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Knowledge of Constituent Ingredients in Enteral Nutrition Formulas Can Make a Difference in Patient Response to Enteral Feeding

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Abstract

Enteral feeding is considered the preferred method for providing a complete or supplemental source of nutrition to patients. Enteral formulas (EFs) are traditionally assessed from general information provided by the manufacturer such as caloric density, percentage of macronutrients, and micronutrients to meet the Recommended Dietary Allowance. Sometimes labeling information highlights particular ingredients to indicate specific properties at a metabolic or nutrition level. However, it is necessary to review the quality and composition of any enteral formula, since the basic components are responsible for tolerance and nutrition efficacy, and this should not be overshadowed by the benefit of a single constituent. Intolerance to EF is commonly attributed to individual patient response or to the means of administration. The objective of this review is to highlight the importance of appraising EFs with regard to composition and effect on the gastrointestinal tract. (*Nutr Clin Pract*. XXXX;xx:xx-xx)

Keywords

enteral formula; enteral nutrition; nutritional support; formulated food; intolerance

Enteral feeding is the preferred method for providing complete or supplemental nutrition to patients.[1] Europe, the United States, and Latin America each have their own regulations for enteral nutrition (EN) formulas, which are classified as "foods for medical purposes."[2–4] Ingredients used in enteral formulas (EFs) must be carefully appraised prior to administration as patient response to them may influence healing and recovery.

EFs are traditionally assessed by general information such as caloric density and percentage of macronutrients. However, the value of a particular macronutrient (eg, a specific carbohydrate) cannot be evaluated solely on the basis of its caloric contribution, because its composition may radically differ from other types of carbohydrates. Moreover, EFs may contain specific added ingredients indicated for particular clinical scenarios, such as the inclusion of ω-3, glutamine, arginine, or fiber, which are added for critical care, perioperative care, cancer, or long-term enteral feeding. EFs may also be classified according to the level of protein hydrolysis, the indication for a specific disease, and whether they are designed to be the sole source of nutrition, a supplement, or a module.[5]

EFs may also be classified by protein content. The protein source and level of hydrolysis affect ease of absorption, gastrointestinal (GI) tolerance, contribution to osmolarity of the EF, and level of protein utilization.[5–10]

Fat composition should be considered on the basis of calorie and fatty acid content and proportion of ω-6 and ω-3.[11–15] This is especially relevant when used by the elderly or patients with chronic diseases, such as cardiovascular disease,[13] in which prolonged EN is indicated.

Although generally considered innocuous, carbohydrates can be a major cause of intolerance that often develops unnoticed. The presence of fermentable fiber, monosaccharides, oligosaccharides, disaccharides, and polyalcohols (known as FODMAPs) can cause intolerance or diarrhea in susceptible patients.[16–20] The addition of fructose as an energy source can impair GI tolerance, increase blood glucose response levels, and accumulate in the liver as fatty acids, and it has recently been shown to be associated with increased cardiovascular risk.[21,22] High-fructose corn syrup and/or corn syrup are added to several EFs to increase their caloric value, improve their flavor, and/or maintain product stability. However, they have been linked to GI disturbances, such as bloating and diarrhea.[16–20,22] In addition, polyols such as mannitol and isomalt are also common components in EN formulas and frequently used as sugar substitutes.[17] Fiber is an important component of a normal diet. It can be classified as fermentable (soluble) or nonfermentable (insoluble) fiber. Soluble fiber includes nonstarch polysaccharides, inulin, guar gum, oat, and fructo-oligosaccharides (FOS).

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Table 1. Comparison of Protein Quality According to Its Origin.

Protein	Protein Efficiency Ratio	Biological Value	Net Protein Utilization, %	PDCAAS	True Digestibility, %	DIAAS, %	% Leucine (g/100 g of Food)
Whey isolate	3.2[40]	≥100[49]	92[49]	1.1–1.7[41]	NA	99[9]	11.7–12.0[42]
Whey concentrate				1.1–1.5[41]	99[49]	95–97[9]	≤6.4[42]
Egg	3.8[40,43]	100[40]	94[40,43]	1.0[40]	98[49]	91[9]	1.07[40]
Whole milk	3.1[40,43]	91[40]	82[40,43]	1.23[41]	95[44]	96[9]	0.32[40]
Collagen	NA	NA	NA	0.08[45]	NA	NA	NA
Beef	2.9[40,43]	80[40]	73[40,43]	1.0[42]	98[44]	NA	NA
Casein	2.7[9]	77[49]	72.1[49]	1.0[49]	99[44]	95[9]	8.68[44]
Soy isolate	2.3[49]	72.8[49]	61.4[49]	1.0[42]	98[44]	92–98[9]	6.78[46]
Soy concentrate				0.94[40]	95[44]	NA	≤4.9[46]
Beans	NA	53[47]	NA	0.68[40]	81[44]	74–78[9]	NA
Soy	2.3[41,43]	73[41,43]	61[41,43]	NA	90[44]	68[9]	0.93[46]

DIAAS, digestible indispensable amino acid score; NA, not available; PDCAAS, protein digestibility-corrected amino acid score.

Resistant starch and lignin are considered insoluble fiber. Elia et al,[23] in their systematic review and meta-analysis, concluded that the inclusion of fiber in EN formulas generates positive physiological effects and clinical benefits. It also has been hypothesized that fermentable carbohydrates may be linked to the development of diarrhea, since they are part of the FODMAPs.[16,18,19] Despite their benefits, such as being the substrate for microflora in the large intestine and increasing the GI gut health, intolerance to FOS may generate bloating, distension, and diarrhea. Therefore, the inclusion of alternative fiber types in the EF may improve clinical and nutrition outcomes[23,24]; for instance, partially hydrolyzed guar gum showed positive results in several studies,[25,26] although its use in critical ill patients remains controversial.[27]

Last but not least, micronutrients should be selected in varying proportions depending on the type of illness and related deficiencies. Common to all nutrition support practice, ingredients need to be tailored in accordance with patient requirements. Particular attention must be paid to satisfy the complex nutrition needs of the critically ill.

Regulatory Position of EFs

EFs are regulated solely in compliance with Good Manufacturing Practice guidelines used for conventional foods.[2] Surprisingly, the labeling requirements are less stringent than those that apply to conventional foods with regard to nutrition facts.[2] In Europe, EN includes all "dietary foods for special medical purposes" (DFSMP).[28] This definition is taken from the European legal regulation of the commission directive 1999/21/EC of March 25, 1999.[3] In the United States, the Food and Drug Administration classifies EFs under the name of "medical foods."[2] The legal definition comes from the Orphan Drug Act of 1988.[29] In Latin America, regulations are country specific, and EFs are commonly listed as "foods for medical purposes."[4] Given that EFs are prescribed to patients with differing levels of clinical nutrition risk, an accurate and detailed composition of DFSMP, together with health-related claims, should be provided by the manufacturer.

Macronutrients in EFs

Macronutrients in EFs vary in chemical forms, molecular sizes, solubility, and quality. These characteristics can affect the osmolarity, absorption, utilization rate, and tolerance of the nutrients, which may directly affect patient recovery. Having eliminated common reasons for EF intolerance such as microbial contamination, concomitant medications, and EF temperature, Barrett et al[19] considered that formula composition may be an important causal factor.

Protein, a Crucial Macronutrient

An important overall consideration when selecting an EF is to establish protein content. Some products continue to be marketed as high in protein but may not contain amounts currently considered optimal for patient requirements. Another important issue is the quality of the protein in the formula, which is determined by the relative amounts of essential and nonessential amino acids demonstrated by the seminal work of Rose[30] 60 years ago. The amount of branched-chain amino acids (BCAAs) also contributes to amino acid balance and protein quality.[6,10,31] In addition, the origin of protein should be considered since vegetable protein is not used as efficiently as protein of milk or egg origin.[8,32–34] The efficiency of clinical recovery may depend on the type of protein administered.[35] High-quality protein derived from animal sources has a protein efficiency ratio (PER), biological value (BV), net protein utilization (NPU), and protein digestibility-corrected amino acid score (PDCAAS) higher than vegetable protein.[7,34] These are methods to assess protein quality.[36] Therefore, the origin of the protein should be determined since it has the potential to affect not only tolerance but also absorption rate and protein utilization[37–39] (Table 1).

Table 2. Composition of Whey Protein in Different Forms.[a]

Type	Protein,[b] %	Lactose,[b] %	Fat,[b] %	Cholesterol,[c] mg
Whey protein concentrate	25–89	4–52	1–9	150
Whey protein isolate	90–95	0.5–1	0.5–1	0
Whey protein hydrolyzed	80–90	0.5–10	0.5–8	0

[a]Product composition may vary slightly by manufacturer.
[b]Modified from Whey Protein Institute (http://www.wheyoflife.org/facts/wheyproteintypes).
[c]Davisco (Eden Prairie, MN).

A protein can be administered in various forms. An EF may provide whole protein, concentrate, isolate or hydrolysate, and free amino acids, even when originating from the same protein source. The selection of protein form as an ingredient in EF depends on various factors, including cost, improvement of the BV, and manufacturing processes. Soy protein is less expensive than whey protein, but soy as an ingredient also affects protein quality and utilization.[33,48] Consequently, to improve its quality, it has to be mixed with animal protein such as casein or whey. Another example is collagen, which is an inexpensive animal protein but has low BV, an incomplete amino acid profile (lacks of tryptophan), and meager amounts of essential amino acids.[49] Therefore, to compensate for these deficiencies, it is mixed with a high-protein value source such as casein, whey, or even soy. Protein from the same source can therefore be present in EF in different forms that modify the amino acid profile and the presence of other nutrition components. This will lead to different rates of digestion, absorption, and utilization.

The relative content of some ingredients varies from one EF to another. For example, whey concentrate has a higher content of cholesterol and lactose, whereas isolates are almost exempt from both[50] (Table 2). It is also important to specify if the protein and its subproducts are derived from whole milk, casein (80%), or whey (20%)[50] (Figure 1). Similarly, the total protein content is higher in soy isolate (>90%) than in soy concentrate (66%–70%).[51] Whey proteins contain all the essential and nonessential amino acids and are rich in BCAAs (valine, leucine, and isoleucine), particularly leucine, a key amino acid for protein synthesis. It is also high in sulfur-containing amino acids (cysteine and methionine) that contribute antioxidant properties and enhance immune function.[52] These protein characteristics may potentially influence patient recovery and therefore length of hospital stay.

Osmolarity must also be taken into account[19] since it is significantly increased by the level of protein hydrolysis in the formula; the smaller the molecule, the greater the osmolarity. The extent of hydrolysis can modify osmolarity, flavor, absorption, and tolerance depending on the molecular weight distribution, the peptide profile, and the amino nitrogen (AN) to total nitrogen (TN) ratio.[53] In Table 3, hydrolysate type 1 is more hydrolyzed since 82.3% of the protein has a molecular weight <1,000 Daltons while hydrolyzed protein type 2 has 40.5%.

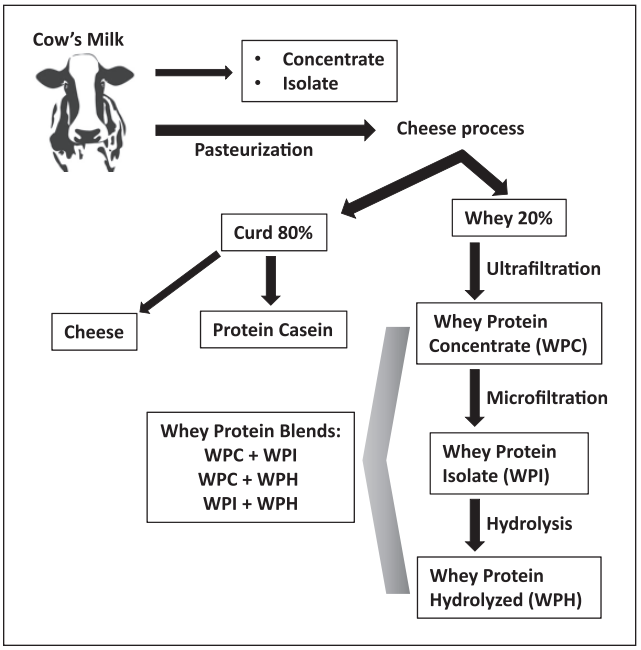

Figure 1. Scheme for the production of whey and by-products. Whole milk is processed into curd or whey. Whey protein concentrate or whey protein isolate contains intact proteins, but nutrient profiles vary after each filtering step. Hydrolysis facilitates protein absorption and increases osmolarity and cost. Whey protein blends have the properties of its major components.

Prior to administration, the proportion, the source (animal or vegetable), and the level of hydrolysis of the EF must be appraised together with the individual amino acids content. These features may change both formula tolerance and cost of the raw ingredients. It is incumbent upon clinicians managing patients to be aware of the protein composition and proportions of an enteral clinical formula. Although it is difficult to know this without chemical analysis, osmolarity can provide a clue to the level of protein hydrolysis present.[19] For example, formulas with low osmolarity cannot contain extensively hydrolyzed protein or substantial quantities of free amino acids

Table 3. Molecular Weight Distribution of 2 Hydrolyzed Whey Proteins.

Daltons	Hydrolyzed Protein Type 1, %[a]	Hydrolyzed Protein Type 2, %[a]
>20,000	1.28	17.0
5000–20,000	2.41	15.6
1000–5000	14.00	26.7
<1000	82.30	40.5
AN/TN	26.00	12.5

AN/TN, amino nitrogen/total nitrogen.
[a]Modified: Hilmar whey protein hydrolysate.[53]

unless the total protein content is low, is mixed, or has a low level of hydrolysis. Manufacturers are required to provide this information as part of the nutrient profile of the EF.

In the past, it was thought that the absorption of amino acids was faster than dipeptides, tripeptides, or whole protein and that this would be beneficial, and as such, amino acids were included in the EF.[54] Optimal utilization of amino acids occurs when digestion and absorption lead to a low but protracted appearance in the portal vein. This allows the liver and other organs to make optimal use of these amino acids for protein synthesis and other metabolic functions such as the synthesis of purines and pyrimidines. Consequently, the indication for hydrolyzed protein or amino acids is limited to severe pancreatic insufficiency and small bowel malfunction.[55,56] Even in these situations, the benefit of predigested protein is uncertain. Moreover, some EFs that contain hydrolyzed protein or amino acids are more expensive, without providing the desired clinical benefit. In a pilot study that compared standard vs a high-protein peptide-based formula in critical care patients, the results suggested that the latter EF could be associated with a statistically significant reduction of adverse events.[57] Unfortunately, the EF had important differences from the composition of other macronutrients that could affect patient tolerance and outcome, such as the amount of carbohydrates and the type of fats, hindering the interpretation attributed to the effect of hydrolyzed whey protein (HWP).[57]

In addition to the degree of hydrolysis, the source of protein may also have an impact on digestion kinetics. Whey protein was shown to stimulate postprandial muscle protein accretion better than casein in the elderly,[39] and in young men, HWP stimulated skeletal muscle protein synthesis better than casein and soy protein.[58] In a randomized controlled trial comparing the use of whey protein and glutamine, a comparable effect on improved intestinal permeability and integrity of the gut mucosal cells was observed in patients with Crohn's disease.[59] HWP was also compared with casein in a double-blind randomized trial in elderly patients with acute ischemic stroke.[60] Patients in the HWP group had higher levels of serum albumin ($P < .01$) and glutathione ($P = .03$) and lower levels of interleukin-6 (IL-6) ($P = .03$), suggesting decreased inflammation and increased antioxidant defenses in this group of patients. In a comprehensive review by Alexander et al,[56] the use of HWP in various diseases was shown to improve health and nutrition outcomes.

Fat: More Than Just Calories

Years ago, fat was considered to have 2 main purposes: caloric provision and providing essential fatty acids (EFAs). Burr and Burr[11] described EFA deficiency in 1929, when rats were fed without fat in their diets and developed dermatitis, hair loss, wasting, and even death. Linoleic acid, when supplied as a minimum of 1% of the total calories, prevents EFA deficiency, but an optimal dosage is recommended to a range of 3%–4% of total calorie intake. In a 1500-kcal diet, the minimum amount of linoleic acid required is between 1.7 and 6.7 g/d.[61] The view that EFAs are necessary led to the notion that total fat intake should be from vegetable oils, such as safflower, sunflower, soy, and corn, based on the rationale that the provision of these fat sources would benefit the patient. However, because these fatty acids are primary sources of ω-6 fatty acids, their administration in excess is harmful due to proinflammatory and immunosuppressive effects.[12,62] Current knowledge suggests that the composition of fat included in an EF should limit but not totally exclude ω-6 fatty acids, provide monounsaturated fatty acids, reduce saturated fats, avoid *trans* fats, and provide ω-3 fatty acids (docosahexaenoic and eicosapentaenoic).[13,14,62] The premise that "if something is good, more is better" is therefore not supported by current research. Moreover, "less is better" when assessing the nutrition requirements of certain critically ill patients,[63] a concept that can also be applied to avoid excess use of ω-6 fatty acids that, in the absence of ω-3 fatty acids, may lead to an unbalanced proinflammatory effect.[62]

The inclusion of structured fats, which were developed in the mid-1980s and contain mixtures of long-chain fatty acids (LCFAs) from the ω-3 family and medium-chain triglycerides (MCTs) with 8–10 carbons in length, have shown better fatty acids absorption, reduction of infection rates, and improvement of hepatic, renal, and immune function.[64,65] Structured fats are absorbed and clarified more efficiently, but cost-benefit and contribution to osmolarity by the MCTs to the EF require further clinical studies.[66,67] Safe doses of ω-3 are between 3 and 5 mg/d,[68] and excess intake may suppress immune function and increase bleeding time.[69] It may also produce an unpleasant taste, nausea, heartburn, gastric intolerance, headache, diarrhea, and odoriferous sweat.[70]

Carbohydrates, Good and Bad

Glucose is a rapid energy source and the only circulating carbohydrate in the body. In a regular diet, carbohydrates should provide 40%–50% of daily calorie intake. It is commonly thought that, with the exception of lactose, carbohydrates are easily tolerated and have no GI side effects. In general, this is

true, but lactose intolerance can be present in a substantial part of the population, especially those of Asian, South American, and African descent.[71] Poor absorption of lactose, a well-known FODMAP, can lead to bloating and diarrhea and is generally omitted from EF. Gibson and Shepherd[72] in 2005 provided evidence that restriction of FODMAPs prevented intolerance symptoms in patients with functional GI disorders. The presence of carbohydrates, corn syrup, solid corn syrup, FOS (fructans), galacto-oligosaccharides (raffinose), fructose, inulin (higher content with a higher degree of polymerization), and polyols (maltitol) present in some artificial sweeteners[16,18] may inadvertently augment the content of FODMAPs in an EF.

Sucrose (also called saccharose) is a disaccharide containing 1 molecule of glucose and 1 molecule of fructose. Some EFs contain up to 25% of the total amount of carbohydrates as sucrose. As a FODMAP, sucrose can be poorly absorbed with similar symptoms to those produced by lactose intolerance. Corn syrup (glucose syrup), corn syrup solids, and high-fructose corn syrup are other examples of FODMAPs. Corn syrup and corn syrup solids are frequently used as the major carbohydrate source in EFs, since they generate a very sweet flavor, do not change the viscosity, and are resistant to high temperatures.[19,73,74] Corn syrup and corn syrup solids can have different proportions of fructose and glucose depending on the manufacturer, and therefore precise detail of composition should be obtained before use. The high content of either of these components can produce negative GI and metabolic effects.[16–20] Monosaccharides, disaccharides, and trisaccharides have high dextrose equivalents (DEs) and therefore high fermentability.[75] In some patients, GI effects such as distension, bloating, and diarrhea are linked to FODMAPs due to their small molecular size and their high osmolarity.[19,20]

Short-chain polysaccharides that are poorly absorbed in the human intestinal tract such as FOS, galacto-oligosaccharides (GOS), and inulin[17] are very common ingredients added to EFs to provide fiber, without increasing thickness and viscosity.[17,18] These fiber sources are also FODMAPs that can trigger GI symptoms.

Polyols such as maltitol and isomalt are added to some EFs and, when given simultaneously with fructose, can worsen the tolerance for an EF.[16–18] In some cases, fructose is supplied as an individual ingredient, but in others, it is part of the corn syrup or corn syrup solids composition.[19] Fructose used to be considered a substitute for glucose, since the first step in its degradation is not insulin dependent. However, this premise was proven false when subsequent steps in its metabolism were shown to require insulin.[21,76] Although fructose intolerance with GI symptoms is only seen in those patients with fructose malabsorption, Barrett et al[77] reported that a third of 82 healthy volunteers could not absorb a fructose load (assessed by breath hydrogen testing), even in the absence of prior GI symptoms, indicating that intolerance to an EF can be due to the presence of fructose in addition to other FODMAPs.

FODMAPs have been shown to produce diarrhea, pain, nausea, and bloating in patients with irritable bowel syndrome (IBS) or with inflammatory bowel disease.[17] The removal of FODMAPs in the diet of these patients led to improvement of GI symptoms.[72,78–82] EFs have FODMAPs as common ingredients, which are rarely considered a cause of GI intolerance.[83] Research done at the Monash University[84] revealed that when comparing a regular Australian diet with EFs, the latter could be 3–7 times more concentrated in FODMAPs.[85] A retrospective study in 160 patients by the same institution further showed that the incidence of diarrhea significantly correlated with the amount of FODMAPs in the EF.[16] Yoon et al[20] studied the effect of 3 EFs with different levels of FODMAPs in a randomized, multicenter, double-blind, clinical trial. Low-FODMAP EF was significantly associated with improvement of diarrhea (reduction in King's Stool scores) relative to moderate-FODMAP and high-FODMAP EF ($P < .05$). The low, moderate, and high formulas contained 0.320 g, 0.753 g, and 1.222 g total FODMAPs per 200-mL can, respectively. Patients were classified depending on their final condition after the intervention: unimproved, normal maintenance, diarrhea improved, constipation improved, and recurrent diarrhea/constipation improved. In those patients with improved GI symptoms, particularly in whom diarrhea was reduced, a significant improvement was observed for the short-term nutrition markers prealbumin and transferrin. This may indicate that a low-FODMAP formula could improve nutrition status and facilitate prompt recovery, although prealbumin and transferrin may also be considered markers of inflammation.[86–88] Halmos[18] also considered that a lower content of FODMAPs in the EF could reduce the incidence of diarrhea.

Negative metabolic effects are related to the consequences of high carbohydrate consumption and the generation of nonalcoholic fatty liver. The World Health Organization (WHO) and the American Heart Association (AHA) have recommended that the total consumption of free sugars should not be greater than 10% or even below 5% of the energetic intake of a healthy diet.[89,90] This means that no more than 100 kcal (25 g) for women and 150 kcal (37.5 g) for men per day should come from added sugars. Although not specifically recommend by the WHO or AHA, these guidelines should also be followed in patients with chronic illness who are being fed at home or on long-term hospitalization to avoid the effects of an unbalanced diet high in simple carbohydrates. Kearns et al,[91] in their clinical review, have linked the effect of added sugar on multiple coronary heart disease (CHD) biomarkers and disease development. In their study, they suggest "that the sugar industry sponsored its first CHD research project in 1965 to downplay early warning signals that sucrose consumption was a risk factor in CHD" and "because CHD is the leading cause of death globally the health community should ensure that CHD risk is evaluated in future risk assessments of added sugars." Carbohydrates constitute the largest energy source in EF, representing between 40% and 60% of the daily total calorie

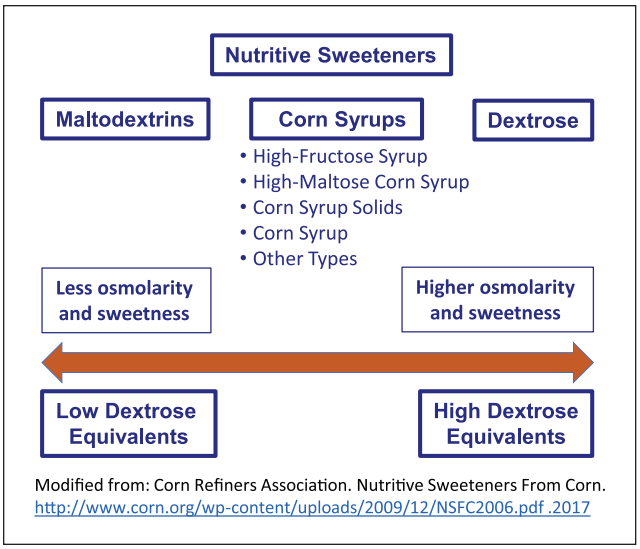

Figure 2. Dextrose equivalents present in nutritive sweeteners.[93] The different carbohydrates used as sweeteners in enteral formulas can be classified by the amount of dextrose equivalents. Enteral formulas with ingredients with high dextrose equivalents are more likely to generate gastrointestinal intolerance or diarrhea.

value. Therefore, the type of carbohydrate selected may affect the metabolic profile of the patient.

Maltodextrin, a polysaccharide commonly used in EFs, is classified by DEs ranging from 3 to 20.[55] Maltodextrins with low DEs have longer chains of glucose molecules and are less sweet and more soluble than those with a high DE (Figure 2). Their osmolarity is 5 times lower than that of glucose. Intolerance to maltodextrins is rare and is dependent on maltase or isomaltase activity at the intestinal brush border as well as by small bowel function.[55] Up to now, negative effects of maltodextrin have not been reported. However, high-grade DEs increase osmolarity and the risk of diarrhea given that delivery of water and fermentable substrates to the colon have been shown to be increased by poorly absorbed short-chain carbohydrates.[17] The clinician should seek information on DEs from the EF manufacturer.

It is my personal view that EFs with high amounts of corn syrup, corn syrup solids, sucrose, and sometimes fructose should be reformulated with other carbohydrate sources (eg, maltodextrins) or alternatively by increasing the amounts of other macronutrients such as protein. The reformulated EF may be better suited to vulnerable populations with a propensity for metabolic diseases such as the elderly, patients with noncommunicable diseases, or when used for long periods.

Vitamins and Minerals: Just the Recommended Daily Intake?

Commonly, information pertaining to the content of vitamin and minerals in EFs confirms that they meet the Recommended Daily Intake (RDI). To provide the RDI, the patient has to be fed a minimum amount of EFs that in general contain between 1200 and 1500 kcal. Few formulas contain the RDI in 1000 kcal. Unfortunately, those that provide the RDI in 1 L are calorically dense (>1.2 kcal/mL) due to an increment in carbohydrates, mainly from corn syrup, corn syrup solids, and sugar. Therefore, formula tolerance may be impaired and sometimes the total desired volume, and thus the RDI, difficult to attain even after several days of EN administration; moreover, micronutrients are not provided in adequate quantities. Patients should receive amounts depending on the most common deficiencies generated by their particular condition and supplemented in some cases. According to Berger,[92] patients with major trauma and burns can benefit from micronutrients supplemented by parenteral infusion. Enteral feeding formulas may not contain sufficient micronutrients to compensate patient losses or are poorly absorbed during the early phase of injury.[93,94]

EF as a Cause of Diarrhea

Thibault et al[95] reported a 14% incidence of diarrhea in a mixed population of patients during the first 2 weeks after admittance to a tertiary referral intensive care unit (ICU). They concluded that diarrhea could occur when >60% of the energy target was given by EN in addition to administering antibiotics or antifungal medications. Since they only used fiber-enriched EFs, they questioned whether the number of calories administered could be increased by using fiber-free EFs. They considered further studies were warranted to better understand the causes of diarrhea.

The inclusion of fiber as FOS may be an important cause of formula intolerance. Inclusion of fiber was originally suggested by Homman et al[25] to improve GI function in intensive care patients. Nevertheless, the inclusion of insoluble fiber in critically ill patients is currently questioned,[27] and new fiber blends for use in EFs to prevent and treat diarrhea are under investigation.[24]

Assessment of the different types of diarrhea in the hospitalized patient is mandatory; de Brito-Ashurst et al[96] classified them as dysmotility, inflammatory or exudative, malabsorptive, osmotic, and secretory. The composition of the EF is rarely taken into account as a causal factor of diarrhea, since detailed labeling information of the formulation of EF products is scarce or unknown in many cases. Ingredients in EF, such as substantial amounts of FODMAPs, can cause malabsorptive/osmotic diarrhea. This situation may be aggravated by an increase in the amount of formula and thus FODMAPs. For example, 1 cup of milk may be tolerated in the presence of mild lactose intolerance, but on drinking 2 or 3 cups of milk per day, GI symptoms of intolerance may become evident.

As diarrhea can be multifactorial in origin, its etiology should be established, including investigation of the EF composition. Thereafter, a treatment protocol can be initiated to improve EF tolerance; prevent dehydration, electrolyte

disturbances, and malnutrition; and reduce length of hospital stay and cost.[97]

Conclusions

The selection of an EF should be a conscientious process based on a number of factors, including the patient's clinical and medical status. The ingredients need to be carefully evaluated in their quality and quantity as they may affect recovery. The content and type of carbohydrates should follow the daily amounts recommended by the WHO. FODMAPs in particular should be assessed since these may be the cause of GI intolerance. Animal protein should be preferred over vegetable sources since utilization and absorption are higher. A balance in the levels of ω-6 and ω-3 fatty acids in the EF may favorably affect the inflammatory response. Additional administration of vitamins and minerals may be required when the volume of the EF supplied does not provide the required daily intake. The selection of an EF should not be determined solely on the basis of the instructions for use provided by the manufacturer; it must result from a judicious appraisal by the clinical team.

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Statement of Authorship

P. Savino contributed to the conception and design, drafted the manuscript, gave final approval, and agrees to be accountable for all aspect of work ensuring integrity and accuracy.

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