SUMMARY

Background
Gastroparesis is a disorder characterized by a delay in gastric emptying of a meal in the absence of a mechanical gastric outlet obstruction.

Aim
To provide an evidence based overview on diagnosis and management of gastroparesis.

Methods
A PubMed search was performed using search terms including gastroparesis, gastric retention, gastric emptying, accommodation, manometry, prokinetics, antiemetics, metoclopramide, domperidone, erythromycin, botulinum toxin, gastric pacing. Relevant studies were identified and original articles and reviews were collected. References in these articles were examined for relevance and included where appropriate.

Results
Diagnosis of gastroparesis is based on the presence of symptoms such as nausea, vomiting and postprandial abdominal fullness and on an objectively determined delay in gastric emptying. The true prevalence of gastroparesis is unknown. Gastric emptying can be assessed by scintigraphy and stable isotope breath tests. Management of gastroparesis consists of dietary and lifestyle measures and/or pharmacological interventions (prokinetics, antiemetics, intrapyloric botulinum toxin injection) or other interventions that focus on adequate nutrient intake either through a nasoduodenal tube, percutaneous gastrostomy or jejunostomy.

Conclusions
Accurate diagnosis of gastroparesis requires an adequate protocol to measure gastric emptying. Treatment options in gastroparesis remain limited despite the disabling nature of the disorder.
INTRODUCTION

Several mechanisms are involved in the process of gastric emptying. Gastric accommodation enables adaptation of the proximal stomach to a liquid or solid volume load, i.e. a meal. Antral contractions are required for grinding and transport of the meal towards the pyloric sphincter. Pyloric relaxation enables the titration of the grinded meal (chyme) into the duodenum and requires coordination of propulsive contractions in the stomach and duodenum. These actions are highly dependent on adequate neuronal and hormonal feedback mechanisms. The rate of gastric emptying is influenced by the composition of the ingested meal. Non-nutrient liquids are emptied almost immediately, whereas nutrient liquids and solids empty after a period of retention (lag phase) in a non-linear manner and linear manner respectively. Especially, fat rich meals show a more prolonged emptying pattern, resulting from duodenal feedback mechanisms, in particular, cholecystokinin. Gastroparesis is a disorder characterized by a delay in gastric emptying of a meal in the absence of a mechanical gastric outlet obstruction.\(^1\)

Prevalence

The true prevalence of gastroparesis remains unknown. It is assumed that up to 4% of the general population experiences symptoms of gastroparesis.\(^2\)

In diabetes mellitus, 5–12% of patients present with symptoms associated with delayed gastric emptying. However, when objectively determined with a gastric emptying test, 30–50% of diabetics have delayed gastric emptying.\(^3\) In functional dyspepsia, 24–40% of patients have delayed gastric emptying.\(^4–7\)

Aetiology

The aetiology of gastroparesis is diverse.\(^8\) In approximately one third of cases, gastroparesis is related to the presence of diabetes mellitus type I or II. Other causes include post-surgical conditions,\(^9–11\) neurological disorders,\(^12, 13\) metabolic and systemic disorders (SLE, systemic sclerosis, amyloidosis, hypothyroidism, HIV)\(^14, 15\) and inflammatory disorders of the gastrointestinal tract.\(^16\) The remaining one third of cases is of unknown cause, i.e. idiopathic.

DIAGNOSIS

The diagnosis of gastroparesis is based on the presence of symptoms or typical signs combined with a delay in gastric emptying proven by objective methods. Mechanical outlet obstruction and other (extra) luminal pathology should be excluded preferably by gastrointestinal endoscopy. The presence of retained food in the stomach while fasting overnight or the presence of a bezoar in the stomach during endoscopy is highly suggestive of delayed gastric emptying. However, objective determination of delayed gastric emptying is required to establish a definite diagnosis of gastroparesis.

Symptoms and signs

Gastroparesis is associated with upper gastrointestinal symptoms such as nausea, vomiting and postprandial fullness.\(^17\) Repeated vomiting several hours after eating is highly suggestive of gastroparesis.\(^1\) Symptoms of idiopathic gastroparesis overlap with those of functional dyspepsia. Abdominal pain and discomfort predominate in functional dyspepsia, whereas nausea, vomiting, bloating, postprandial fullness and early satiety predominate in idiopathic gastroparesis.\(^18\) Although symptoms of nausea, vomiting and postprandial fullness are associated with delayed gastric emptying, the correlation between the presence and intensity of symptoms and the degree of delayed gastric emptying, usually presented as half emptying time or percentage of gastric retention, is poor.\(^19, 20\)

Various systemic or local disorders may give rise to a delay in gastric emptying. Physicians should be aware that patients with gastroparesis may present at various departments depending on the underlying cause of gastroparesis: at the department of gastroenterology, endocrinology (patients with diabetes mellitus), and surgery, but also at the departments of nephrology (chronic renal failure), neurology (Parkinson’s disease, multiple sclerosis, cerebrovascular accidents) and rheumatology (SLE, systemic sclerosis, amyloidosis).

Gastric emptying testing

Scintigraphy

Scintigraphy is the gold standard method to determine gastric emptying. As emptying is influenced not
only by the mechanical properties of the gastrointestinal tract, but also by the composition of the meal, standardized measurement of gastric emptying is required to compare data between patients and institutions. Measurement of gastric emptying should be focused on the solid phase as emptying of the liquid phase is often preserved in gastroparesis. Adequate evaluation of delayed gastric emptying is obtained when the protocol is extended to at least 4 h after meal ingestion. Shorter protocols tend to under-detect patients with delayed gastric emptying. Moreover, dynamic imaging up to 90 min after consumption of the meal provides half emptying times that are derived from mathematical extrapolation and could provide erroneous data, when the actual time point for half-emptying has not been reached. A useful protocol has been proposed, which consists of a low-fat meal and extents for 4 h. Control values for this protocol have been obtained in an international multi-centre study in 123 healthy volunteers, where the presence of gastric retention >60% at 2 h and >10% at 4 h is considered to represent delayed gastric emptying. Control values depend on both the duration of the test and the composition of the meal. When protocols are different between institutions or different from published data, control values need to be determined for each gastric emptying measurement protocol separately.

**Stable isotope breath test**

The non-invasive isotope breath test has been proposed as a valid test to measure gastric emptying of a solid meal in health and disease. Solid gastric emptying requires the use of 13C-octanoic acid or 13C-sodium octanoate as a substrate, whereas liquid gastric emptying requires 13C-sodium acetate as a substrate. The substrate is rapidly absorbed in the duodenum, transported to the liver and oxidized to 13CO2 and exhaled. The ratio of 13CO2/12CO2 in breath is used to determine the gastric emptying function. Breath tests, using the non-radioactive stable isotope 13C, have been validated against scintigraphy for measuring gastric emptying in health and disease and show a good reproducibility. However, it should be noted that the parameters (half-emptying and lag time) derived from scintigraphy and the 13C isotope breath test are not interchangeable.

**Other techniques**

Several authors have pointed out Magnetic Resonance Imaging (MRI) and ultrasound as techniques that allow the measurement of gastric emptying. Few data are available. MRI seems to be a promising technique to measure simultaneously not only gastric emptying but also motility (Figure 1) and intragastric meal distribution. Results obtained with ultrasonography are particularly dependent on expertise and skills of the person performing the ultrasound examination. Both techniques have been used only in research setting and need further validation in health and disease. MRI and ultrasound provide the opportunity to measure non-invasively, not only gastric emptying, but also the mechanisms involved in gastric emptying; accommodation, antral contractions and meal distribution.

**Antropyloroduodenal manometry**

Antro(pyloro)duodenal manometry provides objectively determined data on antral, duodenal and pyloric motor function. In gastroparesis, several motor
patterns are distinguished, including postprandial antral hypomotility because of infrequent contractions and/or low amplitudes, abnormal propagation of antral- duodenal contractions, increased pyloric spasms, characterized by an increased tonic and phasic activity, and abnormal migrating motor complexes (MMC), originating less frequently from the stomach. The different motor patterns provide some insight into the aetiology of the motor dysfunction at hand. Hypomotility that is characterized by low amplitudes is suggestive of an underlying myopathy, whereas hypomotility characterized by infrequent contractions and abnormal propagation is suggestive of an underlying neuropathy.

Antroduodenal manometry requires a water-perfused or solid-state catheter that measures intraluminal pressures in the stomach and small intestine. To determine pyloric function, a challenging method is required, a so-called pyloric sleeve is included in a water-perfused catheter assembly and transmucosal potential difference measurement is used to determine adequate positioning of the sleeve across the pyloric sphincter. Current development in high resolution manometry systems and the possibility to present data as contour plots might simplify measurement of pyloric function.

MANAGEMENT

The goals of treatment in gastroparesis are to reduce symptoms, to maintain a sufficient nutritional state and an optimal weight.

Diet and lifestyle

Dietary measures are important in the management of gastroparesis. Little or no evidence is available that dietary measures work, as they have not been studied in a controlled manner. Advice should be targeted at individual intolerances or difficulties with specific food products. Especially, fat rich items and late evening meals should be avoided. Referral to a dietitian may prove helpful. Dietary and lifestyle advice should at least include the following recommendations: (i) reduce the number of fatty food products, (ii) eat smaller proportions more frequently during the day, (iii) remain in an upright position during and after the course of a meal, (iv) limit the intake of insoluble fibres, (v) stop smoking, although it should be noted that smoking itself triggers the gastrocolonic reflex and accelerates intestinal transit, (vi) screen for deficiencies, especially in patients with weight loss and malnutrition and use multivitamin and/or vitamin supplementation, when needed. In cases with severe weight loss or inadequate nutrient intake, enteral feeding through a nasoduodenal tube should be considered. This allows the time required to gain weight, to improve nutritional status and provide a recovery period for the distended stomach. After 4–6 weeks, the situation should be re-evaluated and in some cases, prolonged enteral nutrition is needed. In these patients, a direct access to the stomach but preferably to the jejunum (gastrostomy with duodenal extension or jejunostomy respectively) should be created.

Prokinetics

Metoclopramide and domperidone

Metoclopramide, a dopamine D2 receptor antagonist has been applied in the treatment of gastroparesis since the early 1970’s. Metoclopramide has both antiemetic and prokinetic properties. The antiemetic effect of metoclopramide is based on the blockade of dopamine D2 receptors in the area postrema, located outside the blood-brain barrier, and the vomiting centre. The prokinetic effect of metoclopramide is based on the blockade of dopamine D2 receptors in the area postrema, located outside the blood-brain barrier, and the vomiting centre.

The prokinetic effect of metoclopramide is based on the blockade of dopamine D2 receptors in the gastrointestinal tract. Dopamine is known to cause inhibition of motility throughout the gastrointestinal tract. It reduces gastric tone and intragastric pressure and decreases antral-duodenal coordination through activation of dopamine D2 receptors. Metoclopramide not only shows dopamine D2 receptor antagonist properties but also shows moderate 5-hydroxytryptamine-4 (5HT4) agonist and 5HT3 antagonist properties.

Domperidone, structurally related to butyrophenones, is also a dopamine D2 receptor antagonist. It has similar effects as metoclopramide; however, it does not cross the blood-brain barrier and thus has a slightly less antiemetic effect.

Both metoclopramide and domperidone may induce hyperprolactinaemia. Metoclopramide induces central nervous system effects (drowsiness, restlessness and fatigue) and extrapyramidal reactions, like Parkinsonism, acute dystonia, akathisia and tardive dyskenesia. These side-effects are believed to be more prevalent after a long-term use, although data are conflicting and incomplete.
Despite the widespread and increasing use of dopamine D2 receptor antagonists, in part because of the withdrawal of the 5HT4 agonist cisapride, most of the available trials (Table 1) have limitations. In two studies, the effects of domperidone and metoclopramide on gastric emptying and symptoms were similar, despite showing a less favourable side-effects profile for metoclopramide.57, 63

Erythromycin

Erythromycin is a motilin agonist that induces phase III MMC contractions.64 Erythromycin enhances gastric emptying, increases antral contractions and antrroduodenal coordination but reduces fundic volume and compliance in health and disease.65, 66

Erythromycin i.v. is primarily used in patients with upper gastrointestinal bleeding to evacuate blood clots and debris from the stomach rapidly before performing an endoscopy.67 Oral administration of erythromycin is the preferred route for chronic use in patients with gastroparesis. The liquid form of erythromycin may be of additional benefit in gastroparesis, as it does not need to be disintegrated in the stomach. Unfortunately, long-term use is limited because of its antibacterial effect and bacterial resistance, and occurrence of desensitization to the therapeutic prokinetic effect. Maganti et al.68 determined the efficacy of oral erythromycin in relieving symptoms attributable to gastroparesis in a systemic review. They identified 35 clinical trials evaluating erythromycin in gastroparesis. Only five of these trials included symptom assessment as a study endpoint. In these studies, sample sizes were small and follow-up was limited to 4 weeks. Although individual symptom scores were available only for 23 out of 60 patients, 11 (48%) showed a clinical response (improvement >25%). In a randomized, double-blind, placebo controlled trial, the motilin agonist ABT-229 was not efficacious in the relief of postprandial symptoms in diabetes mellitus.69 In another randomized, double-blind, placebo controlled trial, the motilin agonist KC-11458 improved neither gastric emptying, nor gastrointestinal symptoms in diabetic gastroparesis.70 Recently, Arts et al.31 studied the effect of erythromycin on gastric emptying and meal related symptoms in patients with functional dyspepsia and delayed gastric emptying. They found erythromycin to enhance gastric emptying; however, the effect of erythromycin on gastrointestinal symptoms was limited, as only bloating improved significantly. Erythromycin improves gastric emptying in gastroparesis; however, the effect on gastrointestinal symptoms remains controversial.

**Table 1. Overview of studies on the effect of metoclopramide on symptoms and gastric emptying in gastroparesis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Aetiology</th>
<th>n</th>
<th>Design</th>
<th>Dose</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkel et al.92</td>
<td>Mixed</td>
<td>28</td>
<td>RDBP</td>
<td>10 mg t.d.s.</td>
<td>3 weeks</td>
<td>Symptom reduction</td>
</tr>
<tr>
<td>Snape et al.?3</td>
<td>Diabetic</td>
<td>10</td>
<td>RDBP</td>
<td>10 mg</td>
<td></td>
<td>Symptom reduction</td>
</tr>
<tr>
<td>McCallum et al.94</td>
<td>Diabetic</td>
<td>40</td>
<td>DBP</td>
<td>10 mg q.d.s.</td>
<td>3 weeks</td>
<td>Symptom reduction</td>
</tr>
<tr>
<td>Schade et al.95</td>
<td>Diabetic</td>
<td>12</td>
<td>OL</td>
<td>10 mg t.d.s.</td>
<td>1 month</td>
<td>No effect</td>
</tr>
<tr>
<td>Ricci et al.96</td>
<td>Diabetic</td>
<td>13</td>
<td>RDBP</td>
<td>10 mg q.d.s.</td>
<td>3 weeks</td>
<td>Symptom reduction of 52.6%</td>
</tr>
<tr>
<td>De Caestecker et al.97</td>
<td>Diabetic</td>
<td>19</td>
<td>DBP</td>
<td>10 mg</td>
<td>8 weeks</td>
<td>GE improvement</td>
</tr>
<tr>
<td>Erbas et al.98</td>
<td>Diabetic</td>
<td>13</td>
<td>OL</td>
<td>10 mg t.d.s.</td>
<td>3 weeks</td>
<td>Symptom reduction</td>
</tr>
<tr>
<td>Patterson et al.57</td>
<td>Diabetic</td>
<td>45</td>
<td>RDB</td>
<td>10 mg q.d.s.</td>
<td>4 weeks</td>
<td>Symptom reduction of 38.9%</td>
</tr>
<tr>
<td>Dumitrascu et al.63</td>
<td>Diabetic</td>
<td>10</td>
<td>DB</td>
<td>10 mg t.d.s.</td>
<td>NA</td>
<td>GE improvement of 16%</td>
</tr>
</tbody>
</table>

DB, double blind; RDB, randomized double blind; RDBP, randomized double blind placebo controlled; OL, open label; NA, not applicable; GE, gastric emptying.

Botulinum toxin

Mearin et al.71 observed an increased prevalence of pyloric activity in diabetics. Pyloric dysmotility in...
Diabetic gastroparesis is manifested primarily by prolongation of periods of normal pyloric activity. In half of these patients, an unusually long and intense tonic pyloric activity was observed.

These results inspired Ezzeddine and others to study the effect of intrapyloric botulinum toxin injection in patients with severe diabetic gastroparesis (Table 2). In recent years, several open-label pilot studies have shown the effect of intrapyloric botulinum toxin injection in severe gastroparesis. In a recent article, Lacy et al. published their data and concluded intrapyloric botulinum toxin to be a possible addition in the treatment of mild-to-moderate diabetic gastroparesis. Miller et al. published their data on the effect of intrapyloric botulinum toxin injection in patients with severe idiopathic gastroparesis and concluded that intrapyloric injection of botulinum toxin accelerated gastric emptying and reduced symptoms of gastroparesis. Arts et al. showed improvement in gastric emptying for solids and symptom score after botulinum toxin injection, but did not show improvement in gastric emptying for liquids. The precise duration of the improvements of intrapyloric botulinum toxin injection on gastric emptying and symptoms is unknown, but previously mentioned open-label pilot studies have shown a duration of up to 6 weeks on gastric emptying and up to 8 weeks on symptoms. All authors acknowledged the need for a further evaluation of intrapyloric botulinum toxin injection in a double-blind, placebo-controlled design. Bromer et al. retrospectively studied the effect of open-label intrapyloric botulinum toxin injection in 63 patients with refractory gastroparesis. They observed a response rate of 43% in symptom improvement for a mean of 2 months. Data by Arts et al., currently published under the Online Accepted collection of this journal, on the effect of intrapyloric botulinum toxin injection in a randomized double-blind cross-over study in a mixed group of patients with gastroparesis are disappointing. They did not observe an additional effect of botulinum toxin injection compared to placebo injection, neither on symptoms nor on gastric emptying and concluded that further study in more specific groups, i.e. with pyloric dysfunction might be appropriate.

**Gastric pacing**

Gastric pacing or gastric electrical stimulation involves the implantation of electrodes in the smooth muscle layer of the gastric wall by laparotomy or laparoscopy. The electrodes are connected to a subcutaneously located device. The device is programmed to stimulate the smooth muscle layer electrically. Various electrical stimuli that differ in pulse width, amplitude and frequency are applied. Initial stimulation was targeted to mimic the physiological frequency of the gastric slow waves (three contractions per minute) observed during electrogastrography and consisted of long-pulse stimulation. Contrary to the long-pulse stimulation, short-pulse stimulation creates a frequency several times higher (12 cpm) than the regular gastric slow wave frequency. Short-pulse stimulation improved symptoms (in particular nausea and vomiting), reduced hospitalizations and improved quality of life in several open-label studies and

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<th>Outcome</th>
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<tbody>
<tr>
<td>Ezzeddine et al.</td>
<td>Diabetic</td>
<td>6</td>
<td>OL</td>
<td>100 IU</td>
<td>6 weeks</td>
<td>Symptom reduction of 55% GE improvement of 52%</td>
</tr>
<tr>
<td>Miller et al.</td>
<td>Idiopathic</td>
<td>10</td>
<td>OL</td>
<td>100 IU</td>
<td>4 weeks</td>
<td>Symptom reduction of 38% GE improvement of 48%</td>
</tr>
<tr>
<td>Lacy et al.</td>
<td>Diabetic</td>
<td>8</td>
<td>OL</td>
<td>200 IU</td>
<td>12 weeks</td>
<td>Symptom reduction of 55% GE improvement of 33%</td>
</tr>
<tr>
<td>Bromer et al.</td>
<td>Mixed</td>
<td>63</td>
<td>OL</td>
<td>200 IU</td>
<td></td>
<td>Symptom reduction in 43% for 2 months</td>
</tr>
<tr>
<td>Arts et al.</td>
<td>Mixed</td>
<td>20</td>
<td>OL</td>
<td>100 IU</td>
<td>1 month</td>
<td>Symptom reduction of 29% GE improvement of 35%</td>
</tr>
</tbody>
</table>

OL, open label; GE, gastric emptying.
one controlled cross-over study,\textsuperscript{89} and had in most studies no effect on gastric emptying. Long-pulse stimulation improved gastric emptying and symptoms in a single open-label study,\textsuperscript{90} although the effect on symptoms has been debated.\textsuperscript{80} Further research is needed to determine the best stimulation algorithm and the mechanisms responsible for clinical improvement in patients. These improvements might be due to central effects.

CONCLUSIONS

The revised Rome III criteria for functional dyspepsia\textsuperscript{91} raise the question whether or not idiopathic gastroparesis should be regarded as a separate clinical diagnosis, as functional dyspepsia type A (postprandial distress syndrome) shows remarkable similarities with idiopathic gastroparesis in symptoms and signs. Moreover, labelling patients with idiopathic gastroparesis as functional dyspepsia will separate this subgroup of patients with functional delayed gastric emptying from those with a well defined aetiology, like gastroparesis caused by diabetes mellitus or other systemic disorders.

When suspected, delayed gastric emptying should be quantified, preferably by scintigraphy or stable isotope breath tests. In all cases, mechanical obstruction should be excluded (endoscopy).

Although current treatment options for gastroparesis are limited, most patients with mild disease will respond to dietary and life style measures and prokinetics such as domperidone, metoclopramide and erythromycin. In patients with gastroparesis that do not respond to standard treatment options, additional investigations may be required. With manometry, antral and duodenal motor function can be evaluated in more detail. High Resolution Manometry might be a tool for further study, as it potentially provides detailed information concerning not only antral and duodenal function but also pyloric function. These methods may help differentiate those patients who might benefit from, intrapyloric botulinum toxin injection, gastric pacing or more radical surgical interventions, such as partial or total gastrectomy.

SUPPLEMENTARY MATERIAL

A video clip is available in association with Fig. 1 of this article. This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1365-2036.2007.03534.x (This link will take you to the article abstract).

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REFERENCES

11 Sodhi SS, Guo JP, Maurer AH, O’Brien G, Srinivasan R, Parkman HP. Gastro-


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Bibliography:


81 Familoni BO, Abell TL, Bhaskar SK, Voeller GR, Blair SR. Gastric electrical stimulation has an immediate antiemetic effect in patients with gastroparesis. Gastrointest Endosc 2002; 56: 1038–46.
