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NUTRITION FACTORS IN GI DISORDERS

Role of FODMAP content in enteral nutrition-associated diarrhea

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Abstract

Gastrointestinal symptoms including diarrhea are common complications of enteral nutrition (EN); however, the cause is unclear. Mode of EN delivery that alters digestion and possibly absorption is suggested to contribute to the high incidence of diarrhea; however, enteral formula is frequently blamed. Most research has focused on fiber-supplemented EN, with a meta-analysis showing that fiber reduces the incidence of diarrhea in non-intensive care unit studies. Other hypotheses include formula osmolality and FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) content. FODMAPs are poorly absorbed short-chain carbohydrates that exert an osmotic effect. Dietary FODMAPs have been shown to reduce gastrointestinal symptoms, including diarrhea, in those with irritable bowel syndrome and, given a high-enough dose, will induce a laxative effect in most people. As FODMAPs are commonly added to enteral formula and EN is frequently used as the main source of nutrition, it is reasonable to hypothesize that EN provides more FODMAPs than usual dietary intake and increases risk for developing diarrhea. This hypothesis was assessed through a retrospective study showing that the standard-use enteral formula Isosource 1.5 had a protective effect of developing diarrhea. The only characteristic unique to Isosource 1.5 was the lower FODMAP content as determined through methodologies previously validated for food analysis. Methodologies for application to enteral formulas are currently undergoing formal validation. Once confirmed for application in enteral formula, future directions include FODMAP analysis of specific ingredients to increase understanding of potential problems associated with enteral formula and a randomized, controlled trial investigating the role of formula FODMAP content.

Causes of diarrhea in hospitalized patients

Enteral nutrition (EN) is widely used in hospitals to provide nutrition to patients unable to obtain all their nutritional requirements orally. While economically and therapeutically beneficial, a common consequence to receiving EN is gastrointestinal (GI) symptoms including diarrhea, with several studies confirming up to 50% prevalence.[1–5] Diarrhea complicates hospital admission resulting in fluid and electrolyte abnormalities[6] requiring fluid support and fecal incontinence[7] potentially resulting in infection of wounds in close proximity of femorally inserted central venous catheter.[8] These outcomes result in increased hospital costs to manage related infections[7,8] and likely increase length of stay. Diarrhea is also burdensome to nursing staff and often distressing for the patient. Prescription of medications is almost always a necessity in hospitalized patients, thus it is acknowledged that there is an increased risk associated with diarrhea from both infectious cause (acquiring *Clostridium difficile* from antibiotic use)[9] and non-infectious cause (use of medications with common side-effect of diarrhea).[10] However, there is an additional element when exposed to EN. The cause of EN-associated diarrhea is unclear but likely multifactorial. Both delivery methods of EN and the enteral formula composition have been blamed, with particular focus on the influence of both longer chain fermentable carbohydrates (fiber), and short-chain, rapidly fermented, and osmotically active carbohydrates termed FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) that may be present in formulas.

EN delivery. A previous Brazilian study has implicated microbial contamination of EN equipment in increasing nosocomial infection and subsequent diarrhea.[2] Independent associations were seen for summer months within the study hospital (hazard ratio [95% confidence interval {CI}] 2.6 [1.6–4.3]) and poor adherence to the study hospital's EN delivery set washing and changing routines (relative risk [95% CI] 3.1 [1.0–9.5] and 3.4 [0.9–13.2],

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respectively). Such risk factors are likely minimal in countries where hospital rooms are climate-controlled as seasonal variation would be negligible to hospital environment and where EN delivery sets are single use and changed 12–24 hourly.

An association with infectious diarrhea from the acquisition of *C. difficile* was seen in enterally fed inpatients receiving post-pyloric feeding.[11] Although as previous literature would confirm, this case control study showed a higher incidence of diarrhea among inpatients receiving EN compared with inpatients who were orally fed, so post-pyloric feeding would not account for all EN-associated diarrhea.

There are also arguments for both continuous feeding and bolus delivery of enteral formula contributing to EN-associated diarrhea. Bolus feeding has been thought to overwhelm the digestive or absorptive capacity of the small intestine[12] and continuous feeding (particularly of small volumes) failing to provoke postprandial GI responses.[12,13] To date, these are theories that the unphysiological nature of EN itself is likely a contributing factor to GI symptoms including diarrhea. Unfortunately, no randomized, controlled trials have tested these hypotheses. Most trials have focused on the role of enteral formula composition.

Enteral formula. Most research into EN-associated diarrhea has centered around the role of fiber-supplemented formulas. A meta-analysis of 51 studies showed that fiber-supplemented enteral formula was associated with decreased severity of diarrhea in non-intensive care unit populations (odds ratio [OR] [95%CI] 0.68 [0.48–0.96]; $P = 0.03$).[14] Interestingly, the extent to which fiber reduced diarrhea was related to the incidence, and little benefit was seen in studies where the incidence of diarrhea was low. There were more than 15 different fiber sources included in the study, and the fiber of most influence in EN-associated diarrhea could not be extrapolated.

Other suggested causes for EN-associated diarrhea are the high osmolality of formulas,[15] of which no data have been published and the higher content of FODMAPs.[16]

FODMAPs

FODMAPs are short-chain carbohydrates that are poorly absorbed. Thus, a proportion contained within food or enteral formulas will exert a luminal osmotic effect, delivering more water to the colon[17] and be associated with gas produced by its bacterial fermentation.[18] FODMAPs that are naturally occurring in the diet include lactose (in milk), fructose in excess of glucose (in mango and honey), oligosaccharides comprising mainly fructans (in onion, garlic, wheat and rye), galacto-oligosaccharides (GOS) (in legumes), and polyols (in stone fruit and some artificial sweeteners).[19] FODMAPs are also commonly added to enteral formula in the form of inulin and fructo-oligosaccharides (FOS), both of which are varying chain lengths of fructans and GOS. In large-enough doses, FODMAPs lead to laxation and distension of the bowel causing bloating, abdominal discomfort, and altered gut motility promoting diarrhea.[17,18] Dietary FODMAPs have been shown to induce symptoms in patients with functional GI symptoms (e.g. people with irritable bowel syndrome [IBS]), and those symptoms are proportionate to FODMAP loading.[18,20] Furthermore, restricting dietary FODMAPs has been shown to relieve functional GI symptoms.[21] The dose indicated for therapeutic benefit in this population is less than 0.5 g FODMAPs per sitting or less than 3 g FODMAPs over a day,[21] which is considerably less than the amount obtainable through the diet, as suggested in a validated food frequency questionnaire of an average Australian diet.[22]

While it may be assumed that the majority of enterally fed patients do not have IBS, symptoms observed in these two populations are similar, abdominal distension[3] and diarrhea[23] being the most reported in EN. Given that a high-enough dose of FODMAPs will induce a laxative effect[24] and that EN is frequently used as the main source of nutrition, it is reasonable to hypothesize that an enterally fed patient would receive more FODMAPs than from usual dietary intake and, therefore, have increased risk for diarrhea.

This hypothesis was first assessed through a retrospective study investigating all possible predictors of diarrhea in 160 hospitalized patients, with a particular focus on enteral formula.[25] Data were collected on any variables that could possibly contribute to diarrhea such as type of diet received, medications used, length of stay, duration of EN, and EN characteristics. These variables underwent multivariate analysis, a statistical method applied to adjust for confounding factors to determine variables independently associated with the development of diarrhea. Inpatients with a longer length of stay and receiving EN for a longer period were positively associated with developing diarrhea. The only negative association with diarrhea developing was patients who had commenced EN with the enteral formula Isosource 1.5 (Novartis Consumer Health Australasia Pty. Ltd., Mulgrave, Victoria, Australia), with a five-fold reduction in risk of developing diarrhea (estimated OR 0.18; $P = 0.029$). Isosource 1.5 is a standard-use formula with a fiber content much smaller than any formula included in the meta-analysis investigating fiber[14] and is also of high osmolality. The only characteristic explaining this protective effect was the FODMAP content, which was 30–53% the content of the other six formulas included in the study.[25] However, whether this measured content of FODMAPs is correct has yet to be validated. The formula characteristics of Isosource 1.5 and the six other formulas included in the study are shown in Table 1.

FODMAP composition

With the exception of the seven formulas included in the retrospective study, FODMAPs have only been identified and quantified in food. The low FODMAP diet for use as management of IBS is now supported by good knowledge in food composition. FODMAP analysis of a wide range of fruits, vegetables, and grains has been completed,[19,26,27] and with the ever-expanding database of FODMAP composition, packaged foodstuff containing ingredients of known FODMAP content is seemingly well predicted by ingredients lists.

The application of the same assays for measurement of FODMAPs in food to enteral formula yielded a FODMAP content of the seven formulas included in the retrospective study from 10.6 to 36.5 g per recommended daily volume,[25] most commonly from oligosaccharides. All of these formulas represent a higher FODMAP content than that seen in a daily dietary oligosaccharide intake.[22] Whether those assays are prone to artifactual influence is currently under evaluation, including the application of

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Table 1 Characteristics of the seven enteral formulas investigated in Halmos *et al.*[25]

Formula†	Clinical indications	Recommended daily volume (mL)	FODMAP content (g/L)	Fiber content (g/L)	Osmolality (mOsm/L)
Isosource 1.5	Standard formula/higher nutritional requirements	930	11.4	8.0	650
Fibersource HN	Standard formula	1200	27.5	10	490
Isosource HN	Standard formula	1200	25.8	0	490
Isosource	Standard formula	1200	26.7	0	490
Resource diabetic TF	Diabetic patients	1200	16.8	14.8	400
Novasource renal	Renal failure	990	23.2	0	700
Novasource 2.0	Cachexia/fluid restriction/very high nutritional requirements	1200	30.4	0	790

†Formulas during the study period were manufactured by Novartis Medical Nutrition (Novartis Consumer Health Australasia Pty. Ltd.).
FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols.

high-performance liquid chromatography (HPLC) techniques and competitive assays.

Considering the suggested link between EN-associated diarrhea and FODMAP intake, the FODMAP content of all enteral formulas may be beneficial in predicting diarrhea development. The ingredients commonly found in enteral formulas are rarely found in food supply, so prediction of FODMAP content of enteral formulas via the ingredients lists may not be as accurate. Comparison of estimated FODMAP content based on ingredients lists to actual measured FODMAP content will indicate whether ingredients lists may be used in the same way as food supply in predicting FODMAP content.

FODMAP composition of enteral formulas

It is thought that any enteral formula containing one or more ingredient of known high FODMAP content—inulin, FOS, GOS, fructose, and milk solids/powder (lactose-containing)—represents a high FODMAP formula. An inaccuracy behind this assumption is that ingredients are seldom quantified. Thus, the influence of these ingredients within an enteral formula may be inaccurate. Additionally, inulin is never described in relation to degree of polymerization (i.e. the number of fructose units per molecule) and is most often referred to as fiber rather than FODMAP. While both terms are acceptable descriptions, effects of inulin of differing chain lengths is likely to also have an influence in the accuracy of FODMAP content and may also overestimate FODMAP content. Inulin of a greater degree of polymerization may have a physiological effect characteristic of a fiber, which is not as rapidly fermented as FODMAPs and has less of an osmotic effect. These symptom-inducing properties are related to the shorter chain length of FODMAPs. Furthermore, our knowledge of the FODMAP content of specific ingredients found in enteral formula is poor, with potential to underestimate FODMAP content. Ingredients lists remain inaccurate predictors of FODMAP content in enteral formulas.

A program of detailed analysis of randomly selected enteral formulas is underway using methodologies that have been developed and well validated for analysis of FODMAPs in food samples.[19,27] These methodologies are being formally validated for application to enteral formulas.

Further research

The appropriateness of using HPLC and enzymatic assays to accurately represent the FODMAP content of enteral formulas is currently under investigation. Once confirmed for application in enteral formulas, the analysis of specific formula ingredients for FODMAP content may assist in better understanding of potential problems associated with enteral formula use. However, the effect of these formulas in inducing GI symptoms including diarrhea needs to be further investigated. A randomized, controlled trial comparing inpatients receiving Isosource 1.5 to inpatients receiving a formula of similar nutrient composition of a higher FODMAP content would confirm or disprove the initial findings of the reduced risk of EN-associated diarrhea. Implications of the higher FODMAP content of enteral formula contributing to EN-associated diarrhea are development of enteral formulas of lower FODMAP content and conducting prospective studies investigating the efficacy of changing formulas once diarrhea has developed.

References

1 Bleichner G, Thomas O, Sollet JP. Diarrhea in intensive care: diagnosis and treatment. *Int. J. Antimicrob. Agents* 1993; **3**: 33–48.
2 Luft VC, Beghetto MG, de Mello ED, Polanczyk CA. Role of enteral nutrition in the incidence of diarrhea among hospitalized adult patients. *Nutrition* 2008; **24**: 528–35.
3 Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. *Crit. Care Med.* 1999; **27**: 1447–53.
4 Pancorbo-Hidalgo PL, García-Fernandez FP, Ramírez-Pérez C. Complications associated with enteral nutrition by nasogastric tube in an internal medicine unit. *J. Clin. Nurs.* 2001; **10**: 482–90.
5 Reese JL, Means ME, Hanrahan K, Clearman B, Colwill M, Dawson C. Diarrhea associated with nasogastric feedings. *Oncol. Nurs. Forum* 1996; **23**: 59–66.
6 Stroud M, Duncan H, Nightingale J. Guidelines for enteral feeding in adult hospital patients. *Gut* 2003; **52**: vii1–12.
7 Bliss DZ, Johnson S, Savik K, Clabots CR, Gerding DN. Fecal incontinence in hospitalized patients who are acutely ill. *Nurs. Res.* 2000; **49**: 101–8.
8 Ferrie S, East V. Managing diarrhoea in intensive care. *Aust. Crit. Care* 2007; **20**: 7–13.

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9 Raveh D, Rabinowitz B, Breuer GS, Rudensky B, Yinnon AM. Risk factors for *Clostridium difficile* toxin-positive nosocomial diarrhoea. *Int. J. Antimicrob. Agents* 2006; **28**: 231–7.
10 Garey KW, Graham G, Gerard L *et al*. Prevalence of diarrhea at a university hospital and association with modifiable risk factors. *Ann. Pharmacother.* 2006; **40**: 1030–4.
11 Bliss DZ, Johnson S, Savik K, Clabots CR, Willard K, Gerding DN. Acquisition of *Clostridium difficile* and *Clostridium difficile*-associated diarrhea in hospitalized patients receiving tube feeding. *Ann. Intern. Med.* 1998; **129**: 1012–19.
12 Debnam ES, Grimble GK. Methods for assessing intestinal absorptive function in relation to enteral nutrition. *Curr. Opin. Clin. Nutr. Metab. Care* 2001; **4**: 355–67.
13 Bowling TE, Silk DBA. Colonic responses to enteral tube feeding. *Gut* 1998; **42**: 147–51.
14 Elia M, Engfer MB, Green CJ, Silk DB. Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. *Aliment. Pharmacol. Ther.* 2008; **27**: 120–45.
15 Pesola GR, Hogg JE, Eissa N, Matthews DE, Carlon GC. Hypertonic nasogastric tube feedings: do they cause diarrhea? *Crit. Care Med.* 1990; **18**: 1378–82.
16 Barrett JS, Shepherd SJ, Gibson PR. Strategies to manage gastrointestinal symptoms complicating enteral feeding. *JPEN J. Parenter. Enteral Nutr.* 2009; **33**: 21–6.
17 Barrett JS, Gearry RB, Muir JG *et al*. Dietary poorly absorbed, short-chain carbohydrates increase delivery of water and fermentable substrates to the proximal colon. *Aliment. Pharmacol. Ther.* 2010; **31**: 874–82.
18 Ong DK, Mitchell SB, Barrett JS *et al*. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J. Gastroenterol. Hepatol.* 2010; **25**: 1366–73.
19 Muir JG, Rose R, Rosella O *et al*. Measurement of short-chain carbohydrates in common australian vegetables and fruits by high-performance liquid chromatography (HPLC). *J. Agric. Food Chem.* 2009; **57**: 554–65.
20 Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin. Gastroenterol. Hepatol.* 2008; **6**: 765–71.
21 Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. *J. Am. Diet. Assoc.* 2006; **106**: 1631–9.
22 Barrett JS, Gibson PR. Development and validation of a comprehensive semi-quantitative food frequency questionnaire that includes FODMAP intake and glycemic index. *J. Am. Diet. Assoc.* 2010; **110**: 1469–76.
23 Whelan K, Hill L, Preedy VR, Judd PA, Taylor MA. Formula delivery in patients receiving enteral tube feeding on general hospital wards: the impact of nasogastric extubation and diarrhea. *Nutrition* 2006; **22**: 1025–31.
24 Olbe L. Concept of Crohn's disease being conditioned by four main components, and irritable bowel syndrome being an incomplete Crohn's disease. *Scand. J. Gastroenterol.* 2008; **43**: 234–41.
25 Halmos EP, Muir JG, Barrett JS, Deng M, Shepherd SJ, Gibson PR. Diarrhoea during enteral nutrition is predicted by the poorly absorbed short-chain carbohydrate (FODMAP) content of the formula. *Aliment. Pharmacol. Ther.* 2010; **32**: 925–33.
26 Biesiekierski JR, Rosella O, Rose R *et al*. Quantification of fructans, galacto-oligosacharides and other short-chain carbohydrates in processed grains and cereals. *J. Hum. Nutr. Diet.* 2011; **24**: 154–76.
27 Muir JG, Shepherd SJ, Rosella O, Rose R, Barrett JS, Gibson PR. Fructan and free fructose content of common Australian vegetables and fruit. *J. Agric. Food Chem.* 2007; **55**: 6619–27.

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