

CHAPTER TEN

Discussion and future perspectives

DISCUSSION

The composition of enteral nutrition influences digestion and absorption of nutrients

Surgery has a major impact on the metabolism of the human body, changing a healthy anabolic state into a catabolic state. To reduce the stress of surgery, to minimize catabolism, and support anabolism throughout surgical treatment, the Enhanced Recovery After Surgery guidelines have been developed to allow patients to recover substantially better and faster. In this thesis insights are provided on how to improve perioperative strategies in the surgical patient, in which the influence of the composition of enteral nutrition on nutrient digestion and absorption plays a major role.

In general, enteral nutrition is well tolerated by surgical patients. However, when gastrointestinal function is impaired, the composition of the enteral nutrition plays a major role in the digestion and absorption of nutrients. For example, a casein based enteral nutrition tends to coagulate, or solidify, in an acidic environment as the stomach. This process of coagulation makes enteral nutrition less accessible for protein digestion and absorption, and may even lead to gastrointestinal obstruction. For that reason enteral nutrition based on non-coagulating proteins, or hydrolysed proteins, lead to less complications in critically ill patients with an altered gastrointestinal function.

Moreover, it has been suggested that insoluble fibers play a role in gastrointestinal obstruction by solidification of enteral nutrition in critically ill patients. In this thesis soluble and insoluble

fibers are studied using an artificial gastrointestinal model developed by TNO (Toegepast-Natuurwetenschappelijk Onderzoek; Dutch Organization for Applied Scientific Research) in collaboration with Nutricia Research. CHAPTER 4 shows that fibers can modulate the coagulating properties of a casein-based enteral nutrition. However, we must emphasize that the concentrations used in this study extensively exceed concentrations added to clinical enteral nutrition. We are of the opinion that the concentrations of fibers used in enteral nutrition will not generate physico-chemical effects which are of biological relevance.

Van den Braak et al. showed that a casein-based enteral nutrition coagulates after artificial gastric digestion, whereas soy, pea, and whey protein, described as non-coagulating proteins, do not coagulate after artificial gastric digestion (1). Apparently, the proportion of casein in enteral nutrition determines whether coagulation will occur, as enteral nutrition containing 25% casein, 35% whey, 20% pea protein, and 20% soy protein does not coagulate in the stomach. For that reason, critically ill patients with an impaired digestion (e.g. after Whipple surgery), should be considered candidates for enteral nutrition with non-coagulating proteins or hydrolysed proteins.

It is important to know that casein protein coagulates in an acidic environment such as in the stomach; this may slow down the availability of proteins in the digestive tract. The study presented in CHAPTER 5 is the first to compare *in vivo* casein digestion and absorption kinetics following jejunal versus gastric casein feeding in healthy young males. To allow *in vivo* assessment of dietary protein digestion and absorption kinetics, intrinsically L-[1-¹³C] phenylalanine-labeled casein protein was applied, which was produced by collecting milk protein from lactating cows that were infused with large amounts of L-[1-¹³C]phenylalanine (2). Jejunal feeding with casein protein is followed by a more rapid release of dietary protein derived amino acids in plasma when compared to gastric feeding. In the light of 'fast' and 'slow' proteins this is a very interesting finding. The coagulation of casein in the stomach changes the micellar structure and makes casein less accessible to luminal digestion, resulting in slower mucosal amino acid absorption following gastric as opposed to jejunal feeding. With gastric feeding casein acts like a 'slow' protein and with jejunal feeding casein acts like a 'fast' protein. In general, it should be emphasized that the route of feeding and the type of protein is essential in nutrient digestion and absorption.

Food intake influences endocrine responses in the gut

Delayed gastric emptying is a major problem in postoperative patients and critically ill patients, because it interferes with the effective delivery of enteral nutrition. Therapeutic interventions to restore gastrointestinal function in critically ill patients like metoclopramide, domperidone, erythromycin, azithromycin, and prucalopride carry limitations in terms of sustained efficacy and side-effects. In the review presented in CHAPTER 7, possible pharmacological interventions were identified targeting gut hormones receptors in order to improve delayed gastric emptying. Motilin receptor agonist with non-macrolide properties (ABT-229, and mitemincal GM-611) are currently the most advanced options in the treatment of delayed gastric emptying. Progress has been made through the development of synthetic non-peptide ghrelin receptor agonist (TZP-101, and TZP-102), competitive CCK-1 receptor agonist (dexloxiglumide), and GLP-1 receptor antagonist (exendin9-39).

Advancements in therapeutic interventions to treat delayed gastric emptying is of utmost importance for critically ill patients. However, prevention of gastrointestinal dysfunction may be even better. Knowledge on gastrointestinal hormones and their function is still lacking. The study in CHAPTER 8 is the first to compare an in vivo endocrine responses following jejunal versus gastric feeding in healthy young males. A non-coagulating polymeric enteral nutrition resulted in similar post-prandial plasma amino acid and glucose concentrations between regimens. However, jejunal feeding resulted in substantially higher peak plasma CCK, PYY, GLP-1, and GLP-2 concentrations. In addition, higher peak plasma PYY and GLP-1 concentrations were observed following jejunal feeding distal to the ligament of Treitz. Nevertheless this has not resulted in a reduced digestion and absorption of nutrients, as suggested by the phenomenon of the 'ileal brake'. To our opinion the composition of enteral nutrition determines nutrient digestion and absorption to a greater extent than the endocrine response; in which the proportion of casein is crucial for the enteral nutrition not to coagulate in the acidic environment of the stomach. Thus, feeding strategy can have a distinct impact on endocrine and exocrine responses.

With our study we were able to create conditions simulating the endocrine response to nutrition comparable to gastric bypass surgery. The improvement in type 2 diabetes after gastric bypass surgery is associated with a rise in GLP-1 levels. GLP-1 is known as an incretin hormone and responsible for reducing fasting and postprandial glycemia. This is in line with our finding, higher levels of GLP-1 following jejunal feeding may therefore improve glycemic control.

Since decreased insulin sensitivity is related to delayed gastric emptying, an integrated protocol which focuses on the prevention of insulin resistance may be effective in the prevention of delayed gastric emptying. Early start of oral nutrition is promoted in most patients undergoing elective colorectal surgery and is an important element of 'fast track' surgery protocols. However, due to post operative ileus or delayed gastric emptying this early approach is not per se successfully in all patients. Early start of oral nutrition can be improved by carbohydrate loading preoperatively; for example with a simple carbohydrate drink like lemonade. Carbohydrate loading reduces postoperative insulin resistance, and may therefore be effective in the prevention of delayed gastric emptying. It is investigated whether preoperative carbohydrate loading compared to fasting could improve postoperative food intake using an intestinal ischemia-reperfusion animal model in CHAPTER 9. In our study, rats started eating earlier voluntarily, which indicates an improved gastrointestinal function. Carbohydrate loading diminishes the effect of major surgery, resulting in comparable outcomes to the sham fasted animals. From this it can be concluded that carbohydrate loading improves gastrointestinal function which facilitates early intake. Also, carbohydrate loading preserves the intestinal barrier function and preserves the functional enterocyte metabolic mass. A simple CHO drink might be the way to preserve the intestinal function in order to accelerate recovery and food intake.

FUTURE PERSPECTIVES

With this thesis we tried to gain insight on how to optimise the nutritional support for the surgical patient. First of all, I would like to emphasize that current guidelines provide clear recommendations, which are not always respected in clinical practice. For example, ERAS guidelines can be used in a broader perspective and in more hospitals worldwide. As physicians we have to take our responsibility and guarantee the best nutritional care for our patients, including perioperative nutrition. Fasting before surgery is outdated, but unfortunately still common practice. The implementation of existing guidelines and new insights obtained from this thesis is probably more challenging than defending this thesis. Only dedicated multidisciplinary teams, in which surgeon, anesthetists, intensivists and dieticians participate, can be expected to have the combined expertise required to remain up to date of the developments in the field.

Tools for measurement of small intestinal function are important in critically ill patients in order to determine the preferred feeding route, timing, and composition of enteral nutrition. Higher levels of the intestinotropic hormone GLP-2 following jejunal feeding may imply a protective effect on the intestine. To substantiate that the increases in GLP-2 reflect an intestinotrophic effect following jejunal feeding, a citrulline generation test with a dipeptide alanine-glutamine drink should be performed.

A recent study by Boelens et al. promotes early enteral nutrition after colorectal surgery (3). Patients were randomly assigned to postoperative enteral nutrition or parenteral nutrition, and all patients were allowed to drink and eat as soon as possible, according to standard care protocols. They conclude that early enteral nutrition is associated with significantly less postoperative ileus, and with less anastomotic leakage. In our opinion the positive effect of early enteral nutrition must be seen in a broader perspective. It improves insulin sensitivity, intestinal barrier function and associated bacterial translocation, and reduces delayed gastric emptying. With this thesis we show that early enteral feeding is possible when patients are given a carbohydrate drink preoperatively. Subsequently, the composition of the enteral nutrition and the site of feeding are determinative for digestion and absorption of nutrients. In this thesis casein protein was extensively studied and recommendations were formulated. These findings need to be translated to critically ill patients, with regard to protein digestion and amino acid absorption and muscle protein synthesis. Knowledge on other amino acid sources like whey, soy, and pea protein is still lacking. We are of the opinion that standard enteral nutrition is well tolerated in the majority of patients. Nevertheless, when gastrointestinal function is compromised by surgery or other trauma we need to provide nutritional support tailored to patient's individual needs. To reach this goal, future studies are warranted to investigate which protein is best absorbed either gastric or jejunal and results in optimal muscle protein synthesis in critically ill patients.

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