CHAPTER TWO

Introduction PART I

PART I of this thesis focuses on the influence of the composition of enteral nutrition on digestion and absorption of nutrients. The composition of enteral nutrition is thoroughly balanced, but there excists a knowledge gap on the actual nutrient digestion and absorption when administering enteral nutrition either gastric or jejunal. In the following part of this thesis we gain insight in the different elements of enteral nutrition and how these are influenced by the gastrointestinal tract and vice versa. Before going more into dept how the research is defined and performed, this chapter starts with a general introduction on the digestive system and the different components of enteral nutrition.

ANATOMY AND PHYSIOLOGY OF THE DIGESTIVE SYSTEM

The digestive system converts food into energy and basic nutrients in order to allow the body to function, grow, and repair itself. Food passes through the gastrointestinal tract, formed by the oral cavity, pharynx, esophagus, stomach, small intestines, and large intestines. There are several important accessory organs that help the body to digest the food. Accessory organs of the digestive system include salivary glands, liver, gallbladder, and the pancreas. To achieve the goal of providing energy and nutrients to the body, six major functions take place in the digestive system: ingestion, secretion, mixing and movement, digestion, absorption, and excretion.

From the oral cavity saliva moistens dry food and contains salivary amylase, a digestive enzyme that is involved in the digestion of carbohydrates. The esophagus is part of the upper gastrointestinal tract and connects the pharynx to the stomach. The esophageal sphincter at

the inferior end closes of the esophagus to prevent reflux from stomach content. Anatomic regions of the stomach include the fundus, corpus, antrum and pylorus. Functionally, the stomach can be divided into the gastric reservoir and the gastric pump (1). The stomach contains both hydrochloric acid and pepsine that are very important in the digestion of food into chyme. Chyme passes through the stomach into the small intestine, which is usually about 6-7 meters long. The small intestine is divided into the duodenum, jejunum and ileum. The jejunum is considered to begin at the attachment of the suspensory muscle of the duodenum to the duodenum, a location called the duodenojejunal flexure also known as the ligament of Treitz. The interior surface of the small intestine is covered with villi to maximize the surface for digestion of food and absorption of nutrients (1). By physical churning and mixing, the stomach breaks down food into proportions that allow pancreatic and small intestinal brush border enzymes to digest it ready for absorption. Fat and fat-soluble vitamins require bile acids, lipase and micelle formation to permit absorption. Proteins require gastric pepsin, pancreatic trypsin and brush border peptidases to break down proteins to absorbable single amino acids or 2-4 amino acid peptides. Carbohydrates require pancreatic amylase, and then brush border disaccharidases, to form monosaccharides which can be absorbed. Calcium, iron and folic acid are absorbed in the duodenum and upper jejunum, whereas vitamin B12 and bile acids are absorbed in the terminal ileum; all other nutrients are absorbed throughout the small intestine. Small intestinal absorption requires active or passive transport across the brush border membrane, transport through the cell (often in Golgi or mitochondria), and then extrusion through the cell's basolateral membrane (2).

The liver has many different functions, amongst others glycogen storage, detoxification of various metabolites, protein synthesis, but the main function in digestion is the production of bile and its secretion into the small intestine. The gallbladder is used to store bile. Bile is used to emulsify large masses of lipids into tiny globules for easy digestion (2). The pancreas is an endocrine gland producing several important hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide which circulate in the blood. The pancreas also has an exocrine function, secreting pancreatic juice containing digestive enzymes, like amylase and lipase, assisting nutrient digestion and absorption in the small intestine.

The large intestine is about 1.5-2 meters long and is divided into the colon ascendens, transverse, descendense, sigmoid, and rectum. The function of the large intestine is to absorbs water and excrete waste. The gut microbiota in the large intestine are responsible for the collection of energy from the fermentation of undigested carbohydrates and subsequent absorption of short-chain fatty acids (3).

ENTERAL NUTRITION

Enteral feeding has a long and fascinating history. Over the past thirty years, there has been a renewed interest in enteral nutrition. This might be the result of a number of inter-related and synergistic factors, in which the industry played an important role by manufacturing complete enteral nutrition ready to use, with a lower risk of microbiological contamination than 'home-brew' feeds made up in hospital kitchens and on wards. Enteral nutrition is more physiological, safer but also a cheaper option than parenteral nutrition. One of the major

scientific developments which has supported the re-introduction of enteral feeding has been the documentation of the importance of luminal nutrition in maintaining gut health and function (4).

Both parenteral and enteral nutrition are used for metabolic support when patients cannot take adequate amounts of macronutrients orally with the primary aim to avoid the occurence of progressive lean tissue catabolism due to starvation. Both enteral and parenteral nutrition can play an important role in preventing these severe catabolic processes. However, there is increasing evidence that significant benefits are gained when nutrients are delivered via the gut compared to the parenteral route. Accordingly, enteral nutrition is preferred over parenteral nutrition, because it preserves the intestinal integrity and prevents mucosal atrophy and bacterial translocation (5). Nevertheless, parenteral feeding is indispensable in prolonged ileus, enterocutaneous fistulas, and in patients with complications inherent to major surgery and critical illness. There are various routes of access to administer EN, including gastric feeding and jejunal feeding. Post-surgical patients and critically ill patients are frequent candidates for jejunal feeding due to their underlying illness and delayed gastric emptying (6).

In the last 35 years the number and variety of enteral nutrition that is available for use has increased. As research and experience have strengthened our knowledge of the nutrient requirements and digestive functions of patients, enteral nutrition has become more sophisticated and diversified to meet patient's nutritional and metabolic needs. Enteral nutrition is classified as standard, elemental or specialized. Many formulas are available within each category, often containing significant differences in nutrient composition. Standard enteral nutrition is defined as nutrition with intact protein containing balanced amounts of macronutrients. It will often meet a patient's nutrient requirements at significantly lower cost than a specialized formula. There is, however, a knowledge gap on the effect of macronutrient compositions on clinical outcome. There are infinite possibilities for the composition of macronutrients in enteral nutrition and the general guidelines in place are broad. Here we refer to the guidelines of the Food and Drug Association (FDA) and the European Food for Specific Medical Purposes. Therefore, there is a need for insight in macronutrient composition of the different specialized formulas. Besides, more clarity is needed on claim substantiation concerning the effect of the macronutrient composition of the specialized formulas on clinical outcome. In the following paragraphs we discuss two important and bioactive categories of macronutrients of enteral nutrition, namely fibers and proteins. Our data from CHAPTERS 3, 4, and 5 suggest that macronutrient composition of enteral nutrition might have major impact on clinical outcome of surgical patients and critically ill patients.

FIBERS

Dietary fibers are a collective term for a variety of plant substances that are resistant to digestion by human gastrointestinal enzymes. Some types of dietary fibers are excreted in the faeces essentially unchanged, while others are partially digested (fermented) by naturally occurring bacteria in the colon with the consequent production of hydrogen, carbon dioxide, methane, water and short-chain fatty acids. Dietary fibers can be classified according to their solubility in water as either soluble or non-soluble. After the discovery of the biological

effect of fermentation by colonic microbiota in humans, fibers were additionally classified as being fermentable and non-fermentable (7). In general, soluble fibers are easily fermentable; whereas insoluble fibers are less easily fermentable.

Fibers became popular because of their positive effect on diabetes, coronary heart disease, colorectal cancer, and gastrointestinal disorders such as constipation, haemorrhoids and diverticular disease. Potential mechanisms for a protective effect include dilution of faecal carcinogens and pro-carcinogens, reduction of transit time of faeces through the bowel, production of short chain fatty acids which promote anti-carcinogenic action, and binding of carcinogenic bile acids (8). Fibers became of great interest for the food industry and even enriching enteral nutrition lead to great benefits. Fibers increase the volume of the intestinal content; both soluble and insoluble fibers add bulk because they are not digested and because they hold and absorb water. Because of this attribute, fibers are added to enteral nutrition, resulting in a reduction of diarrhea and constipation. Some fibers have even been shown to have a prebiotic effect, as they are selectively metabolized by distinct gut bacteria. For example the specific oligosaccharides like GOS and FOS. The prebiotic effect has also been reported to promote gastrointestinal health (9). The fact that different types of fibers have diverse biological effects, the composition of fiber-enriched enteral nutrition has evolved towards blends of soluble and insoluble fibers (10).

PROTEIN

In patients with a body mass index (BMI) < 30, protein requirements should be in the range of 1.2–1.5 g/kg actual body weight per day. In critically ill patients, guidelines recommend use of high-protein enteral nutrition to achieve target protein intake of 1.2 to 2.0 g/kg of body weight per day, supported by recent observational studies showing reduced mortality in ICU patients reaching higher protein targets (11). The observation that exocrine pancreatic function is reduced in sepsis gave rise to concerns about the digestion and absorption of whole protein formulae in critical illness. Nevertheless, there is no clinical evidence for a peptid-based formula in critically ill patients. Therefore, whole protein formula are appropriate in most patients (12).

In this part of the thesis we focus on intact casein protein. It is commonly used in enteral nutrition, because of its high essential amino acid content. Casein is a milk protein; milk consists of 80% casein and 20% whey. Coagulation of casein protein is a physiological process which changes the structure of the casein micelles is such a way that it cloths. This process makes that casein predominant enteral nutrition tends to coagulate in the stomach, due to the precipitation of enteral nutrition in an acidic environment (13). In the stomach, the pH of enteral nutrition is lowered from about 7 to 2. Casein coagulates at its isoelectric point of pH 4.6 (14). Coagulation of enteral nutrition in the gastrointestinal tract could potentially cause serious complications in critically ill patients in those with altered gastrointestinal motility and function. In an in vitro study conducted by Van den Braak et al. the impact of using casein or a non-coagulating protein blend shows that casein protein is the major contributor to the coagulation of enteral nutrition (15). Coagulation can be prevented by the addition of non-coagulating protein to the enteral nutrition, e.g. soy, pea and whey protein. The process

of coagulation of casein in the stomach may slow down the availability of the protein for digestion and absorption. Therefore jejunal casein feeding may result in more rapid digestion and subsequent absorption of dietary protein derived plasma amino acids. Consequently, it is hypothesized that jejunal casein feeding leads to more rapid protein digestion and amino acid absorption when compared to gastric feeding.

DIGESTION AND ABSORPTION OF AMINO ACIDS

Dietary carbohydrates are commonly classified as slow or fast, since it is well recognized that their structure affects their speed of absorption, which in turn has a major impact on the metabolic and hormonal response to a meal (16). On the other hand, little is known about whether postprandial protein kinetics are affected by the speed of absorption of dietary amino acids; the latter is very variable, depending on gastric and intestinal motility, luminal digestion, and finally mucosal absorption. Dietary proteins can also be classified as fast or slow, because it is well recognized that their structure affects their rate of digestion and absorption, which strongly modulates the postprandial hormonal and metabolic response, as well as postprandial protein accretion (17). Intact casein is generally classified as a slowly digestible protein (18). The fact that there is few in vivo data on the impact of gastric versus jejunal feeding on dietary protein digestion and absorption is likely attributed to the obvious methodological limitations of in vivo human research (19). To allow in vivo assessment of dietary protein digestion and absorption kinetics we applied intrinsically L-[1-^{13}C]phenylalanine-labeled protein that was produced by collecting milk protein from lactating cows that were infused with large amounts of L-[1-^{13}C]phenylalanine (20).

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