To keep a balance in disease specific intestinal insufficiency. Diagnostics and practical nutritional aspects

Outline and introduction

Two patients with a ‘newly’ short bowel syndrome after radical intestinal surgery due to inflammatory bowel disease, experiencing problems in their clinical work-up of diagnosis of remnant intestinal function (questioning whether they suffered from intestinal failure or insufficiency), and nutritional balance, were the direct reason to further study diagnostic tests on intestinal function and practical nutritional aspects of intestinal insufficiency.

This thesis provides an introduction with motive and outline of the thesis (chapter 1), the aforementioned case-study (chapter 2), an overview of gastrointestinal (GI) function test (chapter 3), studies on classical methodology of gastrointestinal function in health and disease (chapters 4-8), studies on advanced assessment of intestinal failure by means of citrulline (chapters 9-10) and a general discussion with concluding remarks and a summary (chapters 11-12).

The general aim of this thesis was to (re)develop valid and reproducible diagnostic test(s) to assess intestinal function for clinical use in patients at risk of intestinal failure or intestinal insufficiency. By applying tests to assess digestive function, combined with nutritional assessments tests, we aimed to get a better understanding of the pathophysiological aspects of the individuals, and to improve the (nutritional) treatment and clinical outcome of these patients. Thus, patients played a central role in the creation of this thesis.

The reduction of the intestinal absorptive function is elementary in diagnosis and treatment of patients. When, in case of a reduction of intestinal function, intravenous-supplementation (fluid or nutrition) is required to maintain or attain health or growth, intestinal failure is to be diagnosed; without intravenous-supplementation the syndrome is coined as intestinal insufficiency. Malabsorption, micronutrient deficiencies, fluid and electrolytes disturbances, diarrhea, dehydration or malnutrition comprise symptoms of these two types of intestinal dysfunction.
Main findings

Classical methodology of intestinal function in health and disease

We (re)introduced bomb calorimetry, a conventional technique from the 1950’s, measuring the heat of combustion to assess the energetic content of a standardized (mostly freeze dried) fecal sample by a ballistic bomb calorimeter. We ‘rediscovered’ this methodology, combined it with adequately quantified caloric and macronutrient nutritional intake and proposed it as the putative gold standard test for assessing (remnant) intestinal absorption capacity for daily clinical practice. To start with, normative values of intestinal absorption of energy and macronutrients in healthy adults were provided; these appeared to be 90% or more.

Then, bomb calorimetry was applied in ICU patients, since diarrhea and malnutrition are frequently occurring symptoms at the ICU. Measuring absorption by bomb calorimetry appeared to be logistically challenging, but feasible in this setting. It was shown that malabsorption, defined as an absorption capacity of <85%, was an often overlooked problem, since it occurred in approximately 1 out of 5 hemodynamically stable ICU patients, without clinically evident GI dysfunction a priori. Based on a receiver operating characteristic (ROC) curve, a fecal weight of over 350 g/day was suggested as a valid biomarker (sensitivity and PPV 80%, specificity and NPV 96%) to identify ICU patients at risk for malabsorption in daily practice. Clinical relevance was demonstrated by showing that patients with a fecal production of more than 350 g/day had a mean negative energy balance of over 600 kcal/day.

Another group of patients at risk of intestinal insufficiency or even intestinal failure are patients with celiac disease, characterized by a reduced absorptive surface due to villous atrophy. Malabsorption, measured by bomb calorimetry, appeared to be present in approximately 1 out of 5 newly diagnosed CD patients, representing a mean fecal energetic loss of 277 kcal/day. Malnutrition (defined as BMI <18.5 kg/m² and/or >10% unintentional weight loss in past 6 months) was present in a quarter of the patients, probably due to the fecal losses or to hypermetabolism (defined as a resting energy expenditure (REE) of more than 10% of predicted REE, and encountered in 38% of the patients). Subsequently, malnutrition was observed on micronutrient level as well: 87% of the newly diagnosed CD patients was deficient for at least one serum vitamin
or mineral. We demonstrated that deficiencies are still common in CD patients even though nowadays the prevalence of obesity is rising at initial diagnosis (29% of these patients had a BMI > 25 kg/m²).

Patients with complicated celiac disease, i.e. refractory CD (RCD) or enteropathy associated T-cell lymphoma (EATL), suffered from more severe intestinal insufficiency at presentation than the naïve CD-patients. The presence of diarrhea and fecal losses (energy and fat) was higher and resulted frequently in a serious disturbed nutritional status. RCD patients were characterised more often by a low BMI (chronic malnutrition), whereas EATL patients suffered more often from unintended weight loss (acute malnutrition) and to a greater extent. Hypermetabolism seemed to play an important role in these patients as well (in 60-89% of the patients).

Advanced assessment of intestinal function
With the aim to develop valid, reproducible diagnostic test(s) to assess intestinal function to be clinically used in patients at risk of intestinal failure or -insufficiency, we investigated the citrulline concentration as a diagnostic tool for intestinal function. Citrulline is a non-protein amino acid mainly produced by the enterocytes. Fasting citrulline is hypothesized to be an attractive marker for intestinal mass. We refuted this concept by studying 30 adult patients with a known reduced enterocyte mass (patients with naïve CD, RCD and SBS) and 21 healthy controls. No relation was observed between plasma fasting citrulline concentrations (measured by high performance liquid chromatography (HPLC)) and intestinal energy absorption capacity (by bomb calorimetry). Besides, fasting plasma citrulline levels in patients with a known reduced intestinal mass remained within reference values, herewith turning out to be a poor marker to identify patients with malabsorption.

We developed and proposed a new enterocyte function test; the citrulline generation test (CGT), in which the time dependent rise of plasma citrulline after a fixed oral bolus of the dipeptide alanine-glutamine was measured in patients with decreased enterocyte mass and compared to healthy subjects. With the slope of the citrulline curve from fasting citrulline to peak (after 90 minutes) as well as with the incremental area under the curve (AUC), the CGT was able to distinguish between healthy subjects and those with reduced enterocyte mass. Furthermore, a trend was seen for the correlation between this slope and the intestinal absorption capacity \( r = 0.32, P = 0.06 \). CGT appeared feasible and applicable as enterocyte function test, yet especially in research setting.
Conclusions

In conclusion, malabsorption/diarrhea and malnutrition/nutritional problems are inextricably coupled to intestinal failure and insufficiency. Insights in the mechanism of nutritional balance and means to keep such a nutritional balance is of great importance in patients with intestinal disease. Different diagnostic tools are available to assess the intestinal function. Two tests are extensively described and elaborated in this thesis; the ‘rediscovered’ bomb calorimetry, which seems highly valuable in identifying intestinal impairment, and the citrulline generation test (CGT), proposed to be used as a intestinal mass marker in research setting.

Future studies may focus on adaptation of the CGT to make it feasible for application in clinical practice.

We advocate to treat patients with intestinal failure or insufficiency by a dedicated multidisciplinary team (including dietitian and gastroenterologist), according to a personally adapted management plan, in which the described tests (bomb calorimetry and CGT) may contribute to a better treatment strategy. A work-up for putative intestinal insufficiency with a medical-nutritional focus and treatment is proposed for clinical practice.