Valorization

Part I  Patient-reported outcome measures in functional dyspepsia

Functional dyspepsia is a common functional gastrointestinal disorder with an estimated prevalence of 11-29% in the general population. Due to this high prevalence together with the negative impact on daily life, dyspeptic complaints are associated with a considerable economic burden. First, (functional) dyspepsia is associated with reduced work productivity. In a large study from Brazil, 32% of patients with dyspepsia reported lost hours of work in the preceding week because of dyspeptic symptoms with an average of 2.6 hours per week. In addition, 78% of patients reported reduced work productivity, and the costs of the total work productivity impairment was $3570 annually per employed dyspeptic patient. Besides the impaired work productivity, dyspepsia also increases health care costs. Results from a longitudinal 10-year follow-up study demonstrated that from 3266 included participants, 1738 (53%) had dyspeptic symptoms at any point during this follow-up period. Seven hundred twenty-nine of patients with dyspeptic symptoms (42%) consulted a primary care physician one or more times for their complaints. Sixty percent of patients seeking medical help for their dyspeptic complaints had been prescribed acid suppressant therapy. These results are in line with a population based cohort study including 206 subjects with dyspepsia. In total, 48% of patients consulted a physician for dyspeptic symptoms over 20 years. Of these patients, 13% was referred to a gastroenterologist after their first episode of dyspepsia, 65% had an upper gastrointestinal barium study, 49% had an upper gastrointestinal endoscopy, and 91% received a dyspepsia related medical prescription. In addition, dyspeptic patients report reduced quality of life.

The high prevalence of dyspepsia together with the negative impact on work productivity and health care costs underline the need for (development of) effective treatment options. Treatment of dyspepsia is however challenging due to the multifactorial and incompletely understood pathophysiology. Moreover, symptom assessment is necessary to evaluate treatment efficacy due to the lack of biomarkers or objective outcome measures. In chapter 2 we performed a systematic literature search and identified 20 available outcome measures to assess dyspeptic symptoms. Consequently, clinical trials use different questionnaires which makes comparison of results difficult, and selection of one universal outcome measure seems favorable to uniformly assess FD symptoms in clinical trials.

In chapter 3 we describe the development of a novel ESM-based PROM. Use of a PROM based on the experience sampling technology (ESM) has advantages compared to standard retrospective (end-of-day) questionnaires. First, previous studies compared ESM-PROMs with retrospective (end-of-day) questionnaires and demonstrated over-reporting of symptoms by retrospective (end-of-day)
questionnaires compared to ESM. More accurate reporting of symptoms by ESM might be due to the momentary assessment with a reduction of recall bias.\textsuperscript{5,6}

Another major limitation of retrospective paper questionnaires is non-compliance. A previous study described an actual compliance rate of 10.9\% with paper diaries although subjects reported a compliance rate of 90.5\%, which was however considered ‘fake compliance’. In contrast, a compliance rate of 93.6\% was found with use of an electronic diary.\textsuperscript{7} The experience sampling technology uses 10 random symptom assessments per day with the goal of completing at least six assessments per day. In a small trial with 26 IBS patients, the compliance rate with ESM was 76.8\% (i.e. on 76.8\% of the days at least 6 beeps were completed).\textsuperscript{6}

Due to the repeated symptom assessment per day for several consecutive days, information is obtained about symptom variability with the potential to identify symptom triggers. Examples of potential triggers for dyspeptic symptoms are psychological aspects, contextual factors, nutrition and substance use.\textsuperscript{8,9} Identification of specific triggers per individual might guide therapy and contribute to a shift of a ‘one-size fits all treatment approach’ to a more ‘individualized treatment approach’ which might improve treatment outcome, avoid unnecessary and ineffective treatment strategies, and contribute to cost-effective health care.

Besides use of the ESM-based PROM for evaluation of treatment efficacy and identification of symptom triggers, it can also be used as a therapeutic application. Previous studies in patients with mental disorders described use of ESM as a method to provide personalized feedback on patterns of positive affect. Participants who received personalized feedback together with antidepressant medication demonstrated a greater decline in depressive symptoms compared to the control group who received antidepressant medication only.\textsuperscript{10} In addition, the experience sampling technology can also be used to implement psychotherapy in daily lives.\textsuperscript{11}

In conclusion, use of an ESM-based PROM for symptom assessment in dyspeptic patients seems to have several important advantages compared to retrospective (end-of-day) questionnaires. Future studies are necessary to validate the novel ESM-based PROM before use in clinical trials.

Part II Prediction of treatment outcome in upper gastrointestinal disorders

\textit{Achalasia}

Achalasia is an uncommon esophageal motility disorder with an estimated prevalence of 10 in 100,000.\textsuperscript{12} Treatment of achalasia is focused on improving esophageal emptying by reduction of the relative obstruction at the gastroesophageal junction in order to improve symptoms and reduce the long-term risks of development of a megaesophagus and esophageal cancer. Short-term follow-up of patients after
Treatment is therefore recommended, although patient’s symptoms are not a reliable predictor as symptom resolution might occur without improvement in esophageal emptying.\textsuperscript{13} As a consequence, functional testing is preferred but currently the optimal test has not been defined. In the ACG guideline two diagnostic modalities have been described: (1) timed barium esophagogram (TBE), and (2) esophageal manometry.\textsuperscript{12} Concordance between symptom reduction and improvement in esophageal emptying based on TBE has been found in 52-89% of patients.\textsuperscript{13-16} Due to the lack of concordance in the remaining patients, the ACG guideline recommends to repeat TBE annually to evaluate esophageal emptying.\textsuperscript{12} Important limitation for repetitive use of TBE is the radiation exposure. In addition, although several studies have shown that posttreatment LES pressure $<10 \text{mmHg}$ was predictive of beneficial treatment outcome, a significant proportion of patients with persistent symptoms have a LES pressure below this cut-off value.\textsuperscript{12,14,15,17-19} Consequently, a novel diagnostic modality or parameter is warranted to evaluate treatment outcome and identify patients with need for retreatment. Based on previous studies which described impaired EGJ distensibility in (newly diagnosed) achalasia patients, we evaluated the potential of this novel diagnostic modality in evaluation of treatment outcome (chapter 4).\textsuperscript{20} In our small clinical trial, we were not able to differentiate between patients with good and poor clinical outcome based on EGJ distensibility, although conflicting results have been described by previous studies.\textsuperscript{15} These conflicting results together with the limited availability and expertise of this technique in medical centers, invasiveness of the EndoFLIP procedure, and high costs emphasize the need for additional research before use of this novel technique in routine clinical practice. Moreover, recently novel parameters of high-resolution (impedance) manometry have been proposed as factors predicting treatment outcome, and additional research is necessary to assess the potential for prediction of treatment outcome. Use of diagnostic parameters assessed during high-resolution (impedance) manometry has the benefit of a more worldwide available technology, without need for the purchase of a novel diagnostic modality.

In conclusion, there is need for a diagnostic modality or parameter to evaluate treatment outcome in achalasia patients in order to define the need for retreatment and reduce development of long-term complications. Additional research is necessary to assess the potential of the EndoFLIP technique and novel parameters measured with high-resolution (impedance) manometry.

\textit{Gastroesophageal reflux disease}

The prevalence of gastroesophageal reflux disease (GERD) has increased over the last decades. The prevalence of at least weekly GERD symptoms is greatest in North America (19.8\%) and 15.2\% in Europe.\textsuperscript{21} In the late 1990’s, GERD was found to be the gastrointestinal disorder with the highest annual direct costs in the Unites States of
America accounting for $9.3 billion, which increased to $12.1 billion in 2014. Majority of the direct costs were caused by pharmaceutical prescriptions ($6-10 billion), whereas hospital admissions, physician office visits and hospital outpatient visits made up the remainder of these costs.\textsuperscript{24} Despite the fact that the diagnosis of GERD can usually be made based on symptoms or an empiric trial of acid suppressive medication, 20-30% of 7 million upper gastrointestinal endoscopies performed annually in the USA are due to reflux symptoms. In addition to direct costs, GERD contributes also to indirect costs from missed work, diminished work productivity and impairment in performing daily activities. The estimated value of lost work productivity was $237 per GERD patient over a 3-month period.\textsuperscript{21}

The increasing prevalence of GERD together with the high socio-economic burden underline the need for effective treatment options. Although adequate symptom control is achieved with acid suppressive medication in the majority of patients, a subgroup of patients are considered non-responders, experience adverse effects from medical treatment or are not willing to take lifelong acid suppressive medication. Although (laparoscopic) fundoplication has been proven to be effective, it is accompanied by several perioperative and postoperative complications. One feared complication of antireflux surgery (ARS) is vagal nerve injury, which has been observed in up to 20% of patients undergoing ARS with a negative effect on long-term reflux control and a higher reoperation rate.\textsuperscript{22,23} Moreover, dysphagia might develop in case the surgical fundoplication led to a too tight wrap. The increasing prevalence and potential complications of traditional ARS, led to development of several minimally invasive treatment options including Transoral Incisionless Fundoplication (TIF). Although initial studies described promising short-term results, a recent systematic review and meta-analysis described superiority of laparoscopic Nissen fundoplication compared to TIF with regard to objective reflux control, increase in LES pressure and incidence of persistent esophageal \textsuperscript{24,25} The lack of durability seems an important limitation of TIF, and consequently members of a GERD expert panel were reluctant to advocate for TIF.\textsuperscript{26,27} It is however supposed that a selected subgroup of patients might benefit from TIF, which underlines the need for adequate patient selection. Based on previous studies, patients with no or small hiatal hernia (≤2cm) and Hill grade I/II were considered best candidates for TIF.\textsuperscript{24,28} Both variables are however assessed by gastroenterologists during upper gastrointestinal endoscopy and are at risk for interrater variability. As the goal of ARS is to restore EGJ competence, we evaluated the effect of TIF on EGJ distensibility with the EndoFLIP technique \textit{(chapter 5 & 6)}. Although preoperative EGJ distensibility was an independent predictor of objective treatment outcome after TIF, no difference in EGJ distensibility was found between patients with normalization of esophageal acid exposure time and patients with persistent abnormal acid exposure. Consequently, the role of the EndoFLIP technique in selection of patients for TIF seems limited at this moment. An attractive application of the EndoFLIP seems to be its intraoperative use to guide
calibration of hiatal hernia repair and creation of the surgical fundoplication, although additional studies are necessary to define ‘target values’ for EGJ distensibility in order to improve adequate reflux control.

In conclusion, the increasing prevalence of GERD together with several (long-term) complications of traditional ARS led to development of minimally invasive (endoscopic) treatment options. Main limitation seems to be the limited durability with need for adequate patient selection. Additional research is necessary to identify variables for adequate patient selection.

Gastroparesis

Gastroparesis is a multifactorial disorder with incompletely understood pathophysiology. Treatment of patients with gastroparesis is challenging and treatment outcomes are often disappointing. Despite the fact that the ACG guideline discourages the use of botulinum toxin treatment in gastroparesis due to the lack of superiority compared to placebo in two clinical trials, it is still regularly used due to the lack of established alternatives. Botulinum toxin therapy is expensive with the need for repeated treatment procedures due to the temporary treatment effect. Previous studies described beneficial effects in a subgroup of patients, but identification of these patients is challenging. In chapter 7 we evaluated the potential roles of antroduodenal manometry and scintigraphy as predictors of treatment outcome. Variables of both diagnostic modalities were not able to predict treatment outcome and identify patients with potential beneficial treatment outcome. In addition, antroduodenal manometry is only available in a limited number of medical centers, and it is a cumbersome technique with regard to interpretation of results due to the absence of reference values, availability of different catheters and variations in study protocols. Besides the lack of a correlation with treatment outcome, the major limitation of scintigraphy is radiation exposure.

The lack of available diagnostic modalities to select patients for botulinum toxin treatment, together with the development of novel (endoscopic) treatment options targeted at the pylorus (e.g. gastric peroral pyloromyotomy) warrants the development of a novel technique focused on pyloric functioning. One modality of interest is the EndoFLIP technique as previous studies described impaired pyloric distensibility in a subgroup of gastroparesis patients. Identification of this subgroup might select patients for (endoscopic) pyloric treatment procedures in order to improve clinical outcome, and contribute to cost-effective health care.

In conclusion, identification of gastroparesis with impaired pyloric functioning seems desirable to select patients for (endoscopic) treatment procedures. The EndoFLIP technique seems of interest and additional research is necessary to define the exact role in patient selection.
References