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ORIGINAL ARTICLE

Control of diarrhea by fiber-enriched diet in ICU patients on enteral nutrition: a prospective randomized controlled trial

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Summary *Background & aims*: Enteral fiber-free diets alter intestinal transit and produce diarrhea or constipation. This prospective double blind, controlled study evaluates the use of guar gum, a soluble fiber and a candidate prebiotic in enteral feeds, to prevent diarrhea and potential health benefits in intensive care unit patients.

Methods: Twenty patients on enteral nutrition with persistent diarrhea were randomized to receive a new enteral feed either enriched with 2% soluble guar gum (study group, $n = 10$) or fiber-free (control group, $n = 10$) for 4 successive days.

Results: The number of liquid stools in response to a soluble fiber-enriched diet was 2.0 ± 0.9 (first day) vs. 1.0 ± 0.7 (fourth day) ($P < 0.01$), and in the control group 1.2 ± 0.7 (first day) vs. 2.1 ± 0.8 (fourth day) ($P < 0.05$). In the fiber-enriched feed group, plasma glucose and cholesterol levels at termination of the study, respectively, reached 126 ± 81 and $164 \pm 71\,mg\,dl^{-1}$, as compared to 333 ± 108 and $378 \pm 26\,mg\,dl^{-1}$ on Day first ($P < 0.01$). In the control group, these values on the fourth day were, respectively, 267 ± 94 and 263 ± 79 vs. 247 ± 115 and 315 ± 78 on Day first ($P > 0.05$).

Conclusions: Guar gum-enriched enteral nutrition was related to a decrease of diarrheal episodes in ICU patients with preexisting diarrhea; and to a trend for lower plasma glucose and cholesterol levels.

Introduction

Enteral nutrition (EN) is the first choice route for nutritional support in intensive care unit (ICU) patients with a functioning digestive tract.[1] Unfortunately, in case of diarrhea EN is often reduced or discontinued and its nutritional efficiency is jeopardized. Although the causes of diarrhea are

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diverse, the EN solution is frequently suspected of playing a leading role in causing diarrhea.[2] Attempts to control EN associated diarrhea in the critically ill tube-fed patient by implementing feeding formulas enriched with fiber were mostly unsuccessful. Recently, it was shown that enteral feeding containing soluble partially hydrolyzed guar gum decreased the incidence of diarrhea in a cohort of non-critically ill medicosurgical patients.[3] Addition of guar gum elevated the soluble fiber content from 1% to 6%, and increased proliferation of *Escherichia coli* in the small intestine.[4] Fibers can be divided into soluble and insoluble.[5] Fermentation, the process whereby anaerobic bacteria breakdown carbohydrates to short-chain (C2–C6) fatty acids, mainly as acetate, propionate, and butyrate, is of major importance in the physiological function of soluble dietary fiber and their possible role in prevention of diarrhea.[6,7]

Prebiotics are non-digestible carbohydrate food ingredients which selectively stimulate the activity and/or growth of probiotic bacteria in the gut.[8,9] They can readily be incorporated into enteral feeds with potential benefit.[10–12]

The prebiotics developed so far are the non-digestible oligosaccharides.[13] This prospective double blind, controlled study of twenty patients was designed to investigate the efficacy of the polysaccharide soluble dietary fiber, guar gum, in controlling preexisting diarrhea, as a candidate prebiotic and its potential benefits in ICU patients on EN. It revealed a tendency to decrease diarrheal episodes in the fiber-supplemented patients.

Patients and methods

Twenty consecutive patients, APACHE II 16-22, above 20 years of age, on EN with 3 or more liquid stools per day or grossly in excess of about 300 ml of total volume were randomly allocated to one of two groups. The body weight at admission (kg), body height (cm) and body mass index {weight (kg) · squared height $(m^2)^{-1}$} were reported. The study was approved by the Hospital Ethics Committee and all patients gave written informed consent. The study group ($n = 10$) was given 2% soluble guar gum (Benefiber)-enriched enteral feeds (Sandosource GI Control, Novartis Nutrition GmbH, München, Germany) as the sole source of nutrition for 4 successive days. The study feeds were providing, per 1000 ml feed; 1060 kcal, 41 g protein, 22 g soluble fiber, 700 mg sodium, 1350 mg potassium, 550 mg calcium, 220 mg magnesium, 550 mg phosphorus, 1000 mg chloride and having an osmolality of 275 mOsm kg^{-1} water. The control group ($n = 10$) was given fiber-free enteral feeds for the same period (Propeptide™, Prime, Nutrition Medical, Inc. USA) supplying, per 1000 ml feed; 1000 kcal, 40 g protein, 500 mg sodium, 1252 mg potassium, 800 mg calcium, 400 mg magnesium, 700 mg phosphorus, 1000 mg chloride and having an osmolality of 270 mOsm kg^{-1} water. Sealed numbered envelopes were used to implement the randomization. The subject was assigned to the formula code group on the card inside the envelope from the appropriate randomization block.

Patients with short bowel syndrome, acute bacterial infection, including clostridium difficile infection, mechanical intestinal obstruction, paralytic ileus or known intestinal ischemia, septic patients or hyperthyroidism were excluded from the study.

Table 1 shows the main pathologies and the main treatments of the patient population. All patients were receiving antibiotics, none was receiving any specific hypocholesterolemic, antidiarrheal, laxative or prokinetic drugs. Ten patients were ventilated via Pressure Support Ventilation (PSV)/ Continuous Positive Airway Pressure (CPAP) modes.

Enteral prescription and follow-up

All the enteral feeds were prepared in the hospital pharmacy in similar 1.5 l flexible pouches (Compat-Flexibaggle, Novartis Nutrition GmbH, Germany). Patients and medical staff were blinded as regards the test feeds fiber content. Feeds were delivered to the patients through 10F (French), 120 cm polyurethane nasojejeunal enteral feeding tubes (Compat-Soft M, Novartis Nutrition GmbH, Germany) with their tips distal to the ligament of Treitz inserted endoscopically, under radiographic guidance or in the operating theatre. Energy administration was routinely aimed at between 25 and 35 kcal kg^{-1} day^{-1} to be given during 18–24 h per 24 h at a constant rate through pump-assisted system (Compat-Standard Pump, Novartis Nutrition GmbH, Germany). Although guar gum slightly increases the viscosity of the enteral formula, proper daily flushing (20 ml sterile water) of the feeding tube did prevent occlusion. After 1 day of diarrhea of 3 or more liquid stools or total volume grossly in excess of about 300 ml, patients were considered for inclusion in the study. The previous enteral feeds, that the patients were given, were stopped and either of the study feeds were started. The feeds were built up gradually; 50% of the required energy intake on the first day, 75% on the second day and 100% thereafter on the third and

Table 1 Main diagnostics and main treatments expressed as number of patients in each group.

Main diagnostics	Control group ($n = 10$)	Study group ($n = 10$)	Main treatments*	Control group ($n = 10$)	Study group ($n = 10$)
Aortic aneurysm	1	—	Antibiotics:	10	10
Cerebrovascular stroke	3	3	Cefoperazon/ sulbactum	4	5
Congestive heart failure	—	1	Cetazidine	1	2
Chronic renal failure	1	1	Ceftrixon sodium	2	3
COPD†	—	2	Imipenam	2	—
Fracture base of skull‡	1	1	Neomycin	1	—
Lower limb ischaemia	1	1	Antihypertensives:	3	2
Polytrauma§	3	1	Propranolol	1	—
Diabetes mellitus¶	2	1	Sodium nitroprusside	1	2
			Verapamil	1	1
			Bronchodilators:	3	4
			Salbutamol	2	2
			Theophylline	1	2
			H2 receptor antagonists:	5	4
			Cimetidine	1	—
			Ranitidine	4	4
			Hypoglycaemics	2	1
			Regular insulin	2	1

*Sedation used was dormicum infusion via a syringe pump on hourly basis (1–2 mg/h) even for ventilated patients.
†Chronic obstructive pulmonary disease.
‡Fracture Base of Skull with central nervous system pathologies as evidenced by their magnetic resonance imaging study.
§Polytrauma patients without any neurotrauma.
¶Six patients have been keto-acidotic at the start of the study but only three of them were originally diabetic.

fourth days. The 24 h volume of feed was prescribed as multiple of 250 ml to facilitate the nursing activity.

The number of liquid stools and feeds volume administered on days 1, 2, 3 and 4 were recorded. Tolerance to feeds was daily reported in the form of the presence and the severity of any gastrointestinal symptom in relation to the given feed volume including: nausea, vomiting, flatulence or constipation. Nausea was defined as the unpleasant sensation in the stomach usually accompanied by the urge to vomit. Vomiting was defined as the presence of any amount of diet in the oral cavity or in the oropharynx, observed during the explorative examination of the patient or during hygienic mouth care. Flatulence was defined as the presence of excessive amounts of air or gas in the stomach or intestine, leading to abdominal distention evidenced by increased abdominal girth at the level of the umbilicus. Constipation was defined as the absence of bowel movements for more than 3 days or the inability to pass a bowel movement after straining or pushing for more than 10 min. Nursing and medical staff subjective appreciation was also considered.

The following laboratory indices were measured on the first day and daily for 5 days: hemoglobin, total protein, albumin, cholesterol, calcium, phosphate, magnesium, sodium, potassium, glucose, urea, creatinine, alanine transaminase and aspartate transaminase.

Statistical analysis

Results were expressed as means $\pm$ SD. Daily comparisons between study and control groups as regards parametric data as feeds volume and number of liquid stools were analyzed using unpaired Student's *t*-test. Within group changes were analyzed by repeated measures analysis of variance (ANOVA). When this overall ANOVA resulted in a significant result, it was followed by post hoc comparison (Newman Keules test for multiple comparisons to determine which one differed from the others). Comparisons between both groups regarding nominal data as incidence of gastrointestinal symptoms in response to feeds were analyzed using Fisher's exact test. Severity of gastrointestinal symptoms were compared between

Table 2 Demographic data.

Group	Age (years)		Sex		Weight (kg)		Height (cm)		BMI		APACHE II		SS	
	Mean (SD)	Range	M	F	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Study	53(14)	28–63	6	4	70(13)	60–105	165(8)	150–180	25.1(3.1)	21.0–32.0	18(2)	17–22	7(2)	5–10
Control	62(12)	35–72	5	5	74(11)	60–100	169(5)	160–175	26.0(2.5)	23.4–32.0	18(2)	16–22	7(2)	4–10

BMI = Body mass index, SS = Sickness score.[14]

both groups using Mann–Whitney *U*-test. For all statistical comparisons, a *P* value of <0.05 was considered significant. All statistical analysis was performed using Excel and SPSS 8 package.

Results

Thirty patients were included, but only 20 patients completed the protocol and were included in the data analysis. Ten patients did not complete the protocol due to transfer to parenteral nutrition or oral diet, death or leaving the ICU before completing the study days.

There was no statistical difference between groups with respect to anthropometric and demographic data (Tables 1 and 2).

Fig. 1A shows the daily total enteral feeds volume in the control and study groups. Patients in the study group tolerated (with less gastrointestinal troubles) significantly higher feeds volumes on the first, second and fourth days. On the fourth day, the feeds volumes were 1775 (450) ml in the study group vs. 1070 (604) ml in the control group ($P<0.01$). Moreover, in the study group the feeds volumes on the fourth day were significantly higher than on the first, second and third days. The feeds volumes in the study group were 1070 (221) on the first day vs. 1775 (450) on the fourth day ($P<0.01$).

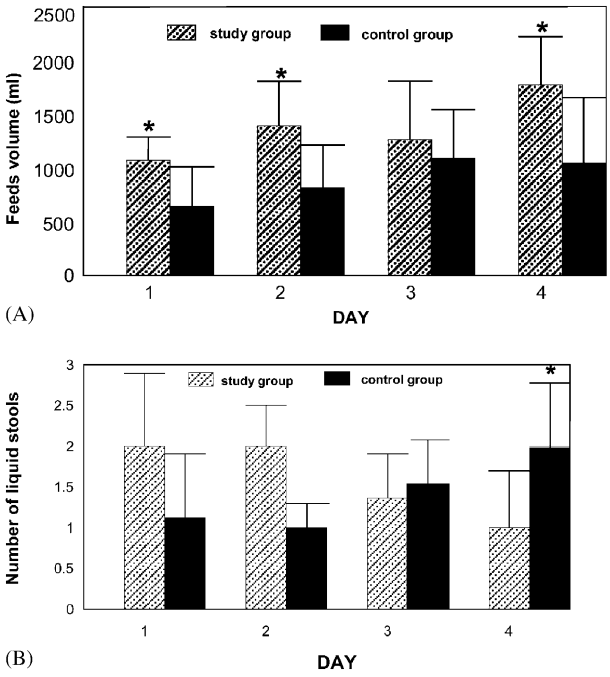

Figure 1 (A) Comparison of volume of feeds between control and study groups. Significantly higher feeds volume has been administered to patients in the study group on the first, second and fourth days than in the control group. On day 3, 2 patients had CT scanning done that resulted in temporary reduction of feed administration. (B) Comparison of the number of liquid stools between the control and study groups. The number of liquid stools is lower significantly on fourth day in study group than in control group. Error bars represent the standard deviation (SD). $^{*}P<0.01$ compared to the same day in the other group.

Tolerance to enteral feeds

Fig. 1B reveals the main data on tolerance to EN. The number of liquid stools was significantly lower on the fourth day in the study group than in control group although there was no statistical difference on the first day. The number of liquid stools on the fourth day in the study group was 1.0 (0.7) vs. 2.1 (0.8) in the control group ($P<0.01$). In the control group, the number of liquid stools recordings were 1.2 (0.7) and 1.0 (0.3) on the first and the second days, respectively, vs. 2.1 (0.8) on the fourth day ($P<0.05$ and $P<0.01$, respectively, as compared to the fourth day) as evidenced in Fig. 2A. In the study group, the number of liquid stools recordings were 2.0 (0.9), 2.0 (0.5), and 1.4 (0.4) on the first, second and third days, respectively, vs. 1.0(0.7) on the fourth day ($P<0.01$ as compared to the fourth day) in spite of a significantly higher feeds volumes on the fourth day than on the first, second and third days (Fig. 2B).

Table 3 sheds light on the gastrointestinal symptoms encountered in the control and study

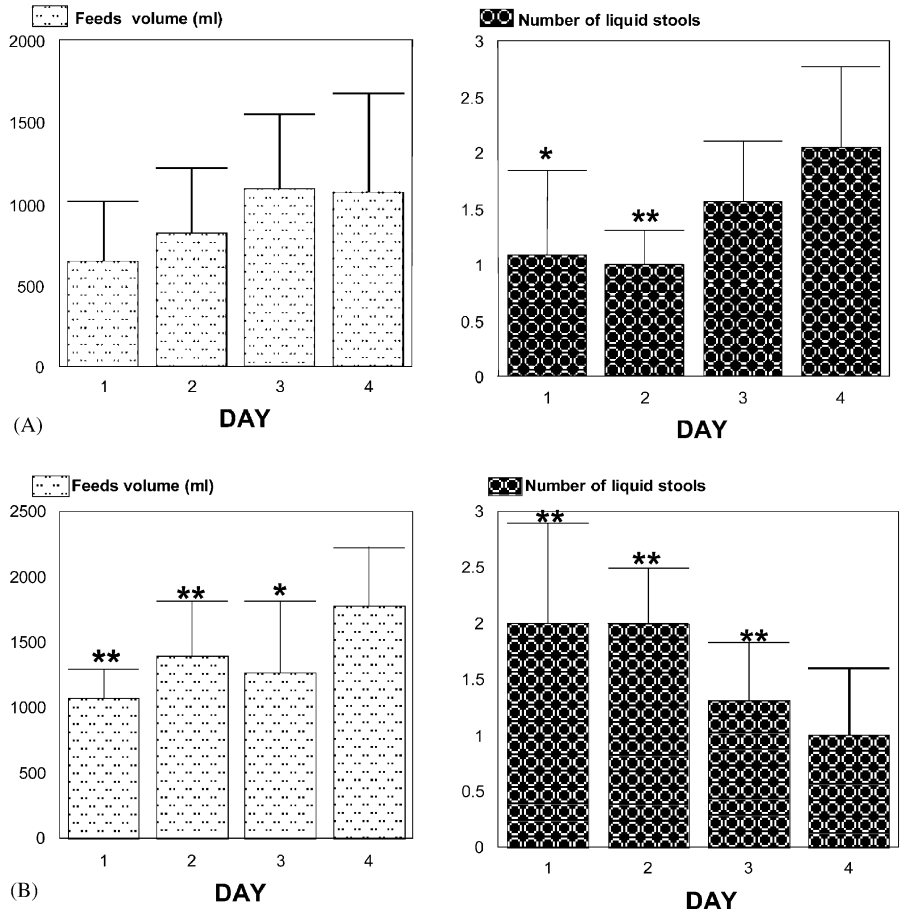

Figure 2 (A) Comparison between the 4 study days; feeds volume and number of liquid stools in the control group. (B) Comparison between the 4 study days; feeds volume and number of liquid stools in the study group. Error bars represent the standard deviation (SD). $^{**}P<0.01$ compared to the fourth day within the same group, $^{*}P<0.05$ compared to the fourth day within the same group.

Table 3 Gastrointestinal symptoms in the control ($n = 10$) and study ($n = 10$) groups.

	Severe nausea*	Vomiting	Flatulence	Constipation
Study group	0	0	2	0
Control group	0	2	4	1

Number specified expresses the number of patients affected in each group.
*Assessed in conscious patients (study group, $n = 4$; control group, $n = 5$).

groups in response to the administered feeds. Throughout the course of this clinical trial, in the fiber-enriched feed group, only two patients complained of flatulence (20%). On the other hand, in the control group, four patients complained of flatulence (40%), two patients got vomiting (20%) and one case of constipation (10%) was reported. However, no statistical significance was found between both groups as regards incidence or severity of gastrointestinal symptoms. None of these symptoms was severe enough to necessitate therapeutic intervention.

Evolution of laboratory tests

Fig. 3 shows the significant laboratory changes met in the study group throughout the 4 study days and at the end of the study on the fifth day. There were significantly lower plasma glucose and cholesterol

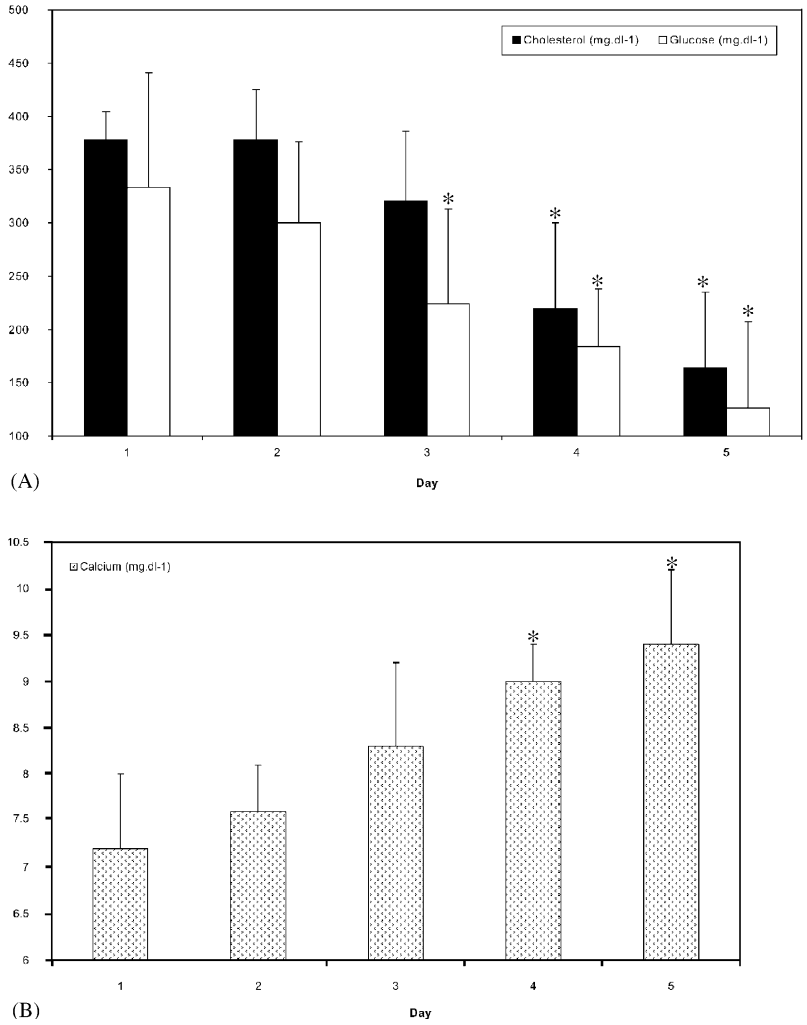

Figure 3 The significant laboratory changes met in the study group throughout the 4 study days and at the end of the study on the fifth day. (A) Comparison between the study days as regards the cholesterol and glucose plasma levels in the study group. Significantly lower levels were met at the end of the study as compared to their corresponding levels on the first day. (B) Comparison between the study days as regards the calcium plasma level in the study group. Significantly higher level was met at the end of the study as compared to its level on the first day. $^{*}P<0.05$ compared to the corresponding plasma level on the first day in the study group.

and higher calcium levels in the study group at termination of the study as compared to their levels on the first day of the study. Plasma glucose at the end of the study was 126 (81) vs. 333 (1 0 8) mg dl^{-1} on the first day ($P<0.01$). Serum cholesterol levels were 164 (71) and 378 (26) mg dl^{-1} at termination of the study and on the first day of the study, respectively ($P<0.01$). Plasma calcium level at the end of the study was 9.4 (0.8) as compared to the first day, 7.2 (0.8) mg dl^{-1} ($P<0.01$). Although the serum magnesium level increased at the end of the study as compared to its level on the first day, this increase did not reach statistical significance. On the other hand, no significant variation was met, as concerns the laboratory indices in the control group, between the first day and after termination of the study.

Discussion

Reducing the occurrence of diarrhea in ICU patients is of utmost clinical importance. Diarrhea is commonly met in ICU patients during enteral feeding impairing their nutritional supply and electrolytes balance. Diarrhea prevention should logically optimize the level of coverage of nutritional needs.

The present study originally showed that soluble fibers-enriched feeds reduce the number of

diarrheal episodes in ICU patients with preexisting diarrhea during EN.

Diarrhea control and tolerance to enteral feeds

All patients were on EN and had persistent diarrhea at inclusion in the study. The number of liquid stools increased significantly in response to a dietary fibers-free diet whereas it decreased significantly in response to a soluble fibers-enriched diet. The number of liquid stools was significantly lower on the fourth day in the study group, mean 1.0 (0.7) than in the control group, 2.1 (0.8) although there was no statistical difference on the first day. This comes in general agreement with the findings of other investigators. Spapen and coworkers[3] noted that the mean frequency of diarrhea days was significantly lower in tube-fed full-resuscitated and mechanically ventilated septic patients receiving soluble fiber than in those on fiber-free feed ($8.8 \pm 10.0\%$ vs. $32.0 \pm 15.3\%$). Homann et al.[2] observed that enteral feeding with a formula supplemented with 2% soluble fiber, containing partially hydrolyzed guar gum (PHGG), reduced the incidence of diarrhea. In the study by Schultz et al.[15] of the effects of the soluble fiber, pectin on diarrhea in critically ill tube-fed patients receiving antibiotics, the trend was toward less diarrhea in the fiber/pectin group. Moreover, in the study by Giaccari et al.[16] subjects affected by irritable colon syndrome and submitted for 24 weeks to a diet supplemented by 5 g a day of PHGG showed positive results in the evacuation frequency at 12th week. In another investigation stool wet weight was found to be higher during self-selected diet than during a polymeric enteral formula supplemented with a mixture of six fibers, Nutrison Multi Fiber.[17] Regarding tolerance of the feeds, our patients in the study group tolerated (with less GIT troubles) higher feeds volumes than in the control group. Throughout the course of this clinical trial, in the study group which included 10 patients, only two patients complained of flatulence (20%). In the study by Homann et al.,[2] none of the patients on PHGG-enriched enteral feeding required discontinued feeding rate because of gastrointestinal side effects. Giaccari et al.[16] observed that subjects affected by irritable bowel syndrome experienced a decrease, after 3 weeks of PHGG intake, in frequency of irritable bowel syndrome symptoms such as flatulence (-5.6%), abdominal tension (-4.7%) and abdominal spasm (-35%). On the other hand, Pedersen et al.[18] reported that the soluble dietary fiber, inulin at a dose of $14\,g\,day^{-1}$ for 4 weeks in a group of 64 women, caused highly significant increases in flatulence, rumbling, stomach and gut cramps and bloating. Twelve percent of the volunteers considered the flatulence severe and unacceptable. The soluble fiber studied in the present clinical trial was guar gum and not inulin. That accounts for the variations in the observations reported. As the increase in fecal output and flatulence is likely to be due to an increase in biomass, that may be why no significant flatulence was noticed with guar gum in our study as compared to Pedersen et al.[18] study using inulin. Moreover, the study period and population studied were also different in both studies.

Hypoalbuminemia has been associated with gastrointestinal intolerance to enteral feeding.[19] In this study, no significant variation was found in the mean albumin level at the start of the study than after its termination in either of the groups studied. No correlation was found between the incidence or severity of diarrhea and the albumin level. Furthermore, gastrointestinal tolerance or intolerance to the enteral feeds could not be attributed to the albumin level in blood. These findings are not consistent with those of Guenter et al.[19] who reported a significantly lower mean albumin level in patients with diarrhea than in those without diarrhea in their study of 100 acutely ill patients receiving enteral feeding. The different sample sizes and methodologies could have been the cause of variation in the results of the present clinical trial from those by Guenter et al.[19]

Diarrhea control and glycemic control

A relatively high dose of guar gum was given per day (22–44 g) to enable the potential metabolic and laboratory effects to evolve early as the total doses of guar gum given in this clinical trial, in 4 days, were comparable to the total doses given in other studies of longer time periods. In our clinical investigation, there was a significantly lower plasma glucose level in the study group at the end of the study as compared to the first day. This compares favorably with the findings of other investigators. A diet rich in viscous dietary fiber from Konjac-mannan was shown to improve glycemic control, suggesting a therapeutic potential in the treatment of the insulin resistance syndrome.[20] Drinks enriched with fructose and soluble food fibers (pectin) were shown to cause a less degree of glycemic response in type II diabetic patients.[21] Guar may work by augmenting the unstirred water layer or by slowing down the diffusion of glucose from the chyme to the intestinal epithelium. This

issue may now be seen differently after the demonstration by Van den Berghe that near-to-normal insulin controlled-glycemia improves the outcome of ICU patients.[22] At the time our study was realized, these data were not available.

Diarrhea and ion status

Regarding calcium level, there was a significantly higher calcium level in the study group at termination of the present study as compared to its level on the first day. Hara et al.[23] reported that ingestion of guar-gum hydrolysate partially restored calcium and magnesium absorption in the large intestine of rats. In the present clinical study, magnesium serum level although reached a higher level at end of study than its level at the beginning, the rise did not reach statistical significance. This may be attributed to the short time interval of the present study as longer study periods and patient follow-up intervals may have been needed. Moreover, Watanabe et al.[24] noted that the apparent calcium absorption was significantly higher in rats fed on the phosphorylated guar gum hydrolysate diet (50 g kg^{-1} of diet) than in rats fed on the control diet. On the other hand, the results of the study by Grudeva-Popova and Sirakova,[25] on the effect of pectin on electrolytes and trace elements in patients with hyperlipoproteinemia, failed to reach statistical significance during the administration of the pectin product. The soluble dietary fiber which they investigated was pectin, not guar gum, and the population they studied was patients with hyperlipoproteinemia. This can account for the different finding met in the present study regarding calcium level variation.

Amongst the study limitations in this clinical trial is that no direct measurement of diarrhea volume, osmolarity or ions content was carried out. It was practically impossible to directly measure diarrhea volume. Although the number of patients was rather small, the bowel movements were carefully assessed during a total of 8 study days in this specific subgroup of patients with preexisting diarrhea.

Conclusion

Guar gum-enriched EN was related to a decrease of diarrheal episodes in ICU patients with preexisting diarrhea; and as a potential prebiotic, to a trend for lower plasma glucose and cholesterol levels and higher plasma calcium level.

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