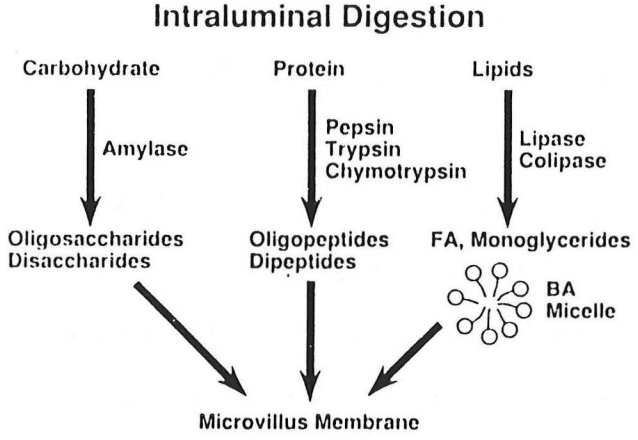


Fig. 1. Intraluminal digestion of nutrients

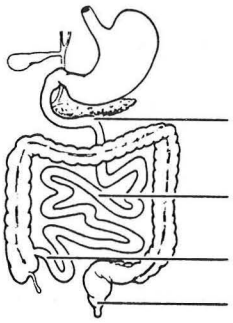
dipeptides and amino acids and fat to monoglycerides and long chain fatty acids. The lipolytic products are water-insoluble and are solubilized in the hydrophobic phase of bile acid micelles whereas the products of protein and carbohydrate digestion are entirely water soluble. Dipeptides, amino acids,

disaccharides and bile acid micelles diffuse through the water phase in the intestinal lumen to the tips of the intestinal villi where further digestion and ultimately absorption takes place. The enterocytes on the intestinal villi are highly specialized cells. The microvilli of these cells are endowed with several enzymes (disaccharidases, dipeptidases) and a number of transport proteins. Disaccharides are hydrolyzed to monosaccharides (glucose, galactose and fructose) and transported into the cells by specific transporters. Dipeptides are taken up by specific dipeptide transporters or split to individual amino acids and taken up by specific amino acid transporters. Currently, there is evidence for up to 6 different amino acid transporters. The uptake of fatty acids and monoglycerides does not require specific transporters and it is thought that these molecules diffuse across the plasma membrane. Borgström and coworkers showed in a classic study that the absorption of the three major nutrients is almost complete within the first 100 cm of the human jejunum (5). A finding that has been confirmed by more recent studies (6-8). Thus, the absorptive surface area of 1 m of jejunum appears to be sufficient to ensure normal nutrient absorption.

The length of the human intestine is about 6 m (range 3 to 7.6 m) which means that there is a large reserve absorptive capacity in normal man (9). It should be emphasized that there is a distinct proximal to distal gradient in terms of villus height, crypt depth, amount of microvillus enzymes/unit length and also absorptive capacity of, for example, glucose/unit length in that all these parameters are several-fold higher in proximal jejunum than in distal ileum (10).

b. Water and electrolytes

The gastrointestinal tract serves an important role in water and electrolyte conservation. The proximal small bowel receives about 9 l of fluid/day from food and secretions (salivary, gastric, biliary and pancreatic) but only 1 l



FLOW RATE ml/day	ION CONCENTRATIONS meq/L Na	K	Cl	HCO_3	OSMOLALITY mOsm/kg
9000	60	15	60	15	Variable
3000	140	6	100	30	Isotonic
1000	140	8	60	70	Isotonic
100	40	90	15	30	Isotonic

Fig. 2. Water and electrolyte movement in the human intestine (from ref. 11)

passes the ileocecal valve in the same time interval (11). The efficient electrolyte and water absorption in the small intestine is accomplished by specific transporters in the microvillus membrane of the enterocytes (12). Sodium is transported into the enterocytes coupled with glucose and amino acids by the specific transporters during meals. Chloride and water follow passively. There is also an electroneutral NaCl transport mechanism by specific exchangers (Na^+/H^+ and Cl^-/HCO_3^-exchange) which may dominate between meals. The active transport of sodium by these transport processes are thought to generate a slightly hyperosmolar condition in the intercellular spaces. The osmotic gradient across the epithelium generates water flow out of the intestinal lumen. Water flow in turn results in further sodium movement by a mechanism called solvent drag. The ability to move sodium against a concentration gradient is determined by the tightness of the intracellular junctions. The human jejunum is a leaky

epithelium whereas both the ileum and colon are more tight (13,14). The active absorption of sodium in the human jejunum is negligible when intraluminal [Na^+] is below 100 meq/l whereas active sodium transport in the ileum and colon is still observed at sodium concentrations below 50 meq/l. This observation is of practical importance in terms of the composition of oral solutions used for patients who are left with a high jejunostomy (15). The tonicity varies in the proximal small intestine depending on the composition of the meal but the intraluminal fluids remain isotonic from midjejunum to rectum. The ionic composition is, however, modified further by specific transport processes in the ileum and colon. There is ongoing sodium-absorption (and water) in the colon accompanied by potassium secretion resulting in a low [Na^+] and high [K^+] in a stool volume of about 100 ml water. As shown in Fig. 2 there is a significant anion gap which is taken up by organic anions (acetate, propionate, butyrate and lactate) generated by bacterial degradation of unabsorbed carbohydrate. It has been estimated that up to 3 to 4 liters of an isotonic salt solution can be absorbed from the colon which again illustrates the large reserve capacity of absorptive function in the gastrointestinal tract (16). The colonic reserve capacity may serve an important function in reducing water and electrolyte losses in conditions where small bowel absorptive function is compromised.

c. Area-dependent absorption

Folate, iron, calcium, phosphate and probably magnesium are predominantly absorbed in the proximal small intestine (duodenum and proximal jejunum) (17). The uptake of these molecules across the microvillus membrane is accomplished by binding to specific proteins and is energy dependent. For example, calcium is bound to calbinding$_{9K}$, which

is vitamin D inducible and found in highest amount in duodenum and proximal jejunum in accordance with the area of maximal absorption. Calbinding$_{9K}$ is undetectable in the ileum and colon (18). The phosphate transporter has a similar distribution (19). The distribution of folate transporters and iron binding proteins has so far not been characterized.

Vitamin B_{12} and bile acids on the other hand are absorbed in the distal small intestine. Vitamin B_{12}-IF complexes are bound to specific receptors in the microvillus membrane of ileal enterocytes and bile acids are taken up by specific bile acid transporters in the same cells in an energy dependent manner and coupled to sodium. Bile acid reabsorption in the distal small intestine is a highly efficient process and an integral part of the entero-hepatic circulation of bile acids. Thus, ileal resection may compromise B_{12} and bile acid absorption whereas jejunal resection may interfere with calcium, iron, folate, phosphate and magnesium absorption.

d. Poorly defined absorptive processes

The intestinal absorption of a number of micronutrients such as water-soluble vitamins and trace elements is currently poorly characterized. The uptake mechanism of several water soluble B vitamins (thiamine, riboflavin, niacin) is compatible with a saturable, energy requiring process (17). The transport proteins, however, have not been identified and the distribution of these proteins in the small intestine is unknown. The fat soluble vitamin (A, D, E and K) are absorbed by passive diffusion but require micellar solubilization due to limited water solubility. They are most likely absorbed in the proximal small intestine with other lipolytic products. Finally, the uptake mechanism of most trace elements such as Cr, Zn, Mn, Se is unknown but the uptake is probably limited to the small intestine. It should be emphasized, however, that it is precisely patients with short

bowel syndrome that has called attention to vitamin and trace element malabsorption and helped define the daily requirement of these micronutrients (20).

Effect of intestinal resection on gastrointestinal hormones and motility

The rate of gastric emptying and the propulsive movement of intestinal contents are regulated by several gastrointestinal hormones and by neural mechanism in a complex manner. The distribution of some of the established hormones is shown in Fig. 3:

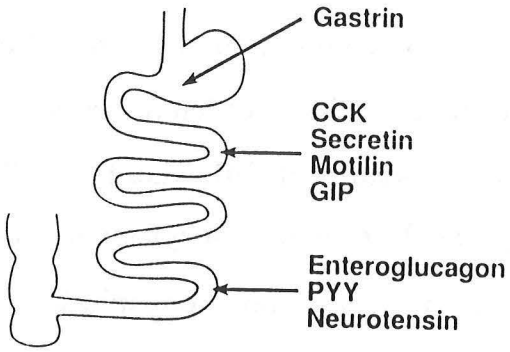


Fig. 3. Distribution of gastrointestinal hormones

Gastrin, CCK, secretin, GIP and motilin are produced in endocrine cells in the mucosa of the stomach and proximal small intestine which is usually left intact even in patients with extensive intestinal resections. All four hormones have direct or indirect effect on the rate of gastric emptying. For example, the acidity of gastric contents which is determined in part by gastrin secretion, influences the emptying rate. An increase in CCK and secretin are also claimed to delay gastric emptying by an unknown mechanism. However, the release of these hormones are probably not altered in patients with short bowel syndrome. The ileum and part or all of the colon are lost in most of these patients, i.e., the area where enteroglucagon, PYY and neurotensin are produced. The action of these

three hormones is not fully defined. It has been shown that infusion of lipids or carbohydrates into the ileum cause a release of both enteroglucagon and PYY which is followed by a delay in gastric emptying and a slowing of intestinal transit (21,22). This phenomenon has been termed the ileal brake. Nutrients do not normally reach the ileum except in conditions with rapid intestinal transit. The ileal brake may serve to counteract rapid transit in the intact intestine. The loss of an ileal brake in patients with short bowel syndrome may in part explain the deranged motility pattern observed in these patients. Motility studies in these patients have shown rapid gastric emptying especially for liquids and increased intestinal transit (23-25). The altered motility may further compromise their nutritional balance by limiting the time for digestion and the contact time with the mucosa.

Management of patients with short bowel syndrome

a. Surgery and immediate postoperative phase

Most patients who require extensive intestinal resections present with an acute abdomen that precludes many diagnostic tests and usually demands immediate surgical intervention. At laparotomy the surgeon should try to salvage all viable intestine and carefully estimate the length of the remaining small and large bowel. In the immediate postoperative phase all patients will need either total parenteral nutrition (TPN) if malnutrition is present due to underlying disease or replacement of fluids and electrolytes as estimated from losses of sodium, potassium and water (3,26,27). Some patients will have significant electrolyte and fluid losses in stomal effluents or stools depending on extent and site of resection even in the immediate postoperative phase when they are still NPO. This response is most likely secondary to gastric hypersecretion. About 50 percent of

patients who undergo small intestinal resections will develop hypergastrinemia and increased gastric secretion (28-31) The mechanism is not well characterized. Hypergastrinemia could be due to removal of an inhibitor of antral G-cells secondary to intestinal resection. Hypergastrinemia and increased acid secretion is observed more often with jejunal than with ileal resection (32). The patients are therefore given H_2 blockers i.v. in the immediate postoperative phase. The H_2-blockers serve a dual purpose. They reduce gastric acid secretion and also reduce secretory losses of fluid and electrolytes (33,34) If secretory losses continue to be excessive despite these measures an antidiarrheal drug (loperamide or codeine) may be added.

b. Late postoperative phase

The patients are usually kept NPO for up to 10 days to allow adequate healing of enteric anastomoses and stomas and also to allow an assessment of basal secretory losses. At this point oral feeding is started with an isotonic glucose saline solution (glucose 50 mM/l and NaCl 120 mM/l) which the patients sip in small volumes throughout the day (3,15,35). The solution is isoosmolar to prevent jejunal secretion and induces Na^+ and water absorption by the coupled Na^+-glucose transport. It corresponds to the oral rehydration solution used in the treatment of cholera. The patients are encouraged to drink up to 1 l/day while fluid and electrolyte losses are monitored carefully. The glucose-saline solution is mainly used in patients with extensive intestinal resections. Patients with less extensive resections are started on a liquid formula diet (36). The response to intake of these solutions may allow an assessment of how they will tolerate a more complex diet.

At this early stage it is not possible to predict how an individual patient with extensive intestinal resection ultimately will fare because of subsequent adaptive changes in the remaining intestine. It may take a year before these patients have fully adapted and during the adaptive phase the diet is continuously modified according to the needs in terms of calories, fluid, electrolytes and minerals. It is apparent from the experience of centers who care for patients with the short bowel syndrome that the length of the remaining small intestine is a major determinant of the final outcome. Patients who have less than 100 cm proximal small bowel left will, in most cases, require parenteral nutritional support (calories, fluid, electrolytes) while patients with 100 to 150 cm jejunum may require i.v. support for fluid and electrolyte replacement but have sufficient oral calorie absorption to maintain weight. Patients with a small intestine longer than 150 cm can often be managed by the oral route alone but may require dietary modifications and oral supplements of minerals and vitamins. These guidelines are naturally not absolute given the notorious inaccuracies of assessing intestinal length during an operation. Thus, there are several possible outcomes of intestinal resections based on extent and site of resection as outlined in the following section.

Types of intestinal resection

1. Extensive jejunal or ileal resection with preservation of ileo-cecal valve and colon.

   a) Extensive jejunal resection: Patients who have an isolated jejunal resection will, in most cases, do well. Ileum will adapt over time and increase its absorptive capacity to an extent that these patients will develop normal absorption of nutrients, electrolytes and fluids. Hence, these patients can consume an unrestricted diet and do not have gastrointestinal

symptoms. Furthermore, because of preserved ileum vitamin B_{12} and bile acid absorption are not compromised and gastrointestinal motility is not significantly altered (preserved ileal brake). Finally, the preserved ileo-cecal valve minimizes the risk of bacterial overgrowth of the small intestine by colonic bacteria. It is possible but not documented that jejunal resection will compromise absorption of calcium, iron, magnesium, phosphate and folate which are predominantly absorbed in the proximal small intestine.

b) Extensive ileal resection: The loss of ileal function on the other hand almost invariably results in either diarrhea or steatorrhea depending on the length of removed ileum (37). If less than 100 cm of ileum has been resected, watery diarrhea predominates due to mild to moderate bile acid malabsorption with maintenance of normal bile acid pool size and, hence, normal fat absorption. Bile acids lost to the colon are deconjugated and

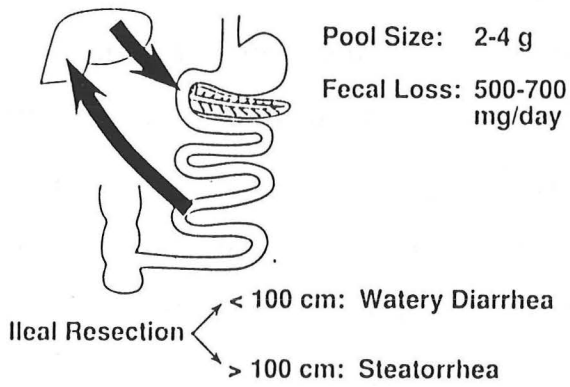


Fig. 4. Enterohepatic circulation of bile acids

dehydroxylated and the dihydroxy bile acids (chenodeoxycholic and deoxycholic acid) are potent colonic secretagogues causing electrolyte and water secretion. A bile acid binding resin such as cholestyramine given with meals is often sufficient to ameliorate the diarrhea.

More extensive ileal resection (more than 100 cm) results in severe bile acid malabsorption exceeding hepatic bile acid synthesis. A new steady

state is established with a reduced bile acid pool size which results in a decreased intraluminal bile acid concentration in the proximal intestine. This, in turn, compromises micellar solubilization of the lipolytic products and causes fat malabsorption. These patients are best managed by modification of their diet with a reduction of the amount of long-chain fatty acid to about 30 g/day and supplementation with medium-chain triglycerides which do not require micellar solubilization.

Since vitamin B_{12} is absorbed only in the distal ileum, patients with ileal resection are also at risk for B_{12} malabsorption. The adequacy of vitamin B_{12} absorption can best be assessed with a Schilling test and the presence of B_{12} malabsorption is easily treated with parenteral B_{12} administration.

Long-term effects of bile acid malabsorption

Cholesterol gallstones: Patients with severe bile acid malabsorption are at a significant risk of developing cholesterol gallstones. Cholesterol in hepatic bile is kept in solution in mixed micelles composed of bile acids and phospholipids. A decrease in bile acid secretion into the bile caniliculi secondary to interruption of the enterohepatic circulation of bile acids will change the relative proportion of bile acids, cholesterol and phospholipids in hepatic bile which becomes supersaturated with respect to cholesterol. With time cholesterol crystals will coalesce to form gallstones. Infants with ileal resection may develop symptomatic gallstones within one year of resection and some authors have suggested prophylactic cholecystectomy at the time of intestinal resection (38).

Oxalate kidney stones: Patients with ileal resection and a preserved colon are also at risk for developing oxalate stones in the kidney (39). Oxalate in the food is normally precipitated out as calcium oxalate in the small

intestine and lost in the stool. In patients with fat malabsorption unabsorbed long chain fatty acids will compete with oxalate for calcium ions. A variable amount of unprecipitated oxalate is lost to the colon where it is absorbed and excreted in the kidney. Thus, these patients should be monitored with urinary oxalate excretion. Hyperoxaluria may be treated with dietary restrictions of oxalate intake (vegetables, tea and chocolate) or with calcium supplements.

2. Extensive small bowel resection and partial colonic resection:

Typical patients in this group are patients with Crohn's disease and bowel infarctions. They are often left with a variable length of proximal small bowel and the left colon. These patients are in general more symptomatic than patients with isolated small bowel resections. In addition to bile acid and B_{12} malabsorption they will also be at higher risk for significant nutrient, fluid and electrolyte malabsorption due to more extensive loss of absorptive surface area. In addition, the colonic microflora may now colonize the small intestinal remnant as the small intestine and colon are no longer separated by a valve. Bacterial overgrowth of the small intestine may worsen malabsorption because bacteria will now compete with the host for the substrates generated by digestion such as amino acids, glucose and B_{12}. Thus, these patients pose a more difficult management problem. The ultimate goal is to ensure a stable condition where all their needs in terms of calories, fluid, electrolytes, minerals and vitamins are met preferably by oral intake alone (40,41). There has been much controversy about the composition of the diet in these patients and whether they should restrict fluid intake during meals to decrease fluid losses. It was initially thought that these patients would benefit from a low fat, high carbohydrate diet supplemented with medium-chain triglycerides (42). Jeejeebhoy's group in

Toronto has recently addressed the question of dietary composition and fluid intake in these patients. In the first study they compared a high carbohydrate diet (60% of calories) with a high fat diet (60% of calories) in a crossover study of stable patients with ileectomy and partial colectomy (43). The diets were isocaloric with a similar protein content (20% of calories) and similar content of calcium, magnesium and zinc. There was no signi-

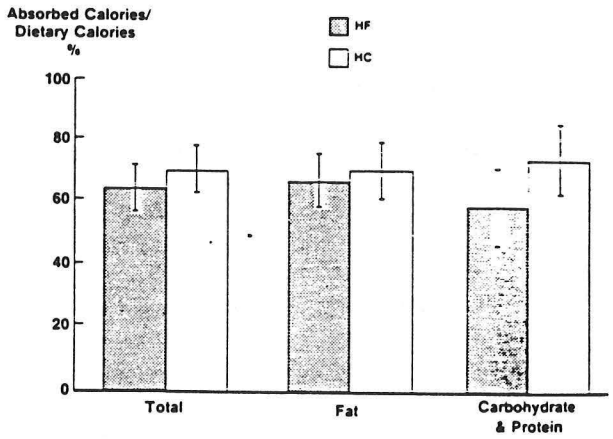


Fig. 5. The percentage calorie absorption in patients on a high fat or a high carbohydrate diet.

ficant difference in the amount of absorbed calories on either diet (about 65% of dietary calories) nor was there a difference in divalent cation absorption. In addition, stool volumes and electrolytes were in the same range on both diets. It was concluded that a low fat diet is not indicated in these patients. Furthermore, a liberal fat intake makes the diet more palatable, ensures an adequate supply of essential fatty acids and is an excellent calorie source (9 kcal/g). In the second study the patients were maintained on a constant diet (22% protein, 32% carbohydrate and 46% fat as calories) and either received fluids or had restricted fluids with meals in a crossover design (44). There was no significant difference in calorie absorption, stool volume or stool electrolytes in the two periods in any of the

TABLE 6. TOTAL CALORIE ABSORPTION (KCAL/DAY)*

	Fat	*Carbohydrate*	*Protein*	*Total absorption*
Diet	871 ± 97	608 ± 56	396 ± 36	1875 ± 174
Stool	405 ± 73	239 ± 42	76 ± 15	719 ± 108
Absorption (%)	54 ± 4	61 ± 7	81 ± 5	62 ± 3

*There was no change in absorption in any of the parameters measured over the 10-day study period.

Table 1. Fat, carbohydrate and protein calorie absorption in patients with extensive small intestinal and colonic resections

patients. Fat absorption was 54% of consumed fat calories, carbohydrate was 61% and protein 81% of carbohydrate and protein intake, respectively. Thus, these patients do not need to restrict fluid intake during meals. It is apparent that fat and carbohydrate absorption are most compromised whereas protein absorption is almost normal. In fact all patients were in a positive nitrogen balance. It was suggested that these patients could meet metabolic demands in terms of calories if they ingested 35-40 kcal/kg/day assuming an average calorie absorption of 60%. A similar conclusion was reached in a recent French study of ten patients with extensive small bowel resection and partial colectomy (45). In this study the average calorie absorption was 67% of ingested calories. Five of these patients were stable on oral intake alone and they could meet their metabolic demands by ingesting 2.5 times the basal energy expenditure. In addition, these patients may need oral supplementations of calcium, magnesium and zinc if they are in a negative balance (46-48).

3. Extensive small bowel resection and total colectomy

These patients fall into the category of severe short bowel syndrome. Patients in this group usually suffer from Crohn's disease or have

sustained a vascular insult of the mesenteric circulation and end up with a short segment of jejunum as the remaining intestine ending in a jejunostomy. Irrespective of the remaining length of functional small intestine the patients should be started on enteral alimentation to induce possible adaptive changes while they continue with parenteral nutrition or fluid and electrolytes according to estimated losses. The enteral alimentation is usually administered through a nasogastric tube with continuous administration of either a glucose-saline solution or a formula diet 24 hrs a day (3,15). The infusion is usually started at a slow rate (25 ml/hr) and gradually increased to 100-125 ml/hr depending on response as estimated from jejunostomy effluent volume. The nasogastric infusion is then gradually replaced by solid food. The use of an elemental or polymeric diet as opposed to solid food does not confer any nutritional or absorptive advantage even in patients with jejunostomies (49). The jejunal efflux in response to food was recently studied in a group of 15 patients with high jejunostomies (residual length < 150 cm): 6 patients who required i.v. nutrition, 3 patients on i.v. fluid and electrolytes and 6 patients on oral supplements (glucose-saline solution) (50). The patients continued on their

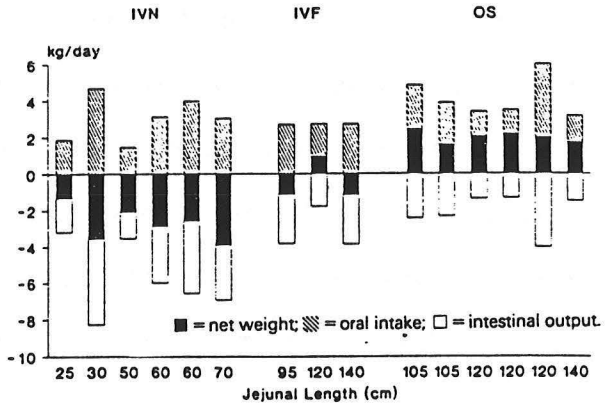


Fig. 6. Oral intake and jejunostomy effluent volume in 15 patients with high jejunostomies

i.v. regimen (group 1 and 2) and the quantity of food and fluid intake varied. As seen in Fig. 6, 8 of 9 patients in group 1 and 2 had a net secretory response to food and oral fluid. All 8 patients were in a negative sodium balance. Only the 6 patients in group 3 had a net absorptive response and were in positive sodium balance. When fluid and sodium balance were correlated with intestinal length it was apparent that only patients with more than 100 cm were in a positive balance. The effect of omeprazole and octreotide was studied in a single patient with only 50 cm remaining jejunum and large output. Omeprazole 40 mg i.v. reduced the output by 3.0 l and octreotide 50 μg b.i.d. i.v. reduced the volume by 2.7 l but a positive balance was not obtained. The secretory response to food in terms of volume secretion is, thus, in part due to gastric secretion as evidenced by the response to omeprazole. It is interesting that the somatostatin analogue which is supposed to also inhibit pancreatic secretion was similar to omeprazole in terms of inhibition of secretion. The results of this study imply that patients with less than 100 cm jejunum have minimal benefit from oral intake and will need continued i.v. supplements of calories, electrolytes and nutrients. Patients with a jejunal length between 100 and 150 cm can usually maintain nutritional balance on oral intake but may need i.v. replacement of fluids and electrolytes due to excessive losses. Some of these patients can be trained to pass an NG-tube for infusion of a glucose-saline solution or a formula diet during sleep (51,52).

A simple test to estimate the functional absorptive capacity of the remaining intestine in short bowel patients has recently been described (53). The authors compared a group of ileostomists with minimal or no small intestinal resections (controls, n=5) with two groups of patients with high jejunostomies: one group (n=7) with a median jejunal length of 110

cm who did not require i.v. nutritional support. The other group (n=5) had a median jejunal length of 50 cm and all were on home parenteral nutrition. The three groups were given 300 ml Ensure with a marker and the stomal outputs were collected over six hours. The marker recovery was complete by six hours. The percent energy absorption, stool dry weight and wet weight and sodium output are listed in Table 2.

Group	*% Energy absorption*	*Dry wt (g)*	*Wet wt (g)*	*Sodium output (mmol)*
1 Ileostomists (n=5)	87 (82–92)	11 (6–14)	299 (132–478)	38 (19–62)
2 Short bowel No IVN (n=7)	67 (59–78)	24 (18–28)	432 (260–613)	53 (31–80)
3 Short bowel IVN (n=5)	27 (2–63)	50 (29–73)	744 (292–1500)	77 (29–144)
Differences * between groups significant at:	1% Level	1% Level	NS	NS

*Mann-Whitney U Test: NS: not significant.

Table 2

The mean energy absorption was 87% in the ileostomists, 67% in patients not on i.v. nutrition and only 27% in patients on parenteral alimentation. Stool volume (wet weight) and sodium output increased progressively from group 1 to 3 as expected. There was a high inverse correlation between energy absorption and dry weight of stomal output (r = -0.99). Thus, this study confirms Jeejeebhoy's observation that patients with more than 100 cm jejunum absorb about 60% of the caloric intake and do not require i.v. nutrition. Patients with a very short jejunum absorb less than one-third of consumed calories and need supplemental parenteral nutrition. The test may allow to discriminate on a more objective basis between these two groups of patients and facilitate decisions on the best management. The

test can also be used longitudinally in individual patients to follow intestinal adaptation.

The somatostatin analog, octreotide, has been used in several small series of patients with high jejunostomies and large stomal outputs. It has been shown to reduce outputs by up to 1.5 l/day and reduce the requirement for supplemental i.v. fluids (54-56). Nutrient absorption is not improved and the main effect of somatostatin is probably a reduction of gastric and possibly pancreatic secretion.

Patients with severely compromised nutrient absorption will be dependent on home parenteral nutrition for life. They will, however, usually be able to lead a normal social life and to return to work (57-60). They restrict their oral intake to a minimum because of unacceptable high jejunostomy outputs and all their needs to maintain nutritional balance are met by parenteral administration which is given overnight. During the first year after intestinal resection, their daily needs in terms of calories, fluid, electrolytes may need several readjustments after which they reach a stable phase. Trace elements and water soluble vitamins are added to the infusions on a daily basis and fat soluble vitamins are usually administered biweekly. Long-term parenteral nutrition is associated with well-known risks such as catheter sepsis, superior vena cava thrombosis and intrahepatic cholestasis (61,62). The latter complication has been a major problem in pediatric patients and was the leading cause of death in several series (38,63). The expenses associated with home parenteral nutrition are high and have been estimated to about $30,000-50,000/yr. It is difficult to assess the incidence of patients who will end up with a severe short bowel syndrome necessitating permanent parenteral nutrition in the U.S. The

incidence was estimated to 2 per million per year at a major center in London (27). This estimate did not include pediatric patients.

Surgical interventions including intestinal transplantation

A number of surgical procedures have been attempted in patients with short bowel syndrome in an effort to improve absorption. Reversal of a short intestinal segment or interposition of a colonic segment (iso- or anti-peristaltic) have been tried in an attempt to delay intestinal transit (64). Generation of a recirculating intestinal loop to increase contact time of intestinal contents with the mucosa has been attempted in a few patients with limited success (65). While some of these procedures have proved of some benefit in animal studies there are only anecdotal reports of the use of any of these in patients and long-term prospective studies have not been conducted (66).

It is not surprising that intestinal transplantation has been attempted in patients with short bowel syndrome especially in pediatric patients. These patients usually do not have residual intestinal disease and may be considered ideal candidates for a transplant. Intestinal transplantation is not considered a difficult procedure from a technical standpoint (67). So far it has met with limited success, however, despite the advent of more potent immunosuppressive regimens. Recently four centers reported on their experience in a total of 12 patients of whom only 2 developed functioning grafts (68). The remaining 10 patients suffered repeated rejection episodes or graft-versus-host disease and the graft had to be removed. The Pittsburg group reported on an additional 4 patients at the recent meeting of the American Society of Transplant Surgeons (69). These patients received FK 506 as primary immunosuppression and all 4 have functioning grafts 6 to 12 months after transplantation. All 4 patients had

stormy early postoperative courses. The small intestine is heavily populated with lymphocytes organized in Peyer's patches and infiltrating the lamina propria which probably accounts for the high rate of early rejection. In the Pittsburg study it was observed that donor lymphocytes in the graft were largely replaced by recipient lymphocytes by day 30 post transplant. Graft-versus-host disease was not observed in this small series. The development of more potent immunosuppressive drugs such as FK 506 may imply that in the future intestinal transplantation can become the ultimate treatment of patients with severe short bowel syndrome.

Intestinal adaptation

The ability of the remaining small intestine to adapt to resection was recognized at the turn of the century and the mechanisms underlying the adaptive response have been studied extensively (70,71). The cells on the intestinal villi are constantly being renewed. The crypts represent the proliferative zone in the intestinal epithelium. Immature crypt cells leave the crypts after differentiation and migrate up the sides of the villi and mature. Synthesis of digestive enzymes and transporters is initiated during maturation and these proteins are expressed in the microvillus and

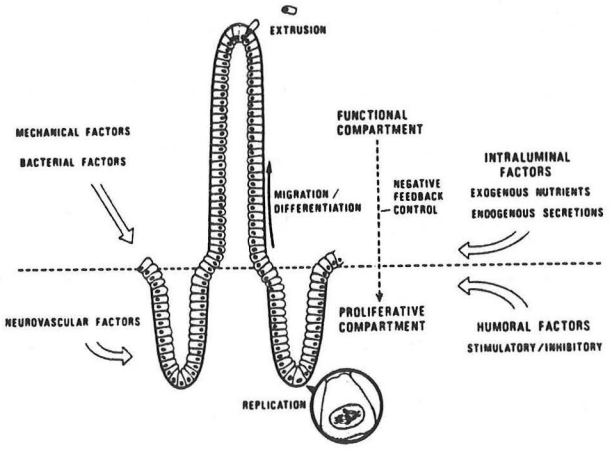


Fig. 7. The crypt-villus axis of intestinal epithelium

basolateral membrane of the mature enterocytes at the tips of the villi where maximal absorption takes place. The cells are finally sloughed off and replaced by new cells. Cell turnover is 2 to 3 days in rodents and 4 to 5 days in man. There is a proximal-distal gradient in villus height and crypt depths with ileal villi being half the size of jejunal villi. Thus, surface area per unit length of intestine is smaller in the ileum which is also reflected in the functional capacity such as enzyme activity or nutrient absorption when compared to unit length of jejunum.

Following jejunectomy with anastomosis of the ileum to the distal duodenum, a characteristic series of changes are observed (72). The crypts become deeper and the villi become taller which is followed by an increase in enzyme activity and absorptive capacity secondary to increased surface area per unit length and probably also increased enzyme and transporter synthesis in individual enterocytes (73). With time there is also an increase in ileal diameter and length. In other words, the adapted ileum attains the histologic and functional characteristics of jejunum in control animals. The changes observed in the jejunum following ileectomy are much less pronounced (74). Conversely, the exclusion of nutrients and pancreatic and biliary secretions from an intestinal segment by establishing a bypassed loop results in hypoplastic changes with a decrease in villus height and to a lesser extent of crypt depth. Similar changes are observed in starved animals and in animals kept NPO but in nutritional balance with parenteral alimentation (75). Thus, it is apparent that the adaptive changes of the intestinal epithelium in some way depend on the presence of nutrients and/or pancreatic and biliary secretions in the intestinal lumen. This observation may also explain the proximal-distal gradient in villus height in normal intestine. The jejunum is exposed to high concentrations

of nutrients, bile acids and pancreatic enzymes after each meal but the ileum is only exposed to bile acids due to efficient nutrient absorption in the proximal jejunum. The adaptive response in the ileum following jejunectomy can also be explained by an action of luminal factors because the ileum is now exposed to the same conditions as the former jejunum. A number of studies have been performed in an effort to separate the effects of nutrients from the effects of pancreatic and biliary secretions. For example, perfusion of bypassed jejunal loops excluded from secretions with solutions of glucose or amino acids or long-chain fatty acid emulsions all prevent mucosal hypoplasia (76). In addition, infusion of pancreatic secretions without nutrients into similar isolated ileal loops cause villus hyperplasia. Moreover, villus hyperplasia is greater in response to pancreatic secretions than to infusions with amino acids (71). It is apparent then that both nutrients and secretions are important for the adaptive response. The studies however have not helped to identify putative "growth factors" which may serve as signals to induce increased crypt cell production. The proliferative response is initiated in the intestinal crypts and possible growth factors must therefore be transported to the crypt zone to initiate a response. The possibility that a gut hormone released by food or secretions could be the mediator of the proliferative response has received increasing attention. The evidence that a blood-borne product was involved stems from cross-circulation experiments in pigs and rats where one animal had a jejunectomy (71). The non-resected parabiont developed increased intestinal weight or increased incorporation of thymidine in the crypts. The possibility that a gut hormone can cause villus hyperplasia was also raised by an interesting case report (77). This patient presented with complaints of constipation, polyuria, generalized edema, hair loss and a

transient erythematous rash. She was found to have mild steatorrhea, normal D-xylose absorption, diabetic glucose tolerance test and B_{12} malabsorption. A small bowel follow through was markedly abnormal with dilated loops, coarse mucosal folds and slow transit (17 hrs). A small bowel biopsy showed strikingly elongated intestinal villi. She was eventually found to have a right kidney tumor which on removal was found to have the characteristics of an islet cell tumor. Immunocytochemistry showed a strong reaction with antiglucagon antiserum. The tumor was originally described as a glucagonoma but on further characterization was later shown to be an enteroglucagonoma ( ). All the symptoms disappeared upon removal of the tumor. Glucagon and enteroglucagon are both processed from the same gene. The precursor is preproglucagon which is shown in Fig. 8. Enteroglucagon is a 69 amino acid peptide which contains

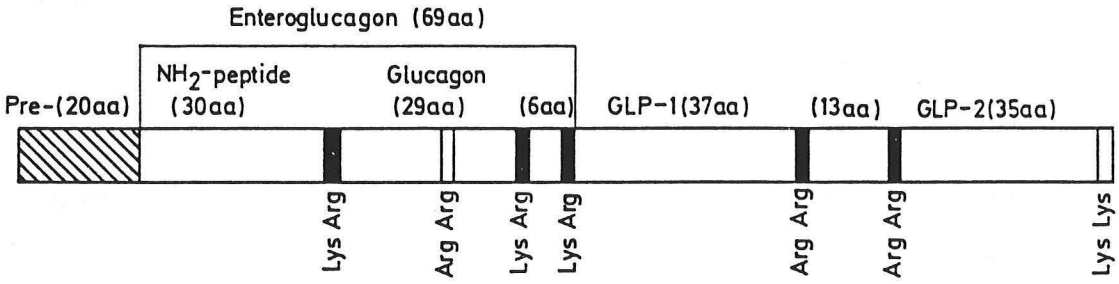


Fig. 8. Sequence of preproglucagon molecule

the entire glucagon sequence. Preproglucagon is differentially processed in the pancreatic α-cells and in the intestinal mucosa such that glucagon is released from the pancreas and enteroglucagon from the intestine. As mentioned previously enteroglucagon containing cells are mainly found in the ileal mucosa and to a lesser extent in the right colon. The striking villus hypertrophy seen in this patient makes enteroglucagon an attractive

candidate as a possible growth factor. Enteroglucagon is released from the ileal mucosa in response to lipid or carbohydrate infusion into a ileal loop. In normal persons there is little change in plasma glucagon levels in response to a meal confirming that lipid and carbohydrates do not reach that area of the intestine. However, there is a three-fold increase in plasma enteroglucagon levels after a meal in patients with a jejuno-ileal bypass and in patients with acute infectious diarrhea (78). In both instances the ileum is exposed to substantial quantities of carbohydrates and lipids. So far enteroglucagon is the only gastrointestinal hormone where changes in plasma levels correlate with crypt cell production rate -- an index of proliferative activity (79). Enteroglucagon has not been synthesized and is not available in a pure form. Therefore, it has not been possible to perform more definitive experiments. When it becomes available it will be interesting to see if chronic administration results in ileal villus hyperplasia and to test whether a response can be blocked by enteroglucagon antibodies.

It is very likely that several growth factors capable of inducing crypt cell proliferation will be identified in the future. Epidermal growth factor secreted by the salivary glands has been proposed as another intestinal growth factor but experimental evidence is so far lacking.

Polyamines and intestinal adaptation

While the search continues for extracellular signals of crypt cell proliferation it is increasingly evident that polyamines play an important role in the intracellular initiation of increased DNA synthesis and increased mitotic activity. The polyamines putrescine, spermidine and spermine are small positively charged molecules found at low concentrations in all cells. Putrescine is generated from ornithine by

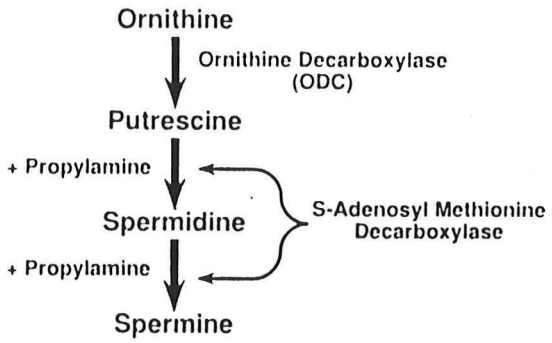


Fig. 9. Pathway of polyamine synthesis

ornithine decarboxylase (ODC) as shown in Fig. 9. ODC is the rate-limiting enzyme in polyamine synthesis and enzyme activity is very low in resting cells. Putrescine is converted to spermidine by S-adenosylmethionine decarboxylase (SDC) that also converts spermidine to spermine. When cells are induced to proliferate in response to a variety of stimuli, there is a rapid increase in ODC activity and polyamine concentrations within a few hours preceding increased DNA synthesis. It is only natural that the role of polyamines in intestinal adaption has attracted increasing attention over the last decade. Luk was one of the first investigators to demonstrate an increase in ODC activity and polyamine synthesis during intestinal maturation in the newborn rat (80). Next, he used the well-tested jejunectomy model and measured ODC and SDC activity and polyamine concentrations in the ileum of resected and control rats at various time points (81). Both ODC and SDC activity increased rapidly on day 1, peaked on day 2 and declined to almost control levels by 2 weeks. The increase in enzyme activity was also reflected in polyamine concentrations. Furthermore, there was a strong correlation between ODC activity and crypt cell production rate, villus and crypt growth. The studies, however, do not prove a causal relationship between polyamine synthesis and crypt

cell proliferation. The increase in enzyme activity and polyamine concentrations may just reflect an enzyme pathway that is turned on by increased mitotic activity. The development of an irreversible inhibitor of ODC, α–difluoromethyl ornithine (DFMO), allowed Luk to further define the role of polyamines in intestinal adaption. Using the same jejunectomy model in two groups of rats, where one group received DFMO in the drinking water, it was observed that DMFO completely suppressed ODC activity, new DNA synthesis and abolished any increase in crypt cell production rate and villus height (82). Thus, these studies point to a critical role of polyamines in the induction of new DNA synthesis and increased crypt cell proliferation. The precise mechanism whereby polyamines regulate DNA synthesis are currently poorly understood. The intense research activity in this area will very likely further define the role of polyamines in cell proliferation in the coming years.

In summary, the symptoms in patients with short bowel syndrome are largely determined by the extent and the area of intestinal resection. Those who are left with only a limited length of jejunum are most symptomatic with severe panmalabsorption and may require parenteral support for life. Patients with more limited resections and preserved colon can usually be managed with oral supplementation according to defined needs and adaptive responses after resection. The role of gastrointestinal hormones as extracellular messengers for the adaptive response is currently being defined. The polyamines on the other hand appear to play a critical role as intracellular initiators of crypt cell proliferation. Finally, intestinal transplantation still awaits further developments in immunosuppression before it can become a valid alternative to conservative management.

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