GASTRIC MOTILITY:
Measurement, symptoms and therapy

Jari Punkkinen

Academic Dissertation
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# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>CRF</td>
<td>chronic renal failure</td>
</tr>
<tr>
<td>EGG</td>
<td>electrogastrography</td>
</tr>
<tr>
<td>EIU</td>
<td>enzyme immune unit</td>
</tr>
<tr>
<td>FD</td>
<td>functional dyspepsia</td>
</tr>
<tr>
<td>GES</td>
<td>gastric electrical stimulation</td>
</tr>
<tr>
<td>HbA₁c</td>
<td>glycosylated haemoglobin A</td>
</tr>
<tr>
<td>In</td>
<td>indium</td>
</tr>
<tr>
<td>MBq</td>
<td>megabecquerel</td>
</tr>
<tr>
<td>mSv</td>
<td>millisievert</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OBT</td>
<td>$^{13}$C-octanoic acid breath test</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>gastric half-emptying time</td>
</tr>
<tr>
<td>Tc</td>
<td>technetium</td>
</tr>
<tr>
<td>$T_{\text{lag}}$</td>
<td>lagtime</td>
</tr>
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</table>
ABSTRACT

Background: Gastric motility disorders, including delayed gastric emptying and gastric myoelectrical disorders, can be related to chronic renal failure, functional dyspepsia (FD), and type 1 diabetes. Scintigraphy is the gold standard in measuring gastric emptying, but it is expensive, requires specific equipment, and exposes patients to radiation. The $^{13}$C-octanoic acid breath test (OBT) is an alternative, indirect method of measuring gastric emptying with a stable isotope. Electrogastrography (EGG) registers the slow wave originating in the pacemaker area of the stomach and regulating the peristaltic contractions of the antrum. This study compares these three methods of measuring gastric motility in patients with type 1 diabetes, functional dyspepsia, and chronic renal failure. Currently no effective drugs for treating gastric motility disorders are available. We studied the effect of nizatidine on gastric emptying, because in preliminary studies this drug has proven to have a prokinetic effect due to its cholinergic properties.

Materials and methods: Patients (n = 23) with chronic renal failure (CRF) on peritoneal dialysis and healthy controls (n = 20) were examined by EGG to investigate the effect of peritoneal dialysis on gastric myoelectrical activity. Patients (n = 21) with functional dyspepsia, all with dyspeptic symptoms but negative findings in gastroscopy and upper abdominal ultrasound, were examined with both dynamic dual tracer scintigraphy and OBT to evaluate the correlation between these methods. Of these 21 patients with FD, 16 were examined in a randomized, double-blinded cross-over study by scintigraphy during treatment with nizatidine or placebo to evaluate the effect of nizatidine on gastric emptying, upper abdominal symptoms, and quality of life. Patients with type 1 diabetes (n = 27) and upper abdominal symptoms but negative findings in gastroscopy and upper abdominal ultrasound were examined both by dynamic, dual-tracer scintigraphy and by simultaneous OBT and EGG. Upper abdominal symptoms and quality of life were evaluated by validated questionnaires, and autonomic neuropathy was evaluated by standard cardiovascular tests. Plasma glucose levels were measured during the gastric emptying studies. Healthy controls (n = 15) were examined with simultaneous OBT and EGG for comparison.

Results: No significant difference appeared in the frequency of the gastric slow waves measured by EGG in the uremic patients and controls. The postprandial power of the slow wave was higher on peritoneal dialysis than for the patients with their peritoneal cavity empty of dialysis fluid (P < 0.05). The correlation between scintigraphy and OBT in FD patients was poor (r = -0.26). Nizatidine improved symptom scores and quality of life in the 16 FD patients evaluated, but not significantly. When measured by scintigraphy and compared to placebo, nizatidine delayed the gastric emptying of solids significantly (P < 0.05). Of the 27 patients with type 1 diabetes, 7 (26%) had delayed gastric emptying of solids and 3 (11%) of liquids as measured by scintigraphy. The percentage of solids in the antrum at 10 min was abnormally high in 10 (37%) patients, indicating impaired fundic relaxation. The autonomic neuropathy score correlated positively with the gastric emptying rate of solids (P = 0.006), but HbA$_{1C}$, plasma glucose levels, or abdominal
symptoms were unrelated to gastric emptying or intragastric distribution of the test meal. When compared to scintigraphy, OBT detected 3 (43%) and EGG 2 (29%) of the 7 patients with delayed gastric emptying of solids, but combined EGG and OBT detected 4 (57%) of these patients. Specificity was 80% each for OBT and EGG but 60% for combined OBT and EGG. Correlation between scintigraphy and OBT was poor in patients with type 1 diabetes, r = 0.16.

**Conclusions:** Dynamic dual-tracer scintigraphy is more accurate than OBT or EGG in measuring gastric emptying of solids. Additionally it provides information about gastric emptying of liquids and the intragastric distribution of the ingested test meal. Combined OBT and EGG detects more patients with delayed gastric emptying of solids than does either of the tests alone, but sensitivity and specificity remain low. Delayed gastric emptying of solids and impaired gastric accommodation are common in patients with type 1 diabetes and upper abdominal symptoms. Autonomic neuropathy is related to impaired gastric emptying of solids in these patients. Instead of enhancing, nizatidine slows gastric emptying in patients with functional dyspepsia. The non-significant improvement in symptom and quality of life scores observed in these patients may be due to acid suppression rather than to any effect on gastric emptying.
1. INTRODUCTION

Gastric motility disorders consist of various motility disturbances of the stomach, including impaired reservoir function of the proximal stomach, delayed postprandial gastric emptying, disorders of gastric myoelectrical activity that regulate the gastric contractions, and disorders of the interdigestive pattern (Smout and Akkermans 1992). Gastric motility disorders can be idiopathic, be due to postsurgical states like vagotomy, or be related to diseases like functional dyspepsia, type 1 diabetes, or chronic renal failure.

Gastric motility disorders are relatively common. In Finnish primary care patients, about 43% of all dyspepsia is functional (Heikkinen et al 1995). Of patients with functional dyspepsia (FD), 30% have delayed gastric emptying, 40% impaired gastric accommodation, and 37% hypersensitivity to gastric distention (Tack and Lee 2005). Diabetic gastroparesis with delayed gastric emptying occurs in 30 to 50% of both type 1 and type 2 diabetes at tertiary centers (Kong et al 1999, Jones et al 2001, De Block et al 2002). Delayed gastric emptying occurs in some 36% of patients with CRF (Strid et al 2004).

Although gastric motility disorders are common, diagnosing and treating them is difficult. Scintigraphy is the gold standard in measuring gastric emptying, but it is expensive, requires specific equipment, and exposes patients to radiation (Mariani et al 2004). Dynamic dual-tracer scintigraphy at Helsinki University Central Hospital costs about 425 euros and involves an effective dose of radiation of 5 mSv, comparable to that of colonography. The $^{13}$C-octanoic acid breath test (OBT) is an alternative, indirect method of measuring gastric emptying with a stable isotope (Delbende et al 2000). Electrogastrography (EGG) registers the slow wave originating in the pacemaker area of the stomach regulating the peristaltic contractions of the antrum (Parkman et al 2003). This study compares these three methods of measuring gastric motility.

Currently no effective drugs for treating gastric motility disorders are available. We studied the effect of nizatidine on gastric emptying, as preliminary studies on this drug have demonstrated a prokinetic effect due to its cholinergic properties (Harasawa and Miwal 1993, Memis et al 2002, Tomokane et al 2004).
2. REVIEW OF THE LITERATURE

2.1. Diseases associated with delayed gastric emptying

2.1.1 Diabetic gastroparesis

Gastroparesis is a state characterized by delayed gastric emptying, resulting in upper abdominal stasis symptoms in the absence of mechanical obstruction (Camilleri 2007). Any disease that results in neuromuscular dysfunction of the gastrointestinal tract, including diabetes, may cause gastroparesis (Hornbuckle and Barnett 2000).

For patients with both type 1 and type 2 diabetes at specialized centers, delayed gastric emptying due to diabetic gastroparesis is detected in 30 to 50% (Kong et al 1999, Jones et al 2001, De Block et al 2002). The prevalence of diabetic gastroparesis in the general population is unclear, but both type 1 and type 2 onset diabetes are associated with increased prevalence of abdominal symptoms, psychological distress, and decreased quality of life in population-based studies (Bytzer et al 2001, Talley et al 2001a, 2001b). Though upper abdominal symptoms, and impaired quality of life are often related to diabetic gastroparesis, it may also appear without symptoms and the correlation between symptoms and gastroparesis is poor (Horowitz et al 1989, Jebbink et al 1993, Novak et al 1995, Farup et al 1998). Asymptomatic diabetic gastroparesis may manifest solely as a disturbance of glucose control, because slow gastric emptying reduces the postprandial glucose peak and the need for insulin (Ishii et al 1994, Schwartz et al 1994).

Autonomic neuropathy has been suggested as an etiological factor for diabetic gastroparesis. In case-controlled studies, delayed gastric emptying has been more common in diabetic patients with autonomic neuropathy than in those without (Keshavarzian et al 1987, Hongo and Okuno 1993). In two studies including 45 and 34 diabetic patients, autonomic neuropathy measured with standard cardiovascular tests was correlated with delayed gastric emptying (Ziegler et al 1996, Merio et al 1997), whereas two studies including 101 and 42 patients failed to detect any relation (Jones et al 2001, De Block et al 2002). Though histopathological abnormalities can be found in other types of diabetic neuropathy, no morphological abnormalities have emerged in the vagus nerve in diabetic patients with gastroparesis (Yoshida et al 1988).

Changes in plasma glucose levels clearly affect gastric emptying rate in type 1 diabetic patients, as hyperglycaemia slows and hypoglycaemia accelerates gastric emptying in these patients, yet these effects are reversible (Fraser et al 1990, Schwarcz et al 1993, 1997, Samsom et al 1997, Rayner et al 2001, Russo et al 2005). High mean glucose concentrations during gastric emptying studies have correlated with delayed gastric emptying rate of solids in diabetic patients (Jones et al 2001); however, not all studies find this correlation (Ziegler et al 1996, Lyrenas et al 1997, Merio et al 1997, De Block et al 2002). Long-term glucose control measured as HbA1C correlated with gastric emptying of solids but not of liquids in the study of 42 diabetic patients mentioned (De Block et al...
2002) and to gastric emptying of a semisolid meal in the study of 40 children with type 1 diabetes (Cucchiara et al 1998), but other studies found no such correlation (Ziegler et al 1996, Merio et al 1997).

Signs of dysfunction of the enteric nervous system, like depletion of neuronal nitric oxide synthase (Takahashi et al 1997, Wrosz et al 1997) and reduction of interstitial cells of Cajal (Ordog 2008) have appeared in diabetic rats in connection with delayed gastric emptying. Thus, the pathophysiological mechanisms causing diabetic gastroparesis may lie within the enteric nervous system rather than in the autonomic nervous system. Gastric autoimmunity, evaluated by measuring parietal cell antibodies and gastrin levels, seems to have no effect on gastric emptying in diabetic patients (De Block et al 2002).

### 2.1.2 Functional dyspepsia

The prevalence of dyspepsia, which can be defined as discomfort or pain in the upper abdomen, is between 15% and 25% in the general population (Agreus et al 1994, Agreus 2002, Talley et al 1992). Functional dyspepsia is a heterogenous disorder defined as constant or recurrent upper abdominal pain or discomfort in the absence of organic disease but often linked to a motility disorder (Talley et al 1999a). FD prevalence has been 12 to 15% in endoscope studies (El-Serag and Talley 2004). In Finnish primary care patients, 43% of dyspepsia appeared to be functional (Heikkinen et al 1995). Excluding the 10% of patients with reflux disease in this study would have resulted in an even higher FD prevalence.

Several classifications of FD have been created for clinical and scientific purposes. Subgrouping has been suggested into reflux-like dyspepsia (heartburn, regurgitation), ulcer-like dyspepsia (epigastric pain), dysmotility-like dyspepsia (nausea, vomiting, early satiety), and nonspecific dyspepsia (Talley 1991), but the usefulness of this subclassification based on symptoms has received criticism (Talley 1993). Detailed criteria (Rome III criteria) for subtypes of FD mainly for scientific purposes have been created based on predominant symptoms (Tack et al 2006). According to these criteria, functional gastroduodenal disorders are classified into FD, belching disorders, functional nausea and vomiting disorders, and the rumination syndrome. FD is further subdivided into postprandial distress syndrome and epigastric pain syndrome.

FD can also be divided into subgroups according to its pathophysiological mechanisms. One meta-analysis of 17 studies showed delayed gastric emptying in 40% of patients (Quartero et al 1998), but in more recent studies prevalence of delayed gastric emptying has been somewhat lower (Talley et al 2001c, Sarnelli et al 2003). In some patients with FD, when examined by scintigraphy or ultrasound, the food in the stomach is abnormally distributed, with accumulation in the distal stomach rather than in the fundus defined as impaired gastric accommodation (Troncon et al 1994, Gilja et al 1996). A proportion of patients with FD have increased sensitivity to distention of the proximal stomach with a balloon; this is defined as visceral hypersensitivity (Tack et al 2001). According to a recent review, in patients with FD, delayed gastric emptying occurs in
about 30%, impaired gastric accommodation in 40%, and hypersensitivity to gastric distention in 37% (Tack and Lee 2005).

The role of *Helicobacter pylori* in functional dyspepsia has been evaluated in many studies. Based on present knowledge, the effect of *Helicobacter pylori* eradication on symptoms is still controversial (Blum et al 1998, Talley et al 1999b,c, Koskenpato et al 2000, Malfertheiner et al 2003). *Helicobacter pylori* does not influence the gastric emptying rate (Koskenpato et al 1998, 2000). However, *Helicobacter pylori* treatment and prokinetic therapy seem to alleviate FD symptoms equally (Ang et al 2006).

### 2.1.3 Chronic renal failure

Upper abdominal symptoms such as nausea, vomiting, abdominal distention, early satiety and anorexia, and impairment of nutritional status and weight loss are often associated with chronic renal failure (CRF), but the mechanisms are unclear. Delayed gastric emptying is often observed in patients with CRF, but no relation to symptoms is evident. Delayed gastric emptying occurred in 14 (36%) of 39 CRF patients, in both predialytic patients and those on peritoneal dialysis when studied by radiopaque markers and fluoroscopy (Strid et al 2004). In a Chinese study of both dialysed and undialysed CRF patients, of 40, 35 (88%) had delayed gastric emptying in scintigraphy compared to healthy controls (Kao et al 1996). In another scintigraphic study, gastric emptying was significantly slower both in haemodialysis and peritoneal dialysis patients than in healthy controls (Guz et al 2004). Gastric emptying was significantly delayed in 56 haemodialysed CRF patients when measured by scintigraphy and compared to the normal reference population (De Schoenmakere et al 2001).

According to some studies, dyspeptic symptoms associated with CRF may be related to delayed gastric emptying. Gastric emptying was significantly slower in dyspeptic haemodialysis patients than in both healthy volunteers and nondyspeptic patients when measured by the $^{13}$C-octanoic acid breath test (Van Vlem et al 2000). In a study of 62 nondialysed CFR patients, the prevalence of dyspepsia was high, 48%, and the gastric emptying of these patients was significantly slower than in the 27 healthy controls (Van Vlem et al 2001). In a study of 21 CRF patients, those with delayed gastric emptying had significantly higher gastrointestinal symptom scores than did those with normal gastric emptying (Hirako et al 2005). Haemodialysis may improve gastric emptying and reduce dyspeptic symptoms in CRF patients (Adachi et al 2007). However, not all studies of CFR patients find a correlation between dyspeptic symptoms and delayed gastric emptying (Strid et al 2004).

The relation between CRF and delayed gastric emptying has been suggested to be due to availability of nitric oxide. Chronic renal failure is associated with decreased production and availability of nitric oxide (Vaziri 2001), which is essential for normal pyloric relaxation and gastric emptying (Tougas et al 1992).
2.2. Methods for measuring gastric motility

2.2.1 Scintigraphy

Scintigraphy is widely considered the gold standard in measuring gastric emptying (Mariani et al 2004). Solids and liquids empty from the stomach by different mechanisms: emptying of solids is linear and depends on antral contractions; emptying of liquids is exponential and depends on fundic tone (Collins et al 1991). A short lag phase precedes the onset of gastric emptying of solids (Christian et al 1991). It is possible to record gastric emptying of solids and liquids simultaneously by use of separate solid and liquid markers. Conventionally, $^{99m}$Tc serves as a solid marker and $^{111}$In-DTPA as a liquid marker (Mariani et al 2004).

Continuous data from scintigraphic scans every 30 to 60 seconds for a total follow-up time of 90 minutes is generally recommended when measuring gastric emptying (Donohoe et al 1999). A longer 2- to 3-hour follow-up time is needed for test-meals of larger volume or higher calorie-, fat-, carbohydrate- and protein-content (Donohoe et al 1999). Extending study length to 4 hours may be necessary to detect delayed gastric emptying in borderline cases (Guo et al 2001). Some investigators oppose 4-hour studies as unnecessarily long and consider follow-up of 90 minutes sufficient to obtain reliable information on gastric emptying of solids, since it is linear (Ziessman et al 2004). An alternative approach is to record data at longer intervals of 15 minutes or only once an hour. However, with this technique it is impossible to record rapid gastric emptying, gastric emptying of liquids, the lag-time before onset of emptying of solids and liquids, or intragastric distribution of the test meal. Solid gastric emptying can be equally well measured by two scintigraphic scans at 0 and 120 minutes instead of continuous data (Halkar et al 1999).

International control values in healthy controls for gastric emptying of solids by scintigraphic scans only at 1 hour, 2 hours, and 4 hours have been established (Tougas et al 2000), but their data are not normally distributed, so the median and $90^{th}$ or $95^{th}$ percentiles are used to determine the normal range rather than mean and standard deviation (Table 1). This method is also recommended by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine for measuring gastric emptying of solids (Abell et al 2008).

Conventionally, gastric half-emptying times from the scintigraphic data have been calculated by fitting the Elashoff power exponential function (Elashoff et al 1982) or modified power exponential function (Siegel et al 1988) to the gastric emptying curve. Estimation of gastric half-emptying time using a linear fit, which combines the lag phase and the rate of emptying into a single value, has been shown to correlate well with gastric half-emptying times calculated using the traditional exponential fit (Ziessman et al 2004).

At Helsinki University Central Hospital, a standardized, dynamic, scintigraphic double-tracer method with a follow-up time of 90 minutes has been described for measuring gastric half-emptying times for solids and liquids and intragastric distribution. This method has been validated in healthy subjects and in patients with functional dyspepsia in different clinical settings (Kairemo et al 1998, Koskenpato et al 1998, 2000).
and has proven well reproducible in a one-year follow-up (Koskenpato et al 2000). Scintigraphic results of healthy controls of the validation study appear in Table 2.

**Table 1.** International control values for gastric emptying of solids measured by scintigraphy (n= 123) by Tougas et al 2000.

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>90&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>95&lt;sup&gt;th&lt;/sup&gt; percentile</th>
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<tr>
<td>Retention (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hr</td>
<td>69</td>
<td>86</td>
<td>90</td>
</tr>
<tr>
<td>2 hr</td>
<td>24</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>4 hr</td>
<td>1.2</td>
<td>6.3</td>
<td>10</td>
</tr>
<tr>
<td>T ½ (min)</td>
<td>83</td>
<td>117</td>
<td>132</td>
</tr>
<tr>
<td>Lag phase (min)</td>
<td>21</td>
<td>44</td>
<td>49</td>
</tr>
</tbody>
</table>

**Table 2.** Control values of dynamic double-tracer scintigraphy of the validation study (n= 11) at Helsinki University Central Hospital by Kairemo et al 1998.

<table>
<thead>
<tr>
<th></th>
<th>Liquid</th>
<th>Solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying (min)</td>
<td>36.2 ± 10.4</td>
<td>76.4 ± 29.4</td>
</tr>
<tr>
<td>Intragastric distribution (% in antrum)</td>
<td>8.0 ± 2.2</td>
<td>5.2 ± 2.3</td>
</tr>
<tr>
<td>Lag phase (min)</td>
<td>2.5 ± 3.1</td>
<td></td>
</tr>
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</table>
2.2.2 $^{13}$C-octanoic acid breath test

OBT is an indirect method of measuring gastric emptying of solids with a stable isotope (Perri et al 2005). After $^{13}$C-octanoate acid from the test meal is absorbed in the duodenum, it is oxidized in the liver, and $^{13}$CO$_2$ is formed (Lacroix et al 1973, Bach and Babayan 1982). Half of the $^{13}$C-octanoate acid remains in the tricarboxylic acid cycle (Van Hall 1999). After passage through the bicarbonate pool, $^{13}$CO$_2$ is exhaled. Passage through the pylorus is considered the rate-limiting step of the process. The breath samples collected can be easily transported elsewhere for analysis by mass spectrometry.

Measuring the percentage of $^{13}$CO$_2$ in the breath test samples results in a bell-shaped curve. After mathematical processing, data can also be expressed as cumulative percentage of dose over time. Gastric half emptying times for solids can be calculated by applying the nonlinear least-squares fitting on the cumulative breath test curve (Ghoos et al 1993, Lee J et al 2000, Chey et al 2001, Bromer et al 2002). The gastric half-emptying time obtained from OBT is longer than the one from scintigraphy, the difference being 66 min in the original study (Ghoos et al 1993). When OBT is extended from 4 to 6 or 8 hours, the gastric half-emptying time is reduced (Bromer et al 2002, Lee J et al 2000, Choi et al 1997). Thus the gastric half-emptying time measured by OBT must be understood to be a calculated mathematical parameter rather than an absolute measurement of the gastric half-emptying time.

The $^{13}$C-octanoic acid breath test (OBT) seems to measure gastric emptying of solids reliably as compared to scintigraphy when these tests are performed simultaneously (Ghoos et al 1993, Lee J et al 2000, Chey et al 2001, Bromer et al 2002, Zahn et al 2003). Not all studies find a good correlation between scintigraphy and OBT, although OBT is considered reproducible and suitable for intraindividual comparison (Choi et al 1997, 1998).

In a European multicenter study of 69 healthy subjects and 54 patients with dyspeptic symptoms, OBT detected delayed gastric emptying of solids with a sensitivity of 67% and specificity of 80% in relation to scintigraphy. The cut-off value for normal scintigraphy was chosen as the 90th percentile of the half-emptying time of healthy subjects (109 min). To determine the best discriminative threshold for OBT, a receiver operating characteristics analysis was performed based on results of simultaneous scintigraphy and OBT. The corresponding cut-off value obtained for the normal gastric half-emptying time of OBT was 124 min. Despite the good correlation, the authors conclude that OBT might be insufficiently accurate to detect delayed gastric emptying in an individual patient (Delbende et al 2000). Because of the processing of $^{13}$C-octanoate acid, it is possible that no true linear correlation exists between the gastric half-emptying time measured by scintigraphy and the one calculated from OBT (Jackson and Bluck 2005).

2.2.3 Electrogastrography

Electrogastrography (EGG) is a method of measuring the gastric slow waves that control gastric emptying by cutaneous electrodes placed on the abdominal skin (Parkman et al
2003, Chang 2005). According to many studies, the gastric slow wave originating in the pacemaker area of the stomach can be measured accurately with cutaneous electrodes when compared to results from serosal electrodes in the stomach (Smout et al 1980, Hamilton et al 1986, Familoni et al 1991, Chen et al 1994a). Spike potentials evoked by neurohumoral stimuli and associated with antral contractions can be detected by EGG as an increase in the power of the gastric slow waves (Chen et al 1994b, Chen and McCallum 1993, 1994). This increase may not be due solely to gastric contractions but also to gastric distention after a meal (Minchev et al 1993). Sham feeding has been shown also to increase the power of the gastric slow waves (Stern et al 1989, Chen et al 1996a).

Specialized software for EGG analysis is essential. The raw EGG signal is transformed from analogue to digital, data are processed to abolish motion and respiratory artefacts, signal analysis is performed with fast Fourier transformation, and results are displayed as running spectral analysis (Parkman et al 2003, Chang 2005). In running spectral analysis, the recording period is usually divided into 2-min strips, and each consecutive recording strip is displayed three-dimensionally, frequency versus power peaks as a function of time.

EGG is considered normal when 2.0- to 3.7-cpm gastric slow waves can be detected for at least 70% of the preprandial and postprandial recording time, and the power ratio (defined as the ratio of postprandial to fasting slow waves power) is greater than one, according to the consensus opinion of the American Motility Society Clinical GI Motility Testing Task Force (Parkman et al 2003) and based on a meta-analysis of four studies (Chen and McCallum 1992, Pfaffenbach et al 1995a, Parkman et al 1996, Lin et al 1999). Lack of normal 2.0 to 3.7 cpm gastric slow waves, abnormally rapid waves defined as tachygastria, and a low power ratio have been associated with delayed gastric emptying measured by conventional methods like scintigraphy or antroduodenal manometry (Koch et al 1989, Chen and McCallum, Chen et al 1996b, Pfaffenbach et al 1997, Hoogewerf et al 1999). According to the meta-analysis of these four studies, the positive predictive value of abnormal EGG to predict delayed gastric emptying is 65% and the negative predictive value of a normal EGG, 76% (Parkman et al 2003).

### 2.2.4 Other tests for measuring gastric emptying

Measuring gastric emptying is possible with a variety of tests not evaluated in our study (Table 3). Gastroscopy must be performed in all patients to exclude gastric outlet obstruction. Food retained in the stomach after a 12-hour fast strongly suggests delayed gastric emptying (Camilleri 2007). Direct tests include intubation and aspiration of a standard volume of fluid through a nasogastric tube, use of a test meal with radiopaque markers and x-ray follow-up, real-time ultrasonography, magnetic resonance imaging, and applied potential tomography; indirect tests include acetaminophen and paracetamol absorption tests and antroduodenal manometry (Hornbuckle and Barnett 2000). Furthermore, $^{13}$C-acetate can be used as a solid marker in the breath test, and some studies detect a good correlation with scintigraphy (Sanaka et al 2004, 2006). In a study comparing scintigraphy, a paracetamol absorption test, and a $^{13}$C-acetate breath test, a correlation appeared only between the paracetamol absorption test and scintigraphy.
(Glerup et al 2007). $^{13}$C-glycine can serve as a marker of the liquid component and the $^{13}$C-glycine breath test and $^{13}$C-octanoic or $^{14}$C-octanoic acid breath test can be performed simultaneously for assessment of both solid and liquid emptying (Maes et al 1994, DeBlock et al 2002).

SmartPill® is a wireless capsule that records luminal pH and temperature and registers pressure changes related to gastric contractions; it was approved by the US Food and Drug Administration in 2006. When the capsule leaves the stomach, it perceives a rapid, sustained pH increase. A study of 15 healthy controls by antroduodenal manometry reveals that SmartPill® primarily empties from the stomach with the return of the phase III migrating motor complex (Cassilly et al 2008a). In a study of 61 gastroparetics and 87 healthy controls, the correlation between gastric emptying times measured by scintigraphy and SmartPill® were 0.73 for 4-hour and 0.63 for 2-hour follow-up times in scintigraphy (Kuo et al 2008).

The Gastroparesis Cardinal Symptom Index, based on scores of post-prandial fullness/early satiety, nausea/vomiting, and bloating, has proven a reliable and valid means of measuring symptom severity in gastroparesis patients (Revič et al 2003, 2004). However, in a study of 269 patients, this index did not identify the patients with delayed gastric emptying in scintigraphy (Cassilly et al 2008b).

### Table 3. Tests for measuring gastric motility. (Based on a review by Hornbuckle and Barnett, 2000, and original articles cited in the text.)

<table>
<thead>
<tr>
<th>Direct tests</th>
<th>Indirect tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scintigraphy</td>
<td>$^{13}$C- and $^{14}$C-octanoic acid breath tests</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
<td>$^{13}$C-acetate breath test</td>
</tr>
<tr>
<td>Radiopaque markers and x-ray follow-up</td>
<td>$^{13}$C-glycine breath test</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Electrogastrography</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Paracetamol absorption test</td>
</tr>
<tr>
<td>Applied potential tomography</td>
<td>Antroduodenal manometry</td>
</tr>
<tr>
<td></td>
<td>Radiotelemetry capsule (SmartPill®)</td>
</tr>
</tbody>
</table>
2.3 Treatment of delayed gastric emptying

2.3.1 Dietary therapy

Guidelines for treatment of gastroparesis have been described in several reviews (Horowitz et al 2001, Rabine and Barnett 2003, Smith and Ferris 2003, Camilleri 2007). Treatment of all types of gastroparesis is similar irrespective of etiology: diabetic, idiopathic or postsurgical. Patients with gastroparesis should eat frequently, meaning four to six small meals per day with low fibre and lipid content, homogenized solids, and increased nutrient liquids. Foods rich in fibre content may lead to bezoar formation, and lipids slow gastric emptying. Because hyperglycemia also slows gastric emptying, aiming at an optimal glucose balance is essential in treatment of diabetic gastroparesis. Not only food composition but particle size influences the gastric emptying rate. The lag phase was shorter and gastric emptying more rapid after a small-particle meal compared to a large-particle meal in a scintigraphic study of diabetic patients and controls (Olausson et al 2008). The nutritionist should always be consulted when one is treating patients with gastroparesis.

2.3.2 Prokinetic therapy

Despite extensive research, no ideal drug for treatment of gastroparesis exists. The ideal drug would alleviate dyspeptic symptoms related to gastroparesis, enhance gastric emptying, and have few or no side-effects. Based on a systematic search of the literature, erythromycin had the strongest effect on gastric emptying and was also the most effective in reducing symptoms when compared to domperidone, metoclopramide, or cisapride, but no association emerged between improvement of gastric emptying and symptoms (Sturm et al 1999). The few available randomized, controlled studies of prokinetics in treatment of gastroparesis have produced mixed results: At best, symptom reduction occurs in about 36 to 42% of patients (Talley 2003).

Some H2-receptor antagonists show an effect on gastric emptying, an effect that is not uniform, as it is related not to H2-antagonism but to cholinergic properties (Ueki et al 1993, Kaneko et al 1995, Parkman et al 1998a, Ueki et al 1999). In a study using guinea pig antral muscle strips, nizatidine and ranitidine led to an increased amplitude of spontaneous phasic antral contractions, but famotidine and cimetidine lacked any effect (Parkman et al 1998a). In a study in healthy men consuming a radiolabelled liquid and solid test meal, ranitidine accelerated gastric emptying of liquids but had no significant effect on gastric emptying of solids (Houghton and Read 1987). In another study in healthy subjects, both ranitidine and famotidine led to enhanced antral contractions measured by manometry but instead of enhancing, caused a delay in gastric emptying of solids, as measured by scintigraphy (Parkman et al 1998b). When measured by the acetaminophen method, nizatidine enhances gastric emptying of liquids in patients with
gastric or duodenal ulcer (Harasawa and Miwa 1993). Nizatidine also reduces gastric volume when administered one hour prior to surgery, as measured by suction through a nasogastric tube (Memis et al 2002). In diabetic patients, nizatidine elevates postprandial EGG peak power, which may indicate promotion of gastric emptying (Tomokane et al 2004).

In patients with diabetic and idiopathic gastroparesis, both intravenous and oral erythromycin improves gastric emptying by stimulating motilin receptors (Janssens et al 1990, Richards et al 1993). Although erythromycin is an effective prokinetic drug, it may cause abdominal symptoms (Saloranta et al 1989), and tachyphylaxis may occur in long-term treatment (Hasler 1999). Erythromycin show similar activity to that of class IA antiarrhythmic drugs and may cause QT prolongation and torsades de pointes, especially when used intravenously (Orban et al 1995). Ghrelin is structurally related to motilin and has been shown to accelerate gastric emptying in diabetic patients (Murray et al 2005) besides playing a role in regulating appetite and body weight. The motilin receptor agonist ABT-229, although prokinetic, has failed to improve symptoms in diabetic patients with normal or delayed gastric emptying (Talley et al 2001b). Mitemcinal has proven prokinetic in patients with idiopathic and diabetic gastroparesis but was only slightly superior to placebo in reducing symptoms (McCallum et al 2007a,b). In healthy volunteers, atilmotin raises the gastric pressure, which may enhance gastric emptying (Korimilli et al 2007).

Dopamine antagonists like metoclopramide (McCallum et al 1983, Ricci et al 1985, Schade et al 1985,) and domperidone (Koch et al 1989, Prakash et al 1998) have both a prokinetic and an antiemetic effect in diabetic gastroparesis. Both are equally effective in reducing symptoms, but metoclopramide causes more central nervous system side-effects (Patterson et al 1999). Common central nervous system side-effects associated with metoclopramide are dystonic reactions, extrapyramidal symptoms, and tardive dyskinesia (Ganzini et al 1993). Domperidone does not cross the blood-brain barrier, and its neurological side-effects are rare, but it may cause hyperprolactinaemia (Prakash et al 1998). Another dopamine agonist, sulpiride, is superior to placebo in treating nausea and vomiting in patients with gastroparesis (Mansi et al 2000). Itopride tends to accelerate gastric emptying of solids and liquids in longstanding diabetes, but its effect is modest (Stevens et al 2008).

The 5HT4 agonist cisapride has proven to accelerate gastric emptying and relieve dyspeptic symptoms in diabetic gastroparesis (Horowitz et al 1987, Horowitz and Roberts 1990, Dworkin et al 1994, Horowitz et al 2002). Cisapride was, however, withdrawn from the market because of serious cardiac side-effects. Another 5HT4 agonist, tegaserod, has proven to accelerate gastric emptying in healthy subjects (Degen et al 2005), but no studies on gastroparesis have appeared. Mosapride enhances the gastric emptying of indigestible solids and improves glycaemic control in diabetic patients (Asakawa et al 2003).
2.3.3 Antiemetic therapy

As mentioned, some of the prokinetic drugs also have antiemetic effects. Patients with severe symptoms may, however, need additional antiemetic treatment. Phenothiazine derivatives like promethazine and prochlorperazine act by antagonizing dopamine receptors similar to the action of metoclopramide, and these drugs may also cause similar extrapyramidal side-effects (Rabine and Barnett 2001). Dimenhydrinate and meclizine may also be useful (Camilleri 2007). None of these drugs has been studied selectively in patients with gastroparesis. Selective 5HT3-receptor antagonists like ondansetron and granisetron are effective antiemetics used in chemotherapy-related nausea. Likewise, no studies of their use in gastroparesis-related nausea are available (Rabine and Barnett 2001, Camilleri 2007).

Table 4. Prokinetic drugs for treating gastroparesis. (Based on original articles cited in the text.)

<table>
<thead>
<tr>
<th>Prokinetic efficacy</th>
<th>Symptom reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motilin receptor agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>+</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>+</td>
</tr>
<tr>
<td>ABT-229</td>
<td>+</td>
</tr>
<tr>
<td>Mitemcinal</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dopamine antagonists</strong></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>+</td>
</tr>
<tr>
<td>Domperidone</td>
<td>+</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>+</td>
</tr>
<tr>
<td>Itopride</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>5HT4 agonists</strong></td>
<td></td>
</tr>
<tr>
<td>Cisapride</td>
<td>+</td>
</tr>
<tr>
<td>Mosapride</td>
<td>+</td>
</tr>
</tbody>
</table>

2.3.4 Treatment of gastroparesis with gastric electrical stimulation (GES)

Gastric pacing was first experimented in animal models in the 1960s, and the first experience of gastric pacing in gastroparesis patients dates to the 1980s (Lin et al 2003). Permanently implantable pulse generators for GES have been manufactured since the late 1990s by Medtronics (Minneapolis, MN, USA) and can be placed surgically via laparotomy or laparoscopy. Two different pacing techniques have been applied to patients with severe gastroparesis: low-frequency GES, also called gastric pacing, uses a frequency close to or slightly higher than the intrinsic 3-cpm slow-wave, high-frequency GES uses a frequency four times or even higher than the normal slow wave.
In a group of 13 patients with severe gastroparesis, low-frequency GES, with a frequency up to 10% higher than the normal gastric slow wave frequency, an amplitude of 4 mA, and pulse width of 300 msec, restored the normal gastric slow waves, and gastric dysrhythmias disappeared (Lin et al 1998). In a study of nine patients with drug-refractory gastroparesis, low-frequency GES for one month before and after meals accelerated gastric emptying (P < 0.05), and of nine patients, eight no longer required jejunal feeding due to their markedly improved symptoms (McCallum et al 1998). This study was not controlled, and use of prokinetic drugs was permitted. Controlled studies would be necessary to define the role of low-frequency GES in treatment of gastroparesis, but the focus of research is at present on high-frequency GES because of better results.

The fact that dyspeptic symptoms correlate poorly with the gastric emptying rate in gastroparesis led to experiments with high-frequency GES aiming at reduction of symptoms rather than at restoring the normal gastric slow waves and gastric emptying. In a single centre study of 25 and multicentre study of 38 gastroparesis patients, both with follow-up of 12 months, high-frequency GES was able to reduce abdominal symptoms significantly, but gastric emptying was accelerated only modestly (Forster et al 2001, Abell et al 2002). In the WAVESS study at 11 centres, 33 patients with chronic gastroparesis were randomized in a double-blind crossover trial to stimulation either ON or OFF for one month followed by a second month with the stimulator in the opposite mode. After this initial 2-month period, came an open follow-up of 10 months with the stimulator ON in all patients. Vomiting frequency was significantly reduced in the ON vs. OFF period (P < 0.05), and at the end of the 12-month follow-up, vomiting frequency, symptom severity, and quality of life were all significantly improved compared to baseline (P < 0.05). Gastric emptying was, however, only moderately accelerated (Abell et al 2003a). These studies included all types of gastroparesis, but the usefulness of GES has been shown also in separate patient groups with diabetic gastroparesis (Lin et al 2004) and with postsurgical gastroparesis (McCallum et al 2005).

Besides reducing symptoms, GES improves nutritional parameters (Abell et al 2003b) and improves metabolic control in diabetic patients measured as reduction in HbA1c (van der Voort 2005). Improvement of symptoms and all measures of clinical outcome were maintained during a 3-year follow-up in 55 gastroparetic patients (Lin et al 2006). During the median follow-up of 4 years in 156 gastroparesis patients, high-frequency GES has proven both effective and safe, with no deaths directly related to the device. Some patients explanted, usually because of pocket infections, were later reimplanted successfully (Anand et al 2007).

Symptom profile may help in selecting patients for GES, because not all patients benefit from this therapy. Nausea and vomiting are commonly reduced, but bloating, fullness, and early satiety to a lesser extent, probably because gastric emptying is not usually accelerated (Namin et al 2005). Moreover, the cause of gastroparesis has an effect on results: The proportion of non-responders was 10% in diabetic, 35% in idiopathic, and 17% in postsurgical gastroparesis in a one-year follow-up of 87 patients (Lin et al 2006). Temporary GES for 2 to 6 weeks before implantation of a permanent device may be useful in identifying the right patients (Abrahamsson et al 2006). The mechanism of the action of GES is unclear. Possible mechanisms include activation of central mechanisms for nausea
and vomiting control, fundus relaxation, augmentation of the postprandial gastric slow wave, increased cholinergic and decreased sympathetic function, and a small improvement in gastric emptying (Namin et al 2005). Gastric barostat measurements suggest enhanced vagal autonomic function and decreased sensitivity to volume distention (McCallum et al 2006). Current reviews suggest GES as an effective treatment alternative for selected patients with drug-refractory, severe gastroparesis (Abrahamsson 2007a,b). The number of patients on GES treatment worldwide is approaching 2000 (Abrahamsson 2007b), with about 60 patients in Sweden and 2 patients in Finland.

2.3.5 Intrapyloric botulinum toxin and surgical therapies

In small open studies, intrapyloric injections of botulinum toxin by gastroscopy have improved dyspeptic symptoms and gastric emptying of patients with gastroparesis (Lacy et al 2002, Arts et al 2006, Ben-Yuossef et al 2006). In controlled studies, however, intrapyloric saline has been equally effective as botulinum toxin (Arts et al 2007, Friedenberg et al 2007). Pyloroplasty may be helpful for a subset of patients with severe gastroparesis, but unfortunately, clinical response to intrapyloric botulinum toxin injection does not help to select those patients who respond to pyloroplasty (Nguyen et al 2007). Based on a systematic review of surgical therapy, jejunostomy has improved symptoms and nutrition in 32 subjects with gastroparesis in three open trials, but gastrectomy relieved symptoms only in postsurgical gastroparesis (Jones and Maganti 2003).
3. AIMS OF THE STUDY

3.1. To compare electrogastrography, scintigraphy, and the $^{13}$C-octanoic acid breath test in measuring gastric motility

A. To assess electrogastrography in patients with chronic renal failure and controls to detect disorders of gastric myoelectrical activity.
B. To compare scintigraphy and the $^{13}$C-octanoic acid breath test in measuring gastric emptying in patients with functional dyspepsia (FD).
C. To compare electrogastrography, scintigraphy, and the $^{13}$C-octanoic acid breath test in measuring gastric motility in patients with type 1 diabetes and controls.

3.2. To explore the relationship of upper abdominal symptoms, glycaemia, and autonomic nerve function to delayed gastric emptying in type 1 diabetes patients

A. To evaluate the causal relationship of upper abdominal symptoms, glycaemia, and autonomic nerve function to gastric emptying in patients with type 1 diabetes.
B. To evaluate the effect of upper abdominal symptoms on quality of life in patients with type 1 diabetes.

3.3 To treat delayed gastric emptying

A. To test the hypothesis that nizatidine accelerates gastric emptying in patients with FD.
B. To evaluate the effect of nizatidine on dyspeptic symptoms and quality of life in patients with FD.
4 MATERIALS AND METHODS

4.1 Study subjects and design

Patients with chronic renal failure. Outpatients with CRF (n = 23, 12 men, 11 women, ages 28-72, mean 51) treated with continuous ambulatory peritoneal dialysis and followed up at Tampere University Hospital, Department of Medicine, were examined by EGG to evaluate the effect of peritoneal dialysis on gastric myoelectrical activity and the relationship of dyspeptic symptoms to disturbances of gastric myoelectrical activity (Study I). Of these patients, 11 had diabetes (6, type 1; 5, type 2). All patients were examined by EGG in a fasting state and after a standard test meal. EGG was recorded from all patients on peritoneal dialysis. Two patients received a kidney transplant, six had to change to haemodialysis, and one patient died. EGG was recorded from the remaining 14 patients also with the peritoneal cavity empty of dialysis fluid. Healthy controls (n = 20, 9 men, 11 women, ages 20-71, mean 40) were examined by EGG for comparison.

Patients with functional dyspepsia. FD patients were enrolled from the basic population of patients sent by primary care physicians for gastroscopy to Helsinki University Central Hospital, Department of Gastroenterology. All patients had dyspeptic symptoms at least once a week, and lasting for at least one month. Symptoms were ulcer-like (pain, nighttime pain or hunger pain) or dysmotility like (nausea or vomiting) or both. Additional reflux-like symptoms (heartburn and regurgitation) were accepted, but patients with predominantly reflux-like symptoms were excluded. Only patients with normal findings in gastroscopy (no ulcers, no erosions, no macroscopic oesophagitis or duodenitis), normal upper abdominal ultrasound, and a normal physical examination were included. Minor inflammatory findings were allowed in the routine biopsies taken from the duodenum, antrum, and corpus, but patients with Helicobacter pylori infection in their specimens were excluded. Patients with lactose intolerance had to have been at least 3 months on a lactose-free diet prior to the study.

In FD patients (n = 21, 8 men, 13 women, ages 40-75, mean 57), gastric emptying was measured with both dynamic dual tracer scintigraphy and OBT within one week to evaluate the correlation between these methods (Study II).

Of these FD patients, 16 (6 men, 10 women; ages 46-71, mean 57) were examined in a randomized, double-blinded cross-over study to evaluate the effect of nizatidine on gastric emptying, upper abdominal symptoms, and quality of life (Study III). Patients were allocated at random into two medication groups. Half received nizatidine 150 mg bd for the first 2 months, followed by a one-month washout period and a 2-month placebo period. The other patients initially received placebo for 2 months followed by the one-month washout period and the 2-month nizatidine period. Thus the patients acted as their own controls. Prior to the study, the washout period was 2 weeks. Gastric emptying was measured by scintigraphy during the last 2 weeks of each medication period. Patients completed symptom and quality of life questionnaires after each of the two medication cycles.
Patients with type 1 diabetes. The type 1 diabetes patients (n = 27, 8 men, 19 women, ages 24-55, mean 42) enrolled for Studies IV and V were suspected cases of diabetic gastroparesis. Patients were referred to Helsinki University Central Hospital, Department of Gastroenterology, because of recurrent or constant upper abdominal symptoms for at least 3 months (upper abdominal pain, fullness, early satiation, nausea or vomiting) but with no findings in gastroscopy or abdominal ultrasound. Helicobacter pylori infection was excluded by negative findings in the gastroscopy biopsies.

All patients were examined both by dynamic dual-tracer scintigraphy and by simultaneous OBT and EGG within 2 weeks. Plasma glucose levels were measured before the test meal (fasting plasma glucose) and at 30, 60, and 90 minutes after the start of scintigraphy by OneTouch Ultra (LifeScan, Inc., Johnson&Johnson company, New Brunswick, NJ, USA). Autonomic nerve function was evaluated by standardised cardiovascular reflex tests. Gastrin 17, pepsinogen I and II levels, and Helicobacter pylori antibodies were measured (Biohit GastroPanel, Väänänen et al 2003). Patients completed symptom- and quality of life questionnaires at the beginning of the study. The 15 healthy controls (3 men, 12 women, ages 19-39, mean 25) were examined with simultaneous OBT and EGG for comparison. The reference group for scintigraphy were the 11 healthy controls from our previous study (4 men, 7 women, ages 28-59, mean 44) (Kairemo et al 1998).

4.2 Electrogastrographic measurements

In Study I, EGG was recorded by a device constructed at Tampere University Hospital and the Ragnar Granit Institute, a division of Tampere University of Technology (Konkka et al 1996). This device consists of a common electrocardiography amplifier (Mingocard 7), a portable PC computer (Toshiba 6600), and a measuring board (DAP 1200). Suitable recording and analysis programs were designed with DigiS, MATLAB, and Visual Basic software. A 30-min EGG recording was performed in the fasting state and after a standard meal (minced beef mixed with an egg, placed on bread, and 200 ml water; 280 kcal). The recording lead is a modification of the limb leads of a standard 12-lead electrocardiogram. The Einthoven triangle is transferred to the stomach so that the midpoint is between the xiphoid process and the navel, and the electrodes (Blue Sensor R-00-3, Medicotest, Ølstykke, Denmark) were placed at the corners of the triangle at a distance of 10 cm. This triangular bipolar lead system is eminently suitable for measurements, because the location and orientation of the antrum show a high interindividual variation. In this system, the orientation of at least one electrode pair is located in the electrically most active area, and thus is suitable for recording gastric myoelectrical activity. In order to reduce resistance, the abdominal skin was gently rubbed with sandpaper (3 M Red Dot Skin Prep, St. Paul, MN, USA) before placement of the electrodes at the recording sites. Hair, if present, was shaved.

In Studies IV and V, EGG was recorded by Synectics Medical Digitrapper EGG, OS Version 3.00, Hardware 03.00 (Synectics Medical, Enfield, UK). A 30-min recording was performed before the test meal and a 60-min recording afterwards. In these studies, EGG
and OBT were performed simultaneously, thus using the same test meal consisting of one fried egg labeled with 91 mg $^{13}$C-octanoic acid mixed in its yolk, 2 slices of wheat toast, and 150 ml of water (180 kcal). The skin was gently rubbed with 2236 Trace Prep (3M Health Care, St. Paul, MN, USA), and Signa electrode cream (Parker Laboratories, Inc., Fairfield, NJ, USA) was used to improve conductance. Hair, if present, was shaved. One active electrode (Cleartrace ECG Electrodes, CONMED Corporation, Utica, NY, USA) was placed on the patient’s ventral mid-line, halfway between the navel and the xiphoid process. The other active electrode was placed 5 cm to the left and at 45° above the first one. A reference electrode was placed at 10- to 15-cm distance to the right of the first one. During the recording, the patient had to lie motionless to prevent movement artefacts on the electrogastrogram. The percentage and power of the normal 2.0 to 3.7 cycles per minute (cpm) slow waves were calculated from the electrogastrogram and displayed as a running spectral analysis (Figure 1).

Figure 1. EGG running spectral analysis. Normal EGG with dominant frequency for 100% of the time in the 2.0- to 3.7-cpm frequency range (normal slow waves) both preprandially and postprandially.
4.3 Scintigraphic measurements of gastric emptying and intragastric distribution

The standardized dynamic scintigraphic double-tracer method used at our clinic has been validated in healthy subjects and in patients with functional dyspepsia and proved to be well reproducible in a follow-up of one year (Kairemo et al 1998, Koskenpato et al 1998, 2000). In healthy controls, the gastric half-emptying time for solids is $76.4 \pm 29.4$ min and for liquids $36.2 \pm 10.4$ min, and the intragastric distribution (percentage in antrum at 10 min) is $5.2 \pm 2.3$ for solids (Kairemo et al 1998).

All patients fasted for 12 hours prior to scintigraphy. The test meal consisted of a lactose- and gluten-free meat cabbage casserole (220 kcal: 10 g protein, 6 g fat, 28 g carbohydrates) labeled with 9.25 MBq $^{111}$In ($^{111}$In chloride), and 150 ml of water labelled with 75 MBq $^{99m}$Tc ($^{99m}$Tc DTPA). The effective dose of radiation resulting was approximately 5 mSv. The diabetic patients took their normal morning dose of short-acting soluble human insulin 30 min before or short-acting insulin-analog just before the test meal, and they were advised to take their long-acting insulin/insulin analog normally.

After the test meal, each patient remained supine for the duration of the study. Dynamic scintigraphy was started immediately after the test meal, with activity distributions of $^{99m}$Tc and $^{111}$In recorded simultaneously. A multiple-window dynamic study was performed in anterior and posterior projections. The acquisition time was one minute, for a total follow-up of 90 minutes. Each dynamic frame was used to generate functional curves for solids and liquids. The regions of interest (ROIs) comprised the entire stomach, corpus, and antrum, the distal part of the esophagus, and the scatter background area near the stomach. The anatomical areas were determined individually for each patient by use of the scintigraphic images of the stomach and the ROI-drawing software of the computer. Both anterior and and posterior images were evaluated to reach an optimal anatomical view for each subject. Time-activity curves were generated by calculating geometrical means of the mean count content of these areas. The background subtraction was based on information from the background curve generated by $^{111}$In and $^{99m}$Tc Compton scatter. A decay correction for $^{99m}$Tc was performed.

Gastric half-emptying times for solids and liquids were determined separately from the dynamic curves (Figure 2). The gastric emptying curves were extrapolated by use of a monoexponential fit for the descending part of the time-activity curve after the lagtime (the delay before gastric emptying starts). The lagtime was determined to end when the time-activity curve for the entire stomach began to descend. Intragastric distribution was calculated at 10 min as the percentage ratio of the geometric means for the anterior and posterior ROI counts between the antrum and the entire stomach.
Figure 2. Scintigraphy of gastric emptying of solids. Above: Scintigraphic scans of gastric contents. Below: Regions of interest of the stomach and time-activity curves for the entire stomach, corpus, antrum, and oesophagus.

4.4 Measuring gastric emptying with the $^{13}$C-octanoic acid breath test

OBT was performed according to a method previously described (Ghoos et al 1993, Delbende et al 2000). All patients fasted 12 hours prior to the breath test. The test meal consisted of one fried egg labeled with 91 mg $^{13}$C-octanoic acid mixed in the yolk, 2 slices of wheat toast, and 150 ml of water (180 kcal). Breath samples were collected into 10-ml tubes at baseline and every 15 minutes after meal ingestion for a 4-hour period. The ratio of $^{13}$CO$_2$ to $^{12}$CO$_2$ was measured in each sample by mass spectrometry. Data were expressed as the percentage of $^{13}$CO$_2$ exhaled per hour and cumulative percentage of dose over time (Figure 3). Carbon dioxide production was assumed to be 300 mmol/m$^2$ body surface area per hour. Body surface was calculated according a validated weight-height formula (Haycock et al 1978).

Gastric half emptying times for solids were calculated by applying the nonlinear least-squares fitting on the cumulative breath test curve (Ghoos et al 1993, Lee J et al 2000, Chey et al 2001, Bromer et al 2002). The percentage $^{13}$CO$_2$ cumulative values were fit by a
modified power exponential model: $y = m(1-e^{-kt})^\beta$, where $y$ is the cumulative percentage of $^{13}$CO$_2$ excretion in the breath at time $t$ (h) and $m$, $k$, and $\beta$ are estimated parameters with $m$ interpreted as the total cumulative $^{13}$C recovery when time is infinite. Cumulative $^{13}$CO$_2$ excretion cannot reach 100% because of fixation of a substantial amount of the orally administered dose in the bicarbonate pool in the body. $T_{1/2B}$ was calculated after estimating $k$ and $\beta$ and using $0.5 \times m$ in the formula instead of $y$: $T_{1/2B} = [-1/k] \times \ln [1 – (0.5)^{1/\beta}]$. $T_{lag}$ was calculated by the same method: $T_{lag} = [-1/k] \times \ln [1 – (0.1)^{1/\beta}]$.

Gastric half emptying times were additionally calculated by the geometrical method for comparison in Study II. This model has been described by Raychaudri et al 1998 and was later used by Ritz et al 2001. It utilizes the $^{13}$CO$_2$ excretion curve expressed as the percentage of $^{13}$CO$_2$ in each sample at 15-minute intervals. First, the area under the observed $^{13}$CO$_2$ curve (AUC) was calculated. The tail area (unobserved AUC) was estimated with a straight line, which was fitted to the last five breath samples and extrapolated to the time axis. If the line did not cross the time axis before 12 hours, the last point observed and the 12-hour point of the time axis were joined. $T_{1/2}$ was then calculated by numerical interpolation of the total (observed and unobserved) AUC.

Figure 3. The $^{13}$C-octanoic acid breath test as a percentage of $^{13}$CO$_2$ in breath samples at 15-minute intervals (bell-shaped curve) and as a cumulative percentage of $^{13}$CO$_2$ excretion over time, an example of normal gastric emptying. Calculations based on 15-minute and 30-minute intervals result in similar curves.
4.5 Measuring autonomic nerve function in type 1 diabetes patients

Autonomic nerve function was evaluated by standardised cardiovascular reflex tests to evaluate parasympathetic and sympathetic nervous function. Heart rate variation was recorded during controlled and deep breathing and during the Valsalva manoeuvre. Other measurements included diastolic blood pressure rise during an isometric handgrip exercise and blood pressure and pulse reactions during an active orthostatic test with measurement of maximum/minimum ratio of heart rate variation. Each single test was evaluated as 0 = normal or 1 = abnormal, and the highest possible score for autonomic neuropathy was 6.

Analysis of the tests utilized the following values: Agelink et al 2001 for deep breathing, controlled breathing, and orthostatic tests, Bannister 1999 for the Valsalva test, and Piha 1991 for the handgrip test. Piha gives normative data for all individual cardiovascular reflex tests in healthy Finnish controls, but the number of individuals in some age cohorts is very small. Using only the normative data of Piha would thus have led to unreliable results. Agelink et al and Bannister give normative data for a larger group of individuals but do not include all cardiovascular reflex tests. Thus, the most reliable result for each individual cardiovascular reflex test came from comparing the findings for each patient to those of age- and gender-matched controls from the largest control group available. If the patient was receiving beta-blocking medication, reduced heart rate variation was not regarded as abnormal. Thus, if reduced heart rate variation was observed in the tests listed above, all these patients were given a score of 0.

4.6 Questionnaires

In Study I we used a questionnaire assessing gastroparesis-like symptoms and their intensities: upper abdominal pain (0-2), nausea (0-2), vomiting (0-2), early satiation (0-2), and bloating (0-2). The questionnaire used in Studies III and IV has been validated in Finnish dyspepsia studies (Heikkinen et al 1995, Koskenpato et al 2001, Heikkinen et al 1998). Dyspepsia score was determined based on ulcer-like symptoms (pain, night-time pain, and hunger pain, 0-8), and dysmotility-like symptoms (nausea and bloating, 0-8). The reflux score was based on heartburn and regurgitation (0-12). Besides these scores used in the other studies, a novel gastroparesis score was designed for Study IV, based on the following symptoms from the questionnaire: abdominal pain (0-4), nausea (0-6), vomiting (0-6), early satiation (0-2), and bloating (0-2). Factors assessed as affecting dyspeptic symptoms were smoking, use of painkillers and other medication, and intestinal symptoms. Quality of life was measured by a validated RAND 36-item Health Survey 1.0 questionnaire, a translated version of the SF-36 questionnaire (Aalto et al 1999) evaluating eight aspects of quality of life: physical functioning, role functioning/physical, role functioning/emotional, vitality, mental health, social functioning, bodily pain, and general health. Its highest possible score is 100% and lowest 0%. Normal values are based on data from 2157 healthy Finnish individuals (969 men, age 48.3 ± 17.2, 1188 women, age 49.2 ± 17.7 (Aalto et al 1999).
4.7 Statistical analysis

In Study I, the percentage and power of the normal slow waves between patients and healthy controls were compared by Student’s t-test. The paired t-test was used for analysis of these parameters in patients on dialysis and with the peritoneal cavity empty of any dialysis fluid. In Study II, gastric half-emptying times obtained by scintigraphy and OBT were analyzed with the Pearson correlation coefficient, matched t-test, and matched signed rank test. In Study III, gastric emptying results, symptom scores, and quality of life scores were analyzed with the Wilcoxon matched pairs signed rank sum test. In Study IV, patients and controls were compared by Student’s t-test. Pearson and Spearman correlations were used for continuous data when appropriate. Differences in distributions of categorial data (smoking, NSAID use) were investigated by Chi-square test. Dependence of rate of gastric emptying on autonomic neuropathy was studied by the Cox regression model. In this analysis, the effect of autonomic neuropathy was taken into account by use of a quantitative scale (dose-response model). Comparison of patient groups with delayed and normal gastric emptying were performed by log-rank (gastric emptying rate of liquids), Mann-Whitney (intragastric distribution), and Chi square test (autonomic neuropathy). In Study V, patients and controls were compared by Student’s T-test, and Mann-Whitney test and Pearson correlations served for continuous data when appropriate. The data from Study I were analysed by Microsoft Excel, data from Studies II and III with BMDP for Windows (Microsoft ), and data from Studies IV and V with SPSS software (SPSS Inc, Chicago, IL, USA). The limit of statistical significance for two-tailed P-values was 0.05. All results are expressed as mean ± SD, except in Study I, as mean ± SEM.
5. RESULTS

5.1 Electrogastrography in patients with chronic renal failure

Percentage of normal slow waves. In Study I, the percentage of normal slow waves was defined as the percentage of time during which 2- to 4-cpm (0.03 – 0.07 Hz) slow waves were present over the entire observation period. No significant differences emerged in percentages of normal slow waves between patients on dialysis and patients with their peritoneal cavity empty of dialysis fluid, whether with symptoms or without, or controls (Table 5).

Power ratio. The frequency at which the power spectrum of the entire 30-min recording had peak power in the range of 0.5 to 9.0 cpm was defined as the dominant frequency, and the power of this frequency was defined as the dominant power. The power ratio was defined as the relative change in dominant power before and after the test meal. The power ratio has been shown to reflect gastric contractility, as described in section 2. All 23 patients were examined on dialysis and 14 of the patients additionally with the peritoneal cavity empty of dialysis fluid. The power ratio was significantly higher when EGG was recorded on dialysis compared to measurement with the peritoneal cavity empty 27.2 ± 10.7 vs. 8.6 ± 4.8, P < 0.05 (Figure 3). The power ratio was also higher in symptom-free patients (n = 5) than in patients with dyspeptic symptoms (n = 18, mean symptom score 3.3 ± 0.5), both on dialysis (39.4 ± 13.7 vs. 12.4 ± 5.3, P < 0.05) and with the peritoneal cavity empty (29.2 ± 21.5 vs. 2.8 ± 0.4, P < 0.05). No difference appeared in the power ratio between patients with peritoneal cavity empty and controls.

Table 5. Normal 2-4 cpm slow waves and power ratio in CRF patients and controls

<table>
<thead>
<tr>
<th>Patients</th>
<th>Slow waves (%) before test meal</th>
<th>Slow waves (%) after test meal</th>
<th>Power ratio</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>On dialysis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>83 ± 3</td>
<td>91 ± 3</td>
<td>19.6 ± 6.8</td>
<td>23</td>
</tr>
<tr>
<td>Symptom-free</td>
<td>71 ± 5</td>
<td>89 ± 10</td>
<td>39.4 ± 13.7*</td>
<td>5</td>
</tr>
<tr>
<td>Dyspeptic</td>
<td>88 ± 3</td>
<td>91 ± 3</td>
<td>12.4 ± 5.2</td>
<td>18</td>
</tr>
<tr>
<td>No dialysis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>88 ± 5</td>
<td>86 ± 4</td>
<td>8.6 ± 4.8</td>
<td>14</td>
</tr>
<tr>
<td>Symptom-free</td>
<td>82 ± 6</td>
<td>93 ± 7</td>
<td>29.2 ± 21.5*</td>
<td>3</td>
</tr>
<tr>
<td>Dyspeptic</td>
<td>81 ± 6</td>
<td>86 ± 7</td>
<td>2.8 ± 0.4</td>
<td>11</td>
</tr>
<tr>
<td>Controls</td>
<td>89 ± 4</td>
<td>83 ± 4</td>
<td>7.5 ± 2.2</td>
<td>20</td>
</tr>
</tbody>
</table>

* Significantly higher power ratio (P < 0.05) in symptom-free patients compared to dyspeptic patients.
Figure 4. Power ratio in patients (n = 14) on dialysis and with peritoneal cavity empty, and controls. Results are presented as mean ± SEM. The power ratio was significantly higher in patients on dialysis than in patients with peritoneal cavity empty (P < 0.05).

### 5.2 Comparison of scintigraphy and the $^{13}$C-octanoic acid breath test in measuring gastric emptying in patients with functional dyspepsia

The gastric half-emptying time of solids measured by OBT ($T_{1/2B}$) was significantly longer than that of solids measured by scintigraphy ($T_{1/2S}$), irrespective of the mathematical model used for calculating $T_{1/2B}$ from the OBT curves (Table 6). Mean $T_{1/2S}$ was 109 ± 74 min, whereas mean $T_{1/2B}$ calculated by the nonlinear least-square method was 167 ± 50 min (P < 0.05) and calculated by the geometrical method it was 185 ± 52 min (P < 0.005). $T_{lag}$ was significantly longer measured by OBT (64 ± 17 min) than by scintigraphy (4 ± 6 min) when calculated by the formula previously described (Lee J et al 2000).

No correlation between $T_{1/2B}$ and $T_{1/2S}$ appeared, irrespective of the mathematical model for calculating $T_{1/2B}$ ($r = -0.26$ for the nonlinear method and $r = -0.13$ for the geometrical method). Mean $T_{1/2B}$ calculated by the nonlinear method and the geometrical method did not differ significantly (167 ± 50 min vs. 185 ± 52 min, P = 0.23). However, the correlation between these two mathematical methods was weak ($r = 0.15$).

When compared to normal values of healthy controls of the validation study, six patients (29%) had delayed gastric emptying of solids ($T_{1/2S} > 137$ min) and eight patients (38%) had abnormally high intragastric distribution of solids (intragastric distribution > 10%). Gastric emptying of liquids in all patients was normal. However, five of the six patients with delayed gastric emptying and five of the eight patients with abnormal intragastric distribution were on nizatidine therapy, as they were also participating in
Study III. These figures thus cannot be used for evaluation of the prevalence of gastric motility disorders in patients with FD.

It is now also possible to compare OBT values of healthy controls from Study V to these patients. In Study V, the gastric half-emptying time of solids by OBT (T_{1/2B}) in the 16 healthy controls calculated by the nonlinear method was 168 ± 47 min. When mean ± 2 x SD (< 272 min) is regarded as normal, one patient in Study II had delayed gastric emptying measured by OBT (T_{1/2B} 333 min), but scintigraphy in this patient was normal. On the other hand, OBT was normal in all the six patients with delayed gastric emptying in scintigraphy. Thus OBT would have been a false positive in one patient case and false negative in all six cases in detecting delayed gastric emptying when compared to scintigraphy.

Table 6. Results of scintigraphy and OBT, n = 21.

<table>
<thead>
<tr>
<th></th>
<th>scintigraphy</th>
<th>OBT, Nonlinear method</th>
<th>OBT, Geometrical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_{1/2 solid} (min)</td>
<td>109 ± 74</td>
<td>167 ± 50\textsuperscript{a}</td>
<td>185 ± 52\textsuperscript{b}</td>
</tr>
<tr>
<td>T_{1/2 liquid} (min)</td>
<td>28 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T_{lag} (min)</td>
<td>4 ± 6</td>
<td>64 ± 17\textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Intragastric</td>
<td>10.1 ± 5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>distribution (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T_{1/2} = gastric half-emptying time, T_{lag} = lagtime. T_{1/2} measured by OBT was significantly longer than measured by scintigraphy by both mathematical models (\textsuperscript{a} P < 0.05, \textsuperscript{b} P < 0.005). T_{lag} measured by OBT was significantly longer than by scintigraphy, \textsuperscript{c} P<0.001.

5.3 Effect of nizatidine on gastric emptying, symptoms, and quality of life in patients with functional dyspepsia

Gastric emptying. Gastric emptying was measured by scintigraphy. The gastric half-emptying time for liquids (T_{1/2 liquid}), the lagtime (T_{lag}) before onset of gastric emptying of solids, and the intragastric distribution of the test meal in the stomach during treatment with placebo and nizatidine were similar. The gastric half-emptying time of solids (T_{1/2 solid}) was significantly slower during nizatidine than during placebo (P = 0.03). Thus, gastric emptying of solids was prolonged during nizatidine therapy, but no significant alterations occurred in other characteristics of gastric emptying (Table 7).

Symptoms and quality of life. Symptom scores for both dyspepsia and reflux improved during nizatidine therapy, but not significantly. Nizatidine improved seven of eight aspects of quality of life compared to the effect of placebo, and improved all aspects of quality of
life compared to baseline. Both at baseline and during treatment with placebo or nizatidine, our patients’ quality of life was lower than that of the general Finnish population, but all differences in the quality of life scores were non-significant.

**Table 7.** Gastric half-emptying time for liquids (T<sub>1/2 liquid</sub>) and solids (T<sub>1/2 solid</sub>), lagtime for emptying of solids (T<sub>lag</sub>), and intragastric distribution of test meal as percentage of gastric contents in the antrum during treatment with placebo and nizatidine.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nizatidine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;lag&lt;/sub&gt; (min)</td>
<td>7.0 ± 5.4</td>
<td>10.0 ± 6.0</td>
<td>0.09</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2 solids&lt;/sub&gt; (min)</td>
<td>65.6 ± 23.2</td>
<td>110.1 ± 76.7</td>
<td>0.03</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2 liquid&lt;/sub&gt; (min)</td>
<td>26.1 ± 6.8</td>
<td>27.9 ± 11.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Intragastric distribution (% in antrum)</td>
<td>9.8 ± 4.5</td>
<td>8.3 ± 3.9</td>
<td>0.20</td>
</tr>
</tbody>
</table>

5.4 Upper abdominal symptoms, glycemia, autonomic nerve function, and motility disorders measured by scintigraphy in type 1 diabetes patients

**Gastric emptying of solids.** Results are displayed in Table 8. Of the 27 patients, 7 (26%) had delayed gastric emptying of solids as compared to controls, when the mean + 2 x SD of healthy controls (< 137 min) was regarded as the upper limit of normal (Kairemo et al 1998). Overall, gastric emptying of solids (T<sub>1/2</sub>) among diabetic patients was slower than among healthy controls, but not significantly (128 ± 116 min vs. 76 ± 29 min).

No correlation appeared between gastric emptying rate of solids and fasting or mean glucose concentration, glucose concentrations during follow-up, change in glucose concentration during follow-up, long-term glucose control as measured by HbA<sub>1c</sub>, age, gender, duration of diabetes, abdominal symptoms, gastrin or pepsinogen level, use of NSAIDs, or smoking.

We observed a positive correlation between gastric half-emptying time both of solids and of liquids and autonomic neuropathy score (Table 9). By the Cox regression model, for each increment of one in autonomic neuropathy score, the emptying rate of solids was 31% shorter (10-47 95% CI; P = 0.006). With the six patients receiving beta-blockers excluded, for each increment of one in the autonomic neuropathy score, the emptying rate of solids was 35% smaller (10-53 95% CI; P = 0.011).

**Intragastric distribution of solids.** Of the 27 patients, 10 (37%) had an abnormally high percentage of solids in the antrum at 10 minutes (intragastric distribution) compared to that of controls when mean ± 2 x SD (3 – 9%) was considered normal. All these patients had normal gastric emptying of solids and liquids. As a whole, percentage of solids in the
antrum at 10 minutes was significantly higher in the patients than in healthy controls (11 ± 9% vs. 5 ± 2%; P < 0.05). When patients were divided into two groups according to normal or delayed gastric emptying of solids, percentage of solids in the antrum at 10 minutes was significantly smaller in the group with delayed compared to those with normal gastric emptying (Table 8).

Intragastrian distribution correlated neither with autonomic neuropathy score, age, gender, duration of diabetes, fasting or mean plasma glucose concentration, glucose concentrations during follow-up, change in glucose concentration during follow-up, HbA1C, abdominal symptoms, nor gastrin or pepsinogen level.

**Gastric emptying of liquids.** Only three of the diabetic patients (11%) experienced delayed gastric emptying of liquids compared to that of healthy controls when mean ± 2 x SD (15-57 min) was considered normal (Kairemo et al 1998). All these three patients also showed delayed gastric emptying of solids. A positive correlation existed between gastric emptying times of liquids and solids in the patients (r = 0.91, P < 0.001).

Gastric emptying of liquids correlated neither with age, gender, duration of diabetes, fasting or mean plasma glucose concentration, glucose concentrations during follow-up, change in glucose concentration during follow-up, HbA1C, abdominal symptoms, nor gastrin nor pepsinogen level.

By Cox regression model, for each increment of one in autonomic neuropathy score, the gastric emptying rate of liquids was 20% smaller (-1 to -37 95% CI; P = 0.06). When the six patients receiving beta-blockers were excluded, for each increment of one in autonomic neuropathy score, the gastric emptying rate of liquids was 21% smaller (-3 to -40 95% CI, P = 0.084).

**Glucose levels during the study.** The mean plasma glucose level in all patients before the test meal (fasting plasma glucose) was 10.0 ± 4.5 mmol/l, and at the end of the 90-minute follow-up, 10.4 ± 3.7 mmol/l. Fasting and mean plasma glucose levels in diabetic patients with delayed and normal gastric emptying were similar, with no significant difference (Table 6).

**Autonomic neuropathy.** Of all 27 patients, 26 were examined by standard cardiovascular tests to detect autonomic neuropathy; one patient withdrew from this part of the study. Of these patients, 16 (62%) had signs of autonomic neuropathy, and the average autonomic neuropathy score was 1.6 ± 1.7. Reduced heart rate variation was not considered abnormal in the six patients receiving beta-blocking medication, and they thus were scored 0 for these tests. When patients were divided into two groups according to normal or delayed gastric emptying of solids, the autonomic neuropathy score in the group with delayed gastric emptying was greater (Table 8).

**Abdominal symptoms and quality of life.** Among all patients, 23 (85%) had ulcer-like symptoms (mean score 4.0 ± 2.2), and 18 (67%) had reflux-like symptoms (mean score 4.0 ± 3.8). All patients had dysmotility-like symptoms (mean 5.2 ± 2.2) and dyspepsia-like symptoms (mean 9.2 ± 3.2) The overall gastroparesis score including abdominal pain,
nausea, vomiting, early satiation, and bloating was $11.2 \pm 3.8$ (maximum score 20). Neither overall gastroparesis symptom score nor individual symptom scores correlated with gastric emptying of solids or liquids, intragastric distribution of solids or HbA$_{1c}$.

Based on the quality of life questionnaires, our patients’ quality of life was significantly lower than that of the general Finnish population for all eight categories. Quality of life showed no statistical correlation with any score for abdominal symptoms, nor HbA$_{1c}$.

**Table 8.** Clinical characteristics and variables in all patients and in relation to gastric emptying rate of solids.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Delayed emptying of solids</th>
<th>Normal emptying of solids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>27</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Men</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Women</td>
<td>19</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$42 \pm 8$</td>
<td>$37 \pm 9$</td>
<td>$43 \pm 7$</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>$29 \pm 11$</td>
<td>$23 \pm 10$</td>
<td>$32 \pm 11$</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>30</td>
<td>57</td>
<td>20</td>
</tr>
<tr>
<td>NSAID user (%)</td>
<td>44</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>$8.4 \pm 1.4$</td>
<td>$9.2 \pm 1.4$</td>
<td>$8.0 \pm 1.4$</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>$85 \pm 60$</td>
<td>$75 \pm 27$</td>
<td>$92 \pm 73$</td>
</tr>
<tr>
<td>Gastrin (pmol/l)</td>
<td>$16.9 \pm 36.8$</td>
<td>$2.3 \pm 1.9$</td>
<td>$22.0 \pm 41.8$</td>
</tr>
<tr>
<td>Pepsinogen I (μg/l)</td>
<td>$95.2 \pm 65.9$</td>
<td>$110.7 \pm 40.0$</td>
<td>$94.1 \pm 74.9$</td>
</tr>
<tr>
<td>Pepsinogen II (μg/l)</td>
<td>$10.5 \pm 11.3$</td>
<td>$7.8 \pm 3.9$</td>
<td>$8.5 \pm 2.7$</td>
</tr>
<tr>
<td>Helicobacter pylori ab (EIU)</td>
<td>$15.3 \pm 12.0$</td>
<td>$15.1 \pm 15.2$</td>
<td>$14.3 \pm 10.0$</td>
</tr>
<tr>
<td>$T_{1/2}$ liquids (min)</td>
<td>$42 \pm 30$</td>
<td>$71 \pm 46$</td>
<td>$31 \pm 8$</td>
</tr>
<tr>
<td>$T_{1/2}$ solids (min)</td>
<td>$128 \pm 116$</td>
<td>$260 \pm 171$</td>
<td>$82 \pm 27$</td>
</tr>
<tr>
<td>Intragastric distribution (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>liquids</td>
<td>$17 \pm 11$</td>
<td>$22.0 \pm 2.2$</td>
<td>$15.7 \pm 8.0$</td>
</tr>
<tr>
<td>solids</td>
<td>$11 \pm 9$</td>
<td>$5.9 \pm 2.9$</td>
<td>$13.7 \pm 9.5$</td>
</tr>
<tr>
<td>Autonomic neuropathy score (0-6)</td>
<td>$1.6 \pm 1.7$</td>
<td>$3.5 \pm 2.1$</td>
<td>$0.9 \pm 1.1$</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>$10.0 \pm 4.5$</td>
<td>$12.3 \pm 6.4$</td>
<td>$9.2 \pm 3.6$</td>
</tr>
<tr>
<td>Mean plasma glucose (mmol/l)</td>
<td>$10.6 \pm 4.1$</td>
<td>$11.4 \pm 5.1$</td>
<td>$10.3 \pm 3.5$</td>
</tr>
</tbody>
</table>


Table 9. Gastric half-emptying time for solids (T_{1/2 solid}) and liquids (T_{1/2 liquid}) in relation to autonomic neuropathy score.

<table>
<thead>
<tr>
<th>Autonomic neuropathy score</th>
<th>N = 26*</th>
<th>T_{1/2 solid} (min)</th>
<th>T_{1/2 liquid} (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>91 ± 34</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>84 ± 24</td>
<td>33 ± 5</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>91 ± 64</td>
<td>29 ± 8</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>112 ± 4</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>195</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>361 ± 244</td>
<td>104 ± 63</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Of the total 27 patients, one withdrew from this part of the study.

5.5 Comparison of scintigraphy, $^{13}$C-octanoic acid breath test, and electrogastrography in diagnosing diabetic gastroparesis

Results of scintigraphy, OBT, and EGG of patients and controls are presented in Table 10. Comparison of scintigraphy, OBT, and EGG appears in Table 11.

**Scintigraphy versus OBT.** When measured by OBT, gastric emptying of solids was slower in the patient group than in controls as a whole, but the difference was non-significant (245 ± 195 min vs. 168 ± 47 min, P = 0.14). Of all 27 patients, 7(26%) showed delayed gastric emptying of solids in OBT compared to normal values of the 15 controls, with a mean T_{1/2} ± 2 x SD (< 272 min) regarded as normal. Of the seven patients with delayed gastric emptying in scintigraphy, only three also showed delayed gastric emptying in OBT. Thus the sensitivity of OBT was 43% in relation to scintigraphy, the gold standard (Table 11). OBT was normal in 16 of the 20 patients with normal scintigraphy, resulting in a specificity of 80%. The correlation between scintigraphy and OBT was poor (r = 0.16).

**Scintigraphy versus EGG.** Overall, no difference appeared in the prevalence of normal 2.0 to 3.7 cpm gastric slow waves between patients and controls either before or after the test meal. Neither was there any difference in the power ratio between patients and controls. Electrogastrography was considered abnormal if normal slow waves were detected in less than 70% of either the preprandial or the postprandial recordings, according to consensus opinion (Parkman et al 2003). Electrogastrography detected only two of the seven patients with delayed gastric emptying of solids in scintigraphy; thus sensitivity was low, 29% (Table 11). EGG was normal in 16 of the 20 patients with normal gastric emptying in scintigraphy, making specificity 80%.
**Scintigraphy versus OBT and EGG combined.** EGG or OBT or both were abnormal in seven patients, but only four of these had delayed gastric emptying in scintigraphy. The sensitivity for combined EGG and OBT was thus 57% in relation to scintigraphy, the gold standard (Table 11). Both EGG and OBT were normal in 12 of the 20 patients with normal gastric emptying in scintigraphy, resulting in a specificity of 60% for combined EGG and OBT.

### Table 10. Values for scintigraphy, $^{13}$C-octanoic acid breath test (OBT), and electrogastrography (EGG) in diabetic patients (n = 27) and OBT and EGG in controls (n = 15).

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scintigraphy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{1/2}$solid (min)</td>
<td>128 ± 116</td>
<td>76 ± 29*</td>
<td>NS</td>
</tr>
<tr>
<td>$T_{1/2}$liquid (min)</td>
<td>42 ± 30</td>
<td>36 ± 10*</td>
<td>NS</td>
</tr>
<tr>
<td>Intragastric distribution of solids ( % in antrum)</td>
<td>11 ± 9</td>
<td>5 ± 2*</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>OBT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_{1/2}$solid (min)</td>
<td>245 ± 195</td>
<td>168 ± 47</td>
<td>NS</td>
</tr>
<tr>
<td><strong>EGG</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow waves, preprandial (%)</td>
<td>87 ± 19</td>
<td>88 ± 23</td>
<td>NS</td>
</tr>
<tr>
<td>Slow waves, postprandial (%)</td>
<td>89 ± 15</td>
<td>89 ± 17</td>
<td>NS</td>
</tr>
<tr>
<td>Power ratio</td>
<td>4.3 ± 5.5</td>
<td>5.4 ± 11.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Scintigraphy figures for controls come from the validation study of Kairemo et al 1998 (n = 11). NS = non-significant.
**Table 11.** Comparision of $^{13}$C-octanoic acid breath test (OBT), electrogastrography (EGG), and combined OBT and EGG in detecting delayed gastric emptying of solids in diabetic patients ($n = 27$) as compared to scintigraphy, the gold standard.

<table>
<thead>
<tr>
<th></th>
<th>OBT</th>
<th>EGG</th>
<th>OBT and EGG combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity (%)</td>
<td>43</td>
<td>29</td>
<td>57</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>80</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>43</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>80</td>
<td>76</td>
<td>80</td>
</tr>
</tbody>
</table>
6. DISCUSSION

6.1 Electrogastrography in evaluation of gastric motor function

EGG measures the gastric slow waves needed for regulation of peristalsis, and the postprandial power increase in these slow waves reflects gastric contractions. In our study with chronic renal failure (CRF) patients we found the power ratio to be greater in those on peritoneal dialysis than in the same patients with the peritoneal cavity empty. This may have been due to the good electrical conductance of the dialysis fluid or the mechanical effect of the fluid pushing the stomach closer to the abdominal wall.

Another group found a non-significant decrease in slow-wave dominant power after peritoneal dialysis, but no EGG was recorded during dialysis, only before and after (Lee S et al 2000). Effect of haemodialysis on gastric slow-wave dominant power is controversial, as in one study the power increased after haemodialysis (Lee S et al 2000), and in another study it decreased (Ko et al 1998). A scintigraphic study of CRF patients both on peritoneal dialysis and with the peritoneal cavity empty showed that the dialysis fluid in the peritoneal cavity has no effect on gastric emptying (Hubalewska et al 2004). EGG should, in fact, always be recorded with the peritoneal cavity empty of dialysis fluid, as measuring the power ratio is not reliable during dialysis.

Additionally, we found that the postprandial power increase of the slow waves was greater in symptom-free patients than in dyspeptic patients, which may indicate faster gastric emptying in symptom-free patients. However, gastric emptying was not measured in our study. We found no significant difference in the EGG parameters between CRF patients and controls overall, nor between type 1 diabetic patients and their controls.

In one Swedish study, in non-diabetic CRF patients on peritoneal dialysis, when measured by scintigraphy, gastric emptying was delayed, but, in agreement with our study, no difference emerged in EGG parameters between those patients and controls (Fernström et al 1999). In another study involving both diabetic and non-diabetic CRF patients, gastric myoelectrical activity was impaired (Lin et al 1997). Hyperglycaemia (Jebbink et al 1994) and autonomic neuropathy (Kawagishi et al 1997) have been associated with gastric myoelectrical disturbances in diabetic patients, and under euglycaemic conditions these disturbances may disappear (Jebbink et al 1994). Not all studies comparing diabetic patients and controls find any difference in gastric myoelectrical activity (Pfaffenbach et al 1995b).

Using validated criteria (Parkman et al 2003), we found that EGG detected only two of the seven type 1 diabetes patients with delayed gastric emptying of solids in scintigraphy, as most of the EGG recordings were normal also in these patients. The one patient with the slowest gastric emptying in scintigraphy also had the most abnormal EGG: The dominant frequency for 30% of the preprandial recording time was in the tachygastric region. Likewise, in some other studies in diabetic patients, correlation between the gastric emptying rate measured by scintigraphy and EGG parameters is poor (Pfaffenbach et al 1995b, Soykan et al 1999). In our experience, EGG lacks the sensitivity to detect diabetic gastroparesis.
6.2 Comparison of scintigraphy and the $^{13}$C-octanoic acid breath test in measuring gastric motor function

In our studies, the correlation between scintigraphy and OBT was poor, both in FD patients and in patients with type 1 diabetes. The ideal method for comparing scintigraphy and OBT would have been performing both measurements simultaneously after the same test meal. A good correlation between scintigraphy and OBT has appeared only with simultaneous measurements (Ghoos et al 1993, Lee J et al 2000, Chey et al 2001, Bromer et al 2002, Zahn et al 2003). Because in our clinic scintigraphy and OBT have been validated for different test meals, this was impossible. As both scintigraphy (Koskenpato et al 1998) and OBT (Choi et al 1997, 1998) have proven to be well reproducible, we considered comparison possible on different days. Our aim was not to measure the gastric emptying of a certain meal at a particular moment in time, but to compare two reproducible methods of measuring gastric emptying in patient populations with a known tendency toward delayed gastric emptying. We assumed that both methods would detect the patients with gastroparesis even if the test meals differed. In our opinion, if correlation between scintigraphy and OBT is limited to simultaneous measurement, the value of OBT as an independent tool for measuring gastric emptying is diminished.

Our scintigraphic method measures gastric emptying for 90 min, which is considered long enough to detect patients with gastroparesis. Longer measurements have been recommended for more accurate results in borderline cases (Guo et al 2001). In the studies that observed a good correlation between scintigraphy and OBT, the scintigraphy follow-up time was 2 hours (Ghoos et al 1993, Zahn et al 2003) or 4 hours (Lee J et al 2000, Bromer et al 2002), which might have resulted in more accurate gastric half-emptying times and explained the better correlation. In the European multicenter study that found a good correlation between scintigraphy and OBT, scintigraphic scans were performed every 15 minutes until 75% of the ingested contents had left the stomach, (Delbende et al 2000).

Does OBT actually measure gastric emptying? OBT and scintigraphy do not actually measure the same phenomena in detail. In OBT, absorption and metabolism of the $^{13}$C-octanoate acid of the test meal are rapid and are not considered rate limiting (Lacroix et al 1973, Bach and Babayan 1982). However, half of the $^{13}$C-octanoate acid remains in the tricarboxylic acid cycle, and $^{13}$CO$_2$ is exhaled only after passage through the bicarbonate pool (Van Hall 1999). Because of this process, it is possible that no true linear correlation exists between the gastric half-emptying times measured by scintigraphy and OBT (Jackson and Bluck 2005). Besides ours, some other studies also have found the correlation between scintigraphy and OBT to be poor (Choi et al 1997, 1998). Furthermore, when OBT is extended from 4 to 6 or 8 hours, the calculated gastric half-emptying time is reduced (Bromer et al 2002, Lee J et al 2000, Choi et al 1997). This means that the gastric half-emptying time measured by OBT is a calculated mathematical parameter rather than an absolute measurement of the gastric half-emptying time.

Besides the non-linear least-squares method and geometrical method used in our studies, another, the Wagner-Nelson method, has been suggested for calculating the gastric half-emptying time of solids from the $^{13}$C-acetate breath test (Sanaka et al 2004,
In this method, the nonlinear least-squares fitting is applied to the bell-shaped breath-test curve and not to the cumulative curve as in the conventional method. This makes the Wagner-Nelson method less stable, because changes in the breath-test curve are sharper than in the cumulative curve. In practice, both methods result in similar gastric emptying times and in similar correlations between breath test and scintigraphy.

Even if OBT resulted in fairly reliable figures as in the European multicenter study, OBT measures only gastric emptying. Besides delayed gastric emptying, abnormal intragastric distribution can also occur in both functional dyspepsia (Tack and Lee 2005) and, according to our study, in type 1 diabetes. With our standardized, dynamic, scintigraphic double-tracer method, it is possible to measure both gastric emptying of solids and liquids and intragastric distribution. Thus, for examining all components of gastric motor function, scintigraphy is irreplaceable.

6.3 Impaired gastric motor function in type 1 diabetes

Of the 27 diabetic patients who all experienced upper abdominal symptoms, only 7 (26%) showed delayed gastric emptying of solids in scintigraphy. The majority of our patients, however, although suffering from abdominal symptoms that significantly impaired their quality of life, had normal gastric emptying of both solids and liquids. This suggests some other explanation for their upper abdominal symptoms than impaired emptying.

In patients with functional dyspepsia, besides delayed gastric emptying, other possible pathophysiological mechanisms for upper abdominal symptoms have been visceral hypersensitivity and impaired gastric accommodation (Tack and Lee 2005). In a study of eight patients with type 1 diabetes mellitus and autonomic neuropathy, a decrease in gastric fundus volume after a liquid test meal was detected by barostat, indicating impaired fundic relaxation (Samsom et al 1998). In our study, an abnormally high percentage of solids in the antrum at 10 minutes appeared in ten (37%) patients, who all had normal gastric emptying of solids and liquids. This indicates another mechanism for upper abdominal symptoms in type 1 diabetes: abnormal intragastric distribution due to impaired fundic relaxation.

We found a dependence between gastric half-emptying time of solids and the autonomic neuropathy score. Similarly, case-controlled studies have shown delayed gastric emptying as being more common in diabetic patients with autonomic neuropathy than in those without (Keshavarzian et al 1987, Hongo and Okuno 1993). In three studies including 67, 34, and 83 diabetic patients, autonomic neuropathy measured by standard cardiovascular tests correlated with delayed gastric emptying (Horowitz et al 1991, Ziegler et al 1996, Merio et al 1997), whereas two studies including 101 and 42 patients failed to detect any such correlation (Jones et al 2001, De Block 2002). Autonomic neuropathy and delayed gastric emptying would logically be interrelated, because gastric emptying is controlled by the autonomic nervous system. Probably the pathophysiological mechanisms causing diabetic gastroparesis lie within the enteric nervous system (Wrzos et al 1997, Takahashi et al 1997, Ordog 2008).
Neither age nor duration of diabetes affected gastric emptying rate in our study or in four other studies (Jones et al 2001, De Block 2002, Hongo and Okuno 1993, Merio et al 1997). Mean ages of patients in our study and in those four studies were similar. Duration of diabetes in our patients (29 ± 11 years) was longer than the other studies’ 16 to 20 years, implying that not even very long diabetes duration affects gastric emptying rate. None of the symptom scores calculated in our study correlated with the gastric emptying rate. Lack of correlation between symptoms and delayed gastric emptying has been an almost uniform finding (Lyrenas et al 1997, Merio et al 1997, DeBlock et al 2002). In one study, the presence of abdominal bloating/fullness was associated with delayed gastric emptying of both solids and liquids (Jones et al 2001). Not even the Gastroparesis Cardinal Symptom Index, which has been validated for evaluation of symptom severity in patients with gastroparesis (Revicki et al 2003, 2004), correlates with gastric emptying rate (Cassilly et al 2008b).

Between patients with delayed and normal gastric emptying of solids, our study found only a trend for a difference in fasting plasma glucose and HbA1c. In most studies, the adverse effect of hyperglycaemia on gastric emptying has been evident (Fraser et al 1990, Schvarcz et al 1993, 1997 Samsom et al 1997, Rayner et al 2001, Russo et al 2005, Jones et al 2001). However, similar to our study, some studies fail to detect any correlation between glucose levels and gastric emptying in diabetic patients (De Block et al 2002, Ziegler et al 1996, Merio et al 1997, Lyrenas et al 1997). As gastric emptying is affected by many factors, it is not always possible to detect such correlation in clinical studies. Long-term glucose control – measured as HbA1c – was related to gastric emptying of a solid (De Block et al 2002) and of a semisolid meal (Cucchiara et al 1998) in diabetic patients, but other studies (Ziegler et al 1996, Merio et al 1997) found no such correlations. To what extent long-term glucose control contributes to gastric emptying in diabetic patients remains unclear.

6.4 Nizatidine in functional dyspepsia patients

According to a meta-analysis of 17 studies, delayed gastric emptying appears in up to 40% of patients with functional dyspepsia (Quartero et al 1998). However, all of our FD patients had normal gastric emptying of solids (T1/2 solid ≤ 137 min) and liquids (T1/2 liquid ≤ 58 min) during treatment with placebo when compared to normal values obtained from the validation study (Kairemo et al 1998). Only during nizatidine treatment did five patients show abnormally slow gastric emptying of solids. Delayed gastric emptying was therefore not the cause of their dyspeptic symptoms. Besides slow gastric emptying, abnormal distribution of a meal due to impaired gastric accommodation can cause FD symptoms (Tack and Lee 2005). In our study, intragastric distribution of the test meal during placebo and nizatidine treatment was similar. However, when compared to the normal values of the validation study, six FD patients (38%) had abnormally high intragastric distribution during placebo and five patients (33%) during nizatidine. It may be that impaired gastric
accommodation rather than delayed gastric emptying was the cause of some of our patients’ dyspeptic symptoms.

Nizatidine enhances gastric emptying in studies by indirect methods like the acetaminophen method, EGG, and measurement of intragastric volume through a nasogastric tube (Harasawa et al 1993, Memis et al 2002, Tomokane et al 2004). In contrast, in our study with a validated scintigraphic method, nizatidine delayed gastric emptying significantly. It is possible that nizatidine delays gastric emptying by reducing gastric acid secretion similar to the action of ranitidine. In healthy controls, despite increasing antral contractility, ranitidine delays gastric emptying of solids because of decreased acid secretion (Parkman et al 1998b). Nizatidine and ranitidine have equal cholinergic properties, and both of them increase antral contractions in guinea pig muscle strips (Parkman et al 1998a). Decreased acid secretion inhibits the conversion of pepsinogen to pepsin, resulting in impaired hydrolysis of dietary proteins and delayed gastric emptying of solids (Kerrigan et al 1991, Kittang et al 1985). Acid suppression also raises serum gastrin levels, which is associated with delayed gastric emptying (Hamilton et al 1976, MacGregor et al 1978).

In our FD patients, nizatidine relieved both reflux-like symptoms and other dyspeptic symptoms slightly (ulcer–like and dysmotility-like), but the result was non-significant for all symptom scores. We evaluated dyspeptic symptoms by a previously validated questionnaire (Heikkinen et al 1995, 1998, Koskenpato et al 2001) including ulcer-like, dysmotility-like, and reflux-like symptoms. Acid suppression reduces ulcer-like and reflux-like symptoms in FD patients (Talley et al 1998), which is also the most likely explanation for symptom relief in our patients, rather than any effect of nizatidine on gastric emptying. According to present criteria, FD studies should not include patients with reflux-like symptoms (Tack and Lee 2005). Although patients with predominant reflux-like symptoms were excluded from our study, it is possible that some reflux-disease patients participated. Excluding patients with reflux disease with certainty would have required 24-hour oesophageal pH-monitoring prior to the study.

Similar to our study, symptoms of FD patients correlated with poor quality of life in one study based on questionnaires, especially in the areas of physical and social functioning (Jones et al 2005). Our FD patients’ quality of life, though lower than in the general population both at baseline and during treatment, improved with nizatidine modestly. This non-significant improvement in quality of life was probably due to acid suppression rather than to any effect on gastric emptying.
7. CONCLUSIONS

Gastric motility disorders can be related to several diseases such as type 1 diabetes, functional dyspepsia, and chronic renal failure. As new treatment options emerge, demand is increasing for methods of measuring gastric motor function. Dynamic dual tracer scintigraphy is more accurate than OBT or EGG in measuring gastric emptying of solids. Besides, it also measures gastric emptying of liquids and the intragastric distribution of the ingested test meal. Combining OBT and EGG detects more patients with delayed gastric emptying of solids than does performance of one of the tests alone, but sensitivity and specificity remain low.

In patients with type 1 diabetes and upper abdominal symptoms, delayed gastric emptying of solids and impaired gastric accommodation are common. Dependence exists between autonomic neuropathy score and delayed gastric emptying of solids in these patients. Neither age nor long duration of diabetes affect the gastric emptying rate, and symptom scores correlate poorly with delayed gastric emptying. Good long-term glucose balance does not affect the gastric emptying rate, but as it reduces the risk for autonomic neuropathy, aiming at optimal glucose balance is important in preventing diabetic gastroparesis.

No optimal drug exists for treating gastric motility disorders and related symptoms. This may be due to the fact that not only delayed gastric emptying but also other pathophysiological mechanisms are involved and cannot be treated by a single drug. Gastric electrical stimulation is a promising treatment method for severe gastroparesis. It reduces symptoms and improves quality of life and glucose balance but enhances gastric emptying only modestly. Nizatidine delays gastric emptying in patients with functional dyspepsia, and tends to improve symptoms and quality of life scores in these patients, but this is due to acid suppression rather than to any effect on gastric emptying.
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Jari Punkkinen
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