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ORIGINAL CONTRIBUTIONS

Treatment of Severe Protein Malnutrition After Bariatric Surgery

Carlijn Kuin[1] · Floor den Ouden[1] · Hans Brandts[2] · Laura Deden[3,4] · Eric Hazebroek[3,4] · Marcel van Borren[5] · Hans de Boer[6]

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Abstract

Background Severe protein malnutrition, with a serum albumin < 25 g/L, is one of the complications that may develop after bariatric surgery. It is associated with increased morbidity and mortality and requires timely diagnosis and appropriate treatment to prevent rapid clinical deterioration. However, evidence-based recommendations for a specific treatment approach are currently not available. The present study describes the efficacy of a newly developed treatment regimen for post-bariatric patients presenting with severe hypoalbuminemia.

Methods A single-centre, retrospective analysis of eleven post-bariatric patients presenting with severe hypoalbuminemia, treated with continuous 24 h nasal-jejunal tube feeding of a medium chain triglyceride (MCT) formulation in combination with pancreatic enzyme supplementation every 3 h.

Results Duration of tube feeding ranged from 25 to 156 days (median 64 days) and pancreatic enzyme was supplemented for 22–195 days (median 75 days). An increase in serum albumin levels of 5 g/L and 10 g/L was achieved after a median period of 20 (range 6–26 days) and 36 days (range 21–57 days), respectively. Albumin levels were > 35 g/L after a median period of 58 days (range 44–171 days).

Conclusion In this case series, a continuous 24-h nasal-jejunal MCT tube feed combined with frequent pancreatic enzyme supplementation was effective in all patients presenting with severe post-bariatric hypoalbuminemia and was not associated with adverse effects.

Keywords Bariatric surgery · Hypoalbuminemia · Hyperammonemia · Nutrition · Pancreatic enzymes · Tube feeding

Introduction

Bariatric surgery is currently the most effective treatment for weight loss in patients with morbid obesity [1]. It achieves much better long-term results than lifestyle interventions or medical treatments and leads to major and sustainable weight loss together with a reduction or reversion of comorbidities [1, 2]. However, bariatric surgery is not without risks. Dietary changes and physiological alterations of the digestive tract put these patients at risk for nutritional deficiencies [2]. Protein malnutrition is one of the more severe complications that may occur [3]. It is associated with an annual hospitalization rate of 1% per year [2]. Current dietary guidelines for patients after bariatric surgery recommend an average daily protein intake of 60–120 g or 1.1–1.5 g/kg of ideal body weight. An additional 30% increase is recommended for patients who underwent biliopancreatic diversion (BPD) [4, 5]. However, in case of reduced intake, protein intolerance, excessive malabsorption, or gastrointestinal complications, patients are prone to become protein deficient rapidly.

Protein malnutrition after bariatric surgery can be recognized by a serum albumin level < 35 g/L (normal range 35–50 g/L) that is not explained by either hepatic failure, or renal or gastrointestinal protein loss [5]. Albumin levels of 30–35 g/L are generally classified as mild, 25–30 g/L as moderate and levels < 25 g/L as severe hypoalbuminemia. Severe medical

Carlijn Kuin and Floor den Ouden contributed equally to this work.

✉ Hans de Boer
hdeboer@rijnstate.nl

[1] Division of Human Nutrition, Wageningen University Research, Wageningen, The Netherlands

[2] Department of Clinical Nutrition, Rijnstate Hospital, Arnhem, The Netherlands

[3] Department of Surgery, Rijnstate Hospital, Arnhem, The Netherlands

[4] Vitalys Clinic, Velp, The Netherlands

[5] Department of Clinical Chemistry, Rijnstate Hospital, Arnhem, The Netherlands

[6] Department of Internal Medicine, Rijnstate Hospital, Wagnerlaan 55, 6800, TA Arnhem, The Netherlands

conditions may develop when serum albumin levels drop below 25 g/L. This is usually associated with symptoms of general weakness and may lead to oedema, multi-organ failure and even death [5].

The incidence of post-operative hypoalbuminemia depends on the type of bariatric surgery [6]. It is relatively low after restrictive procedures such as gastric banding and gastric sleeve and ranges from 0 to 2% [6, 7]. The incidence is higher after procedures with a malabsorptive component, with the highest incidence after procedures with the most extensive malabsorptive component. Protein malnutrition was observed in 5% of patients after proximal RYGB, in 13% after distal RYGB [8], in 3–18% after biliopancreatic diversion (BPD) [9] and in 6–23% after single anastomosis duodenal-ileal bypass (SADI) [10].

Severe hypoalbuminemia is associated with increased morbidity and mortality and therefore requires timely diagnosis and appropriate treatment [5]. Depending on the degree of severity, patients have been treated with a large variety of oral, protein-rich supplements, enteral feeding or parenteral nutrition [4, 5]. However, the efficacy of such regimens has not been studied systematically and evidence-based recommendations for specific treatments of protein malnutrition after bariatric surgery are currently not available [5].

Therefore, we developed a treatment strategy for post-bariatric patients presenting with severe protein malnutrition. This treatment was designed to improve digestion and absorption and to increase the feeding time. It consists of continuous 24-h nasal-jejunal tube feeding of a medium chain triglyceride (MCT) formulation, enriched with essential amino acids and combined with pancreatic enzyme supplementation every 3 h to improve digestion and absorption in the alimentary limb. The present study is a retrospective evaluation of the efficacy of this regimen.

Patients and Methods

This is a single centre, retrospective analysis of the efficacy of a continuous 24-h nasal-jejunal tube feed regimen in post-bariatric patients presenting with symptoms of severe protein malnutrition and a plasma albumin level < 25 g/L. All patients presenting with severe hypoalbuminemia between February 2015 and May 2018 were included if they had no evidence of hepatic failure or renal or gastrointestinal protein loss and had been treated according to the newly developed protocol for protein malnutrition in post-bariatric patients under supervision of an internist and dietician. Data were obtained by patient chart review. The study was performed according to the regulations of the local ethical committee.

Dietary intake was assessed by dietician's interview. All patients were hospitalized to start nasal-jejunal tube feeding. An 8-French feeding tube was positioned in the proximal jejunum by endoscopy. Perative® (Abbott, UK) was administered continuously over 24 h by FreeGo® pump (Abbott, UK) [11]. Oral supplementation of a pancreatic enzyme mixture (Panzytrat 25.000®, Pharm-Allergan GmbH, Germany) was given every 3 h, which was continued during the night [12]. Patients were hospitalized for at least 1 week to monitor their initial response. TF was started at a rate of 500 mL/24 h and if tolerated increased by 500 mL/day until the daily required amount was reached. Laboratory screening for refeeding syndrome was performed three times a week on a Modular P800 (Roche) and GEM4000 (Werfen BV) and included measurement of creatinine, urea, ammonia, sodium, potassium, calcium, magnesium, phosphate, total protein, albumin and capillary blood gas. Patients were discharged when plasma albumin had increased by at least 5 g/L. Thereafter, TF was continued at home with laboratory checks every 1 to 2 weeks until plasma albumin was > 30 g/L and then monthly until albumin was > 35 g/L. Additional oral food intake was allowed. TF was gradually tapered by 500 mL/24 h weekly if serum albumin had increased to a level of at least 35 g/L. Oral protein supplements were started when TF was reduced to ≤ 1000 mL/24 h. The duration of TF varied per patient, depending on the albumin response. After completion of TF, patients continued on oral, protein-rich supplements.

Tube Feed and Pancreatic Enzyme Supplementation

Perative® is an energy and protein-rich TF that has been developed for patients with malabsorption and poor feed tolerance. It is composed of 54.1% carbohydrate, 20.5% protein and 25.4% fat and contains 1.3 kcal/mL. The carbohydrate fraction consists of 100% maltodextrin. The protein fraction consists of small peptides (72.2% hydrolysed sodium caseinate and 27.8% hydrolysed whey concentrate) that can be processed and absorbed rapidly. Moreover, the protein formulation contains more essential amino acids compared to other products and has been enriched with arginine, which may be an advantage in patients with severe protein malnutrition associated with an acquired urea cycle defect. The lipid fraction consists of 40% median-chain triglycerides (MCT) (hexanoic acid, octanoic acid, decanoic acid, dodecanoic acid) derived from palm kernel oil. These MCT consists of short fatty acid chains of only 6–12 carbon atoms. The reduced chain length facilitates absorption and allows direct transport by the portal system to the liver [13]. Patient-specific caloric requirements were calculated, based on the Harris-Benedict formula + 30% (an additional factor for disease and physical activity), and protein requirements were calculated using 1.5 g protein/kg ideal body weight (i.e. a BMI of 25 kg/m^2).

One capsule of the pancreatic enzyme mixture Panzytrat® contains 25.000 lipase, 15.000 amylase and 800 protease I.U. Panzytrat® was administered every 3 h to improve digestion and absorption in the alimentary limb.

Results

Patient Characteristics

In total, eleven consecutive patients (eight women, three men) with severe hypoalbuminemia were treated according to protocol. One patient needed treatment twice (patient no 6A/6B). Patient characteristics are summarized in Table 1. Six patients underwent RYGB surgery, three patients underwent RYGB with distalization at a later stage, one patient had a BPD according to Scopinaro and one patient underwent a BPD with duodenal switch. In RYGB patients, common channel length was estimated to be at least 200 cm (remaining small bowel after construction of alimentary and biliary limb). In patients with distal RYGB, BPD and BPD-DS surgeries, common channel length was 50–100 cm.

Post-operative weight loss was observed in all patients (EWL 88 ± 9.3%, TWL 37 ± 3.8%, mean ± SEM; Table 1). Six patients required first treatment for hypoalbuminemia within 1 year after their most recent procedure; in two patients, hypoalbuminemia treatment was more than 10 years after bariatric surgery.

At admission, albumin levels ranged between 10 and 23 g/L. Eight patients had albumin levels < 30 g/L 5 to 10 months before admission that had not improved despite protein enriched oral supplements. Accelerated deterioration in serum albumin was observed in six patients in the last months before admission (median decrease of 11 g/L). At admission, all patients had symptoms of general weakness, oedema of varying severity and a history of poor calorie and protein intake before hypoalbuminemia was diagnosed. None of the patients was suspected of intentional food restriction. The estimated mean calorie and protein intake assessed by dietary interview were 1358 kcal and 72 g respectively. On average, this was about 70% of their total daily needs, based on the Harris Benedict formula + 30% and 1.5 g protein/kg ideal body weight. Eight patients used multi-vitamin supplements. An initiating event for the development of malnutrition was observed in five patients: ulceration at the gastrointestinal anastomosis ($N = 3$), gastrointestinal obstruction ($N = 1$), chronic diarrhoea ($N = 1$) and depression ($N = 1$). In six patients, malnutrition was attributed to the malabsorptive nature of the surgical procedure, in combination with a poor feeding habit.

Additional laboratory screening at hospitalization revealed an elevated plasma ammonia level in three patients (range 63–158 μmol/L, normal range < 50 μmol/L), renal insufficiency (creatinine 145 μmol/L) attributed to dehydration in one patient and vitamin A, zinc and selenium deficiency in 9, 6 and 4 patients, respectively. During the in-hospital refeeding period, two patients developed mild hypokalaemia that required temporary supplementation. Clinically significant hypophosphatemia or hypomagnesemia was not observed.

Treatment Results

Maintenance TF infusion rates ranged from 1000 to 2000 mL/24 h (median 1500 mL/24 h); most patients reached their calculated TF dose within 3–4 days. Duration of TF ranged from 25 to 156 days (median 64) and duration of pancreatic enzyme supplementation ranged from 22 to 195 days (median 75). The course of serum albumin levels from the start of treatment until 6-month follow-up is shown in Fig. 1. Albumin levels increased by 5 g/L and 10 g/L after a median period of 20 (range 6–26) and 36 days (range 21–57), respectively. In most patients, a rapid increase in serum albumin was observed, with a rise above 25 g/L within 15–20 days (Fig. 1). Thereafter, the increase in albumin continued, but at a more gradual pace. The median duration until albumin levels were > 35 g/L was 58 days (range 44–171). Plasma ammonia levels remained within, or decreased to the normal range in all patients during treatment (data not shown). After completion of TF, median BMI had increased by 1.9 kg/m^2 (range 0.1–4.2 kg/m^2).

Two patients had an unusual clinical course. Patient no. 6 showed an initial rise in serum albumin from 20 to 29 g/L during the first TF episode but then refused further treatment. Seven months later, he returned with severe hypoalbuminemia (12 g/L), was hospitalized again and continued treatment until albumin had increased to a level of 35 g/L after 171 days. Patient no. 5 was admitted because of severe weakness, somnolence and extensive bilateral leg oedema that had developed during a 3-month period of diarrhoea and poor intake. Laboratory examination revealed a glomerular filtration rate of 32 mL/min, a serum albumin level of 14 g/L without proteinuria, and a plasma NH_3 level of 158 μmol/L (normal value < 50 μmol/L), with mildly increased liver enzymes, and a mildly prolonged APTT and PTT. Somnolence was attributed to ammonia encephalopathy and lactulose was started in a dose of 10 g TID. This led to a normalization of ammonia levels within 4 days. After exclusion of primary liver disease, a diagnosis of non-hepatic hyperammonemia was made. TF and pancreatic enzyme supplementation were started with frequent monitoring of plasma ammonia levels. Spironolactone 100 mg/day was added to treat oedema. Two weeks later, she had improved markedly with a disappearance of oedema (associated weight loss of 11 kg in 2 weeks), a rise in serum albumin to 21 g/L without an increase in plasma NH_3 and a normalization of serum creatinine. Screening for congenital urea cycle disorders was negative. Urinary orotic acid levels were within the normal range, and DNA analysis did not reveal any known mutations in the OTC, NASG or UMPS genes.

Table 1 Summary of clinical and laboratory findings in patients presenting with severe hypoalbuminemia after bariatric surgery

Patient	Age (years)	Sex	BMI-I[(1)] (kg/m^2)	1st surgery BPL; AL (cm)	2nd surgery CC (cm)	Initiating event	Reduced intake	Clinical presentation at hospitalization
1	41	F	38.9	RYGB 50; 150	D-RYGB 100	None	No	General weakness, severe weight loss, hypotension
2	46	F	51.9	RYGB 50; 150	D-RYGB 100	None	No	General weakness
3	39	F	52.5	BPD[(3)] NA; 200	NA 50	None	Yes	General weakness, chronic diarrhoea
4	56	F	68.1	BPD-DS[(4)] NA; 250	NA 75	Depression	Yes	General weakness
5	56	F	42.6	RYGB 50; 150	NA	Chronic diarrhoea	Yes	General weakness, elevated NH_3, oedema
6A	63	M	36.4	RYGB 150; 75	NA	Ulceration GI anastomosis	Yes	General weakness, cachexia
6B	64	M	36.4	RYGB 150; 75	NA	NA	Yes	Fatigue, oedema
7	58	F	55.9	RYGB 75; 100	D-RYGB 125	None	Yes	General weakness
8	67	F	53.4	RYGB 75; 150	NA	None	Yes (nausea)	General weakness, cachexia, oedema
9	55	M	41.6	RYGB 150; 100	NA	Ulceration GI anastomosis	Yes	General weakness, cachexia
10	38	F	43.6	RYGB 150; 100	NA	Ulceration GI anastomosis	Yes	General weakness, dizziness, melena
11	62	M	34.9	RYGB 150; 100	NA	GI obstruction	Yes	General weakness, oedema

Patient	Months since Surgery	BMI-II[(1)] (kg/m^2)	BMI-III[(1)] (kg/m^2)	Albumin[(2)] (g/L)	Tube feed (days)	Pancreatic enzymes (days)	Albumin > 35 g/L (days)
1	12	22.8	26.8	21	74	74	46
2	21	37.0	37.8	22	48	48	48
3	155	34.5	37.1	23	49	49	57
4	131	22.7	24.4	18	59	48	69
5	11	26.9	28.9	10	69	195	137
6A	12	21.9	23.5	18	25	22	–
6B	22	22.7	23.1	12	77	40	171
7	83	42.1	42.1	16	118	110	110
8	13	33.9	34.0	13	156	149	103
9	12	21.3	25.5	13	72	145	44
10	10	26.4	29.4	16	58	119	58
11	19	27.1	25.2	20	53	101	47

AL alimentary limb, *BMI* body mass index, *BPD* biliopancreatic diversion, *BPL* biliopancreatic limb length, *CC* common channel, *D-RYGB* distal RYGB, *F* female, *GI* gastro-intestinal, *M* male, *NA* not applicable, *RYGB* Roux-en-Y gastric bypass

[(1)] BMI-I: before bariatric surgery, BMI-II: at hospitalization, BMI-III: at end of tube feeding

[(2)] Serum Albumin at start of tube feeding

[(3)] Length of common channel was 50 cm; length of BPL was the length of the remaining small bowel

[(4)] Length of common channel was 75 cm; length of BPL was the length of the remaining small bowel

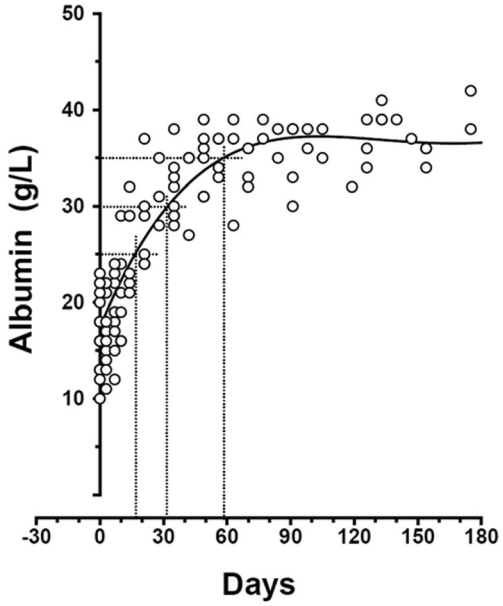

Fig. 1 Serum albumin levels in response to treatment

Discussion

This case series describes the efficacy of a newly developed treatment regimen in eleven consecutive post-bariatric patients presenting with severe protein malnutrition. Treatment with continuous 24 h nasal-jejunal tube feeding of a MCT formulation in combination with pancreatic enzyme supplementation every three hours induced a rapid rise in albumin levels, with a rise above 25 g/L within 15–20 days in most patients. Thereafter, the increase in serum albumin continued at a lower rate. In most patients, albumin levels stabilized around 35 g/L within three months. TF did not induce hyperammonemia and was not associated with unexpected sided effects. Only two patients developed mild hypokalemia during the first week of treatment which was easily corrected.

Several studies have assessed the incidence of hypoalbuminemia after bariatric surgery and most used albumin cut-off levels of 30–35 g/L. The number of studies reporting on severe hypoalbuminemia (< 25 g/L) is limited. A summary of the available literature is presented in Table 2, showing type of surgery, limb length, number of included patients, follow-up period and incidence of hypoalbuminemia (either moderate, mild or severe) [14–25]. No studies were found describing protein malnutrition after gastric banding. The single study available after gastric sleeve reported a prevalence of 3.2% [25]. The weighted mean reported incidence of severe hypoalbuminemia from all studies combined was 2.7% after RYGB, 3.8% after one-anastomosis gastric bypass, 4.6% after BPD and 10% after SADI (Table 2—final column). In case of SADI, the information on severe hypoalbuminemia was limited to one small study only that reported severe hypoalbuminemia in three out of 30 patients [24]. The risk of protein malnutrition is low after restrictive procedures and increases with extension of the malabsorptive component. After standard RYGB procedure, the incidence is relatively small, and in the majority of patients, an initiating event can be identified. In our series, five out of six patients after standard RYGB had such an initiating event, i.e. ulceration of the gastro-intestinal anastomosis, chronic diarrhoea or intestinal obstruction (see Table 1). Variation in pre-existent small bowel length may also have put some of them at risk to receive a too short common channel, even after standard RYGB [26].

The current lack of an appropriate treatment protocol for severe protein malnutrition after bariatric surgery may lead to serious adverse events [27–34]. Three of these reports describe the course and treatment of patients presenting with severe hypoalbuminemia [27–29]. One of them died, possibly as a complication of excessive protein feeding. The remaining reports describe cases presenting with a combination of severe hypoalbuminemia and non-hepatic hyperammonemia, a life-threatening condition with a mortality rate of > 50% [30–34]. Poor calorie and protein intake for several months prior to admission was common in these patients. Nutritional treatment differed and consisted either of high oral protein supplementation, enteral feeding through a gastric feeding tube or total parenteral nutrition (TPN). High protein feeding is not without risk and may be fatal, in particular in those presenting with severe energy and protein depletion [29, 30, 32]. In such patients, endogenous proteins are broken down to provide the amino acids necessary for glucose production, a process known as gluconeogenesis. The combination of enhanced amino acid release and high protein feeding may cause symptomatic hyperammonemia [30–34].

Elevated ammonia levels in post-bariatric patients with hypoalbuminemia may be related to a urea cycle defect (UCD) [35]. This cycle predominantly occurs in the liver and converts ammonia into urea to enable urinary excretion of waste nitrogen, a process that requires proper function of six different enzymes [36, 37]. In most cases, UCD is caused by a congenital enzyme defect or deficiency and is usually discovered within the first days of life. However, mild deficiencies may have gone unnoticed and become manifest in adulthood when the cycle is stressed, for example in case of increased ammonia production due to protein catabolism [35]. Ornithine transcarbamylase (OTC) deficiency is the most common congenital cause, with an estimated prevalence ranging from 1 in 14.000 to 1 in 77.000 [38]. In view of the very low prevalence of these congenital UCDs, an acquired (partial) defect caused by nutritional deficiencies of amino acids essential to build these enzymes is much more likely in post-bariatric adult patients presenting with de novo non-hepatic hyperammonemia. Enzyme suppression by drug interaction or zinc deficiency should also be considered as a cause [39]. In post-bariatric patients suspected of acquired UCD, protein feeding must be stopped immediately and should be replaced by high-dose intravenous glucose infusion to block ammonia production

Table 2 Summary of studies reporting the incidence of hypoalbuminemia after bariatric surgery

Study	Type surgery	BPL (cm)	AL (cm)	CC (cm)	Number	Follow-up	Albumin cut-off value (g/L)	Incidence (%)	Weighted mean incidence (%)
[14]	RYGB	50	150	Remaining part	90	30 days – 5 year	< 30	2.2	Mild: 9.9
[15]	RYGB	50–150	50–250	150–200	92	2 year	< 35	8.7	Moderate: 2.7
[16]	RYGB	75	150	Remaining part	39	2 year	< 35	13.0	Severe: 2.6
							< 21	5.1	
[17]	RYGB	50	100	Remaining part	65	2 year	< 25	1.5	
[18]	RYGB	Unknown	Unknown	Unknown	75	2 year	< 30	5.3	
[19]	RYGB	50	150	Remaining part	295	2 year	< 30	2.2	
	OAGB				473		< 30	9.3	
							< 25	3.8	
[14]	BPD	Remaining part	400	100	699	30 days–5 year	< 30	3.7	Mild: 17.0
[15]	BPD	50	300	Remaining part	121	2 year	< 35	14.9	Moderate: 2.6
[17]	BPD	150	Remaining part	100	65	2 year	< 35	8.2	Severe: 4.6
							< 25	4.6	
[20]	BPD	Remaining part	200	100	874	1 year	< 33	18.0	
							< 30	1.7	
[21]	SADI	–	–	250	100	2 year	< 35	6.0	Mild: 11.3
[22]	SADI	–	–	250	97	1 year	< 35	13.7	Moderate: –
						3 year		12.0	Severe: 10.0
[23]	SADI	–	–	200	50	2 year	< 35	10.0	
[24]	SADI	–	–	250	30	2 year	< 35	23.0	
							< 25	10.0	

AL alimentary limb, *BPL* biliopancreatic limb, *CC* common channel, *N* number, *RYGB* Roux-en-Y gastric bypass, *OAGB* one-anastomosis gastric bypass, *BPD* biliopancreatic diversion, *SADI* single anastomosis duodenal-ileal bypass

induced by protein catabolism [40]. When ammonia levels have normalized, low-dose protein feeding should be started slowly to correct the amino acid depletion that has caused the urea cycle enzyme deficiencies. The amino acid composition of the tube feed we have used has a well-balanced profile of essential amino acids that is also enriched with arginine. The latter is often recommended as additional treatment in congenital UCD because it improves urea cycle function. Intravenous protein feeding is not recommended because it will increase the risk of hyperammonemia.

In conclusion, severe hypoalbuminemia after bariatric surgery should be regarded as a serious condition requiring timely care by professionals with nutritional experience. Regular monitoring of serum albumin is strongly recommended to prevent the development of severe protein malnutrition after the more severe malabsorptive procedures, such as SADI, distal RYGB and BPD. In our experience, oral protein supplements may be useful to treat mild hypoalbuminemia but are ineffective for the treatment of severe hypoalbuminemia. We recommend 24-h enteral feeding with a high-energy feed containing MCTs, enriched with essential amino acids and supported by frequent administration of a pancreatic enzyme mixture in patients presenting with albumin levels < 25 mmol/L. This proved to be effective and safe in all patients we have treated so far. Although non-hepatic hyperammonemia was not observed during this treatment, we strongly recommend that ammonia levels are monitored closely to adjust protein intake if necessary.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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