Prevalence of Gastroparesis in Type 1 Diabetes Mellitus and its Relationship to Dyspeptic Symptoms

Catalin Sfarti, Anca Trifan, Catalin Hutanasu, Camelia Cojocariu, Ana-Maria Singeap, Carol Stanciu

University of Medicine and Pharmacy "Gr. T. Popa" Iasi, Romania

Abstract

Background and Aim: Gastroparesis and/or dyspeptic symptoms occur in around 50% of type 1 diabetic patients. The aim of our study was to evaluate the prevalence of gastroparesis in patients with type 1 diabetes using $^{13}$C-octanoic acid breath test ($^{13}$C-OBT) and the relationship between dyspeptic symptoms and gastric emptying.

Methods: Gastric emptying of solids was evaluated prospectively in euglycemic conditions in 69 type 1 diabetic patients (male/female: 36/33; mean age 49.5 ± 14.2 years; mean duration of diabetes 20.4 ± 8.2 years) and 40 healthy volunteers (male/female 17/23; mean age 34.3 ± 16 years) using $^{13}$C-OBT. Dyspeptic symptoms, autonomic nerve function and Helicobacter pylori (H. pylori) status were assessed.

Results: Solid gastric emptying was slower in diabetic patients (T1/2=125.36 ± 31.5min) than in healthy subjects (T1/2=88.5 ± 27.3 min) (p<0.05). Gastric emptying was slower in diabetic female compared to diabetic male patients (p<0.05). Body mass index (BMI) was the only independent predictor for delayed solid gastric emptying in a logistic regression model testing HbA1c, BMI, age, diabetes duration, H. pylori status, peripheral neuropathy, retinopathy, nephropathy, and autonomic neuropathy. Abdominal bloating and upper abdominal pain were associated with delayed gastric emptying.

Conclusions: We found that 33.7% of type 1 diabetic patients had delayed gastric emptying that correlated with female gender, increased BMI, abdominal bloating and upper abdominal pain.

Key words


Introduction

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of a mechanical obstruction. It is generally associated with nausea, vomiting, early satiety, postprandial fullness, bloating and upper abdominal pain, but there are also asymptomatic cases [1-3].

The prevalence of gastroparesis in the general population is difficult to evaluate, due to the weak correlation between symptoms and gastric emptying [4-6] and the need to apply a complex diagnostic test to a large community [7]. The results of the studies regarding the prevalence of gastroparesis in diabetic patients are rather controversial. Most studies use the scintigraphic method to measure gastric emptying which, although considered to be the "gold-standard", limits the number of patients studied and therefore the statistical power of the research [8-10]. Furthermore, certain studies included selected diabetic patients with gastrointestinal symptoms or those without a strict euglycemic control during evaluation, aspects that can induce a false increase in the prevalence of delayed gastric emptying in the study group [11, 12].

The current opinion is that gastroparesis cannot be diagnosed based on symptoms alone and confirmation of delayed gastric emptying is required [13, 14]. Few studies have examined the predictive value of the symptoms reported by patients during the gastric emptying test for the rate of gastric emptying, as a response to the same stimulus (a standardized lunch), an aspect which we are going to monitor in our study.

The aim of this study was to evaluate the prevalence of diabetic gastroparesis and its possible role in dyspeptic symptoms in patients with type 1 diabetes mellitus.

Methods

We prospectively studied a consecutive series of 72 patients referred to the Institute of Gastroenterology and Hepatology and the Diabetes Centre of "Sf. Spiridon" Hospital, Iasi (North-Eastern Romania) during a 6-month period (September 2008 - February 2009). The patients with previous cholecystectomy or major gastrointestinal surgery, clinically significant digestive, renal, pulmonary, cardiovascular or neuropsychiatric diseases and ongoing
pregnancy were excluded as were those receiving antibiotics, nonsteroidal anti-inflammatory drugs, prokinetic or antisecretory treatment. The control group consisted of 40 healthy volunteers (students and medical staff). The study was carried out in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the Ethics Committee of Institute of Gastroenterology and Hepatology.

During the screening visit, each participant was subject to a clinical assessment, filled in the gastroparesis symptom questionnaire and underwent an abdominal ultrasound; the diabetic patients also had an upper gastrointestinal endoscopy in order to exclude any potential digestive pathology which might explain their complaints. HbA1c was measured in all diabetic patients in order to establish a correlation between this value and the gastric emptying rate. H. pylori infection was evaluated by histology, rapid urease test or 13C-urea breath test in diabetic patients and only by 13C-urea breath test in healthy subjects.

Autonomic nerve function was assessed by standardized cardiovascular reflex tests [7]. Parasympathetic function was evaluated by the variation (RR interval) of the heart rate during deep breathing and the immediate heart rate response to standing. Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The result of each of these tests was scored as 0=normal, 1=borderline, or 2=abnormal. A total score of minimum 3 was considered to indicate autonomic nerve damage. The diabetic patients included in the study underwent examination by specialists to assess the presence of chronic complications of diabetes: peripheral neuropathy, retinopathy and nephropathy.

The main visit consisted of undergoing a 13C-OBT to evaluate gastric emptying of solids and completing the symptom questionnaire during the test. Diabetic patients followed the usual treatment during the previous day and received the morning dose of insulin in the test day. Patients’ glycaemia was monitored before the breath test was started and the procedure was initiated only if patients were euglycemic. Glucose and insulin were administered intravenously to the subjects who were not euglycemic in order to obtain normal glycaemic values. Glyceemic control was monitored prior to study initiation and during measurements at 30, 60, 90, 120 and 240 minutes, after the test meal.

The symptoms (postprandial fullness, early satiety, bloating, nausea, vomiting and upper abdominal pain) were graded from 0 to 3 (0=none; 1=mild; 2=moderate; 3=severe). The maximum possible score was 18. Patients filled in the questionnaire once during the screening visit and then during the gastric emptying test.

The breath test was performed by using the method previously standardized and was adjusted to the recommendations made by the manufacturer of the IRIS infrared spectrophotometer (Wagner-Analysen Technik, Bremen, Germany). The patients consumed the meals with 100 ml of water in an upright sitting position. The caloric intake was 250 Kcal, and the composition consisted of 42% carbohydrates, 18% proteins and 40% lipids. The test meal was consumed within 10 minutes.

**Statistical analysis**

Continuous variables were reported as mean ± standard deviation and categorical variables as frequencies or percentages. Differences between groups were analyzed using the χ² test for categorical data and the Student t test for quantitative data. Bivariate correlations between continuous variables were calculated using the Pearson test. All reported P values are 2-sided, and P values lower than 0.05 were considered to indicate significance.

**Results**

The characteristics of the patients and controls are presented in Table I.

One control and 12 postprandial measurements were made. The test meal consisted of two slices of white bread, one scrambled egg with the yolk doped with 100 mg of 13C-octanoic acid (Wagner-Analysen Technik, Bremen, Germany). The patients consumed the meals with 100 ml of water in a upright sitting position. The caloric intake was 250 Kcal, and the composition consisted of 42% carbohydrates, 18% proteins and 40% lipids. The test meal was consumed within 10 minutes.

**Table I. Characteristics of the diabetic patients and healthy subjects**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean ± SD</th>
<th>Women</th>
<th>Men</th>
<th>34.3 ± 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%) (mean ± SD)</td>
<td>8.4 ± 2.1</td>
<td>16 (23.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td>12 (17.4)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>5 (7.2)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>24 (34.8)</td>
<td>-</td>
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</tbody>
</table>
| HbA1c (%) (mean ± SD) | 91.3 ± 10.8mg/dl | after extra administration of insulin doses in the patients whose values exceeded the normal limits. The average HbA1c value was 8.4 ± 2.1% in the entire group, and 8.82 ± 2.48% in the group with delayed emptying of solids. Eight (11.6%) patients had values within the normal range (3.5–6.0%), 31 (44.9%) patients had values

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<table>
<thead>
<tr>
<th>Gender</th>
<th>Diabetic patients (n=69)</th>
<th>Control group (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>Women</td>
</tr>
<tr>
<td>HbA1c (%) (mean ± SD)</td>
<td>8.4 ± 2.1</td>
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</tr>
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</table>
in the 6.1–9.0% range, 23 (33.3%) within the 9.1-12.0% range and 7 (10.2%) patients had values above 12.0%.

There were sixteen (23.2%) patients with peripheral neuropathy, 12 (17.4%) with diabetic retinopathy, 5 (7.2%) with diabetic nephropathy and 24 (34.8%) patients with autonomic neuropathy.

H. pylori infection was present in 49 (71%) diabetic patients and 25 (62.5%) control subjects, the difference being statistically not significant.

The calculation of the body mass index (BMI) identified 41 (59.4%) overweight patients, of whom 19 (27.5%) obese in the diabetic group and 15 (37.5%) overweight individuals and 7 (17.5%) obese were identified in the control group. Body mass index was the only independent predictor for delayed solid gastric emptying in a logistic regression model testing HbA1c, BMI, age, diabetes duration, H. pylori status, peripheral neuropathy, retinopathy, nephropathy, and autonomic neuropathy (Table II).

The average T1/2 value in diabetic patients was 125.36 ± 31.5 min as compared to the control group where the average T1/2 value was 88.5 ± 27.3 min, the difference being statistically significant (p<0.05). Gastric emptying coefficient was lower in diabetic patients than in the control group (p<0.05) (Table III). We considered as patients with delayed gastric emptying those with both parameters out of the normal range. There were 26 diabetic patients (37.7%) with delayed gastric emptying for solids using these criteria. The cut-off values of the monitored parameters were: T1/2=135 min and GEC=3.1.

Gastric emptying was significantly slower in diabetic female (T1/2=133 ± 27.5 min) compared to diabetic male patients (T1/2=117 ± 24.3 min) (p<0.05). The BMI was an independent predictor of slower solid gastric emptying (p<0.05).

No statistically significant correlations were identified between the gastric emptying rate and age (p=0.32), diabetes duration (p=0.33), HbA1c value (p=0.06), H. pylori status (p=0.05). In addition, the chronic complications of diabetes (peripheral neuropathy, retinopathy, nephropathy or autonomic neuropathy) did not cause any significant differences of gastric emptying rate (p>0.05).

The percentage of diabetic patients with gastrointestinal symptoms detected by the symptom questionnaire was 65.2%. The average symptom score for the patients with diabetes was 3.45 ± 2.7, significantly higher than in the control group (0.41 ± 0.8) (p = 0.044). The total symptom score for diabetic patients with delayed gastric emptying was 6.58 ± 4.1 higher than in diabetic patients with normal gastric emptying: 2.74 ± 2.1 but without statistical significance (p = 0.73). The symptom distribution and scores for the diabetic patients are summarized in Table IV.

Abdominal bloating and upper abdominal pain were more frequently present in diabetic patients with delayed gastric emptying as compared to those with normal gastric emptying (p<0.05). No significant association was established between postprandial fullness, nausea, vomiting and early satiety (Table V).

**Discussion**

Impairment of gastric emptying is well recognized in patients with diabetes mellitus, especially those with long-standing type 1 diabetes mellitus (15-17). Blood glucose level, disease duration, female gender and autonomic neuropathy are known to be independent predictors of delayed gastric emptying [17-19].

The current gold-standard for evaluation of patients with
suspected gastroparesis is quantitative scintigraphy [20]. However, scintigraphy has several limitations, including high cost, radiation exposure and the need for specialized equipment [20, 21]. Breath tests using stable isotopes offer an alternative to scintigraphic techniques for the measurement of gastric emptying. Among breath tests, $^{13}$C-OBT has proved useful for studying gastric emptying in various clinical settings of diabetic patients [22-26].

In the present study, we used $^{13}$C-OBT to measure gastric emptying in type 1 diabetes patients consecutively recruited, regardless of gastrointestinal symptoms and disease duration and to compare the results with those obtained in healthy subjects (control group). The type 1 diabetic patients were prospectively studied and the results showed a 37.7% prevalence of delayed gastric emptying of solids, significantly higher than in healthy volunteers (8.3%; p<0.05), a figure which is in the range of those reported in the literature [27-30].

Thus, De Block et al [31] reported a 40% prevalence of impaired gastric emptying of solids in a group of 42 patients with type 1 diabetes mellitus, whereas Samsom et al [32] showed that delayed gastric emptying of solids occurred only in 28% of the 186 diabetic patients. It is worth mentioning that both studies have included diabetic patients regardless of symptoms or diabetes duration, but De Block et al evaluated only patients with type 1 diabetes mellitus, whereas Samsom et al included patients with type 1 and type 2 diabetes mellitus. More recently, Matsumoto et al [22] reported that both type 1 and type 2 diabetic patients showed delayed gastric emptying compared with controls, but patients with type 1 diabetes showed more delayed gastric emptying than type 2 diabetes patients. In earlier studies, Horowitz et al [10] found even a higher prevalence (47%) of delayed gastric emptying in diabetic patients and Jones et al [17] reported values that reached 57%. However, in these studies euglycemia was not maintained during patients’ assessment, and it is known that hyperglycemia delays gastric emptying rate [33, 34]. In our study, gastric emptying was measured while patients were in an euglycemic state and this might explain why the prevalence was lower than in the above mentioned studies.

We found that the diabetic patients with delayed gastric emptying had more symptoms than those with emptying times within normal limits. Similar results have been reported by Samsom et al [32] and Keshavarzian et al [35]. As regards the symptoms evaluated through the symptom questionnaire, 45 (65.2%) of our patients had upper abdominal symptoms, but only bloating and upper abdominal pain were significantly correlated with delayed gastric emptying. In contrast, nausea, vomiting, postprandial fullness and early satiety were not related to gastric emptying. Samsom et al [32] reported that gastric emptying was significantly slower in diabetic patients with complaints of upper abdominal pain and fullness. Jones et al [17] found statistical correlations between abdominal bloating, postprandial fullness and gastric emptying of solids. Most of the published studies [10, 17, 32, 36, 37] have identified certain correlations between various symptoms and the gastric emptying rate, but none of them established a permanent association between a certain symptom and the impaired gastric emptying rate of solids. Furthermore, some studies [38, 39] showed no correlation between symptoms and gastric emptying. These differences between studies may be explained by patients’ selection (diabetes duration, diabetes control, selection of symptomatic patients only) and the evaluation method of gastric emptying (scintigraphy or breath test).

We did not find a significant correlation between long-term glycemic control (evaluated by HbA1c) and the solid gastric emptying rate, which is in line with other studies [17, 32, 40], but disagree with that published by Bytzer et al [41], which suggests that dyspeptic symptoms are related to poor glycemic control. In our study, diabetic patients were evaluated under euglycemic conditions and therefore, we were unable to establish a relation between poor glycemic control and delayed gastric emptying.

Most of the previous studies [17, 32, 42-44] reported a gender difference in gastric emptying both in healthy control subjects and diabetic patients which was slower in females. We also found that gastric emptying was significantly slower in diabetic women than in men. The explanation for this difference can only be speculative at this moment, being most probably related to the hormonal differences between the two genders, as recent studies identified an important role of oxytocin in the gastric emptying rate [45].

H. pylori infection was not an independent factor of correlation with gastric emptying. Our results are in concordance with most previous studies [46-52], which have suggested that there is no correlation between H. pylori infection and gastric emptying whether evaluated by scintigraphy [53] or by $^{13}$C-OBT [54].

In the present study, we found a correlation between higher BMI and delayed gastric emptying. A significant difference was observed between the solid gastric emptying rate in obese diabetic patients and that in diabetics with

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**Table V.** The association between gastric emptying rate and symptoms

<table>
<thead>
<tr>
<th>Gastric emptying</th>
<th>Patients (no.)</th>
<th>Symptoms no. (%)</th>
<th>Symptom</th>
<th>Patients (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed</td>
<td>26</td>
<td>Nausea 11 (42.3%)</td>
<td>Early satiety 13 (50%)</td>
<td>Bloating 21 (80.7%)</td>
</tr>
<tr>
<td>Normal</td>
<td>43</td>
<td>Nausea 17 (39.5%)</td>
<td>Early satiety 20 (46.5%)</td>
<td>Bloating 16 (37.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p value</th>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8231</td>
<td>0.7773</td>
<td>&lt; 0.05</td>
<td>0.4348</td>
<td>&lt; 0.05</td>
<td>0.7007</td>
<td></td>
</tr>
</tbody>
</table>

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normal weight. This relation between high BMI and delayed solid gastric emptying should be further confirmed in other studies, since the current data are contradictory [17, 55, 56].

We found no significant differences in the gastric emptying rate between diabetic patients with and without complications (peripheral neuropathy, retinopathy, nephropathy, autonomic neuropathy) which is in line with some studies [32] and disagrees with others [17, 31, 35].

Conclusion
Our study showed a 37.7% prevalence of delayed gastric emptying in unselected patients with type 1 diabetes mellitus and identified abdominal bloating, upper abdominal pain, female gender and increased body mass index as independent factors of correlation with delayed gastric emptying.

Conflicts of interest
None to declare.

References