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Cent. Eur. J. Med. • 7(1) • 2012 • 20-24
DOI: 10.2478/s11536-011-0099-9

Central European Journal of **Medicine**

Correlation between symptoms of diabetic gastroparesis and results of gastric scintigraphy

Research Article

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Received 17 November 2010; Accepted 17 August 2011

Abstract: Background: delayed gastric emptying is detectable in 20-40% of patients with type 1 and type 2 diabetes. The prevalence of symptoms suggestive for diabetic gastroparesis is much lower. The aim of the study was to evaluate the gastric emptying and to correlate the results with dyspeptic symptoms. Methods: we included 55 patients with diabetes mellitus (32F/ 23M; mean age 60.34 ±4.71) and 50 controls (30F/20M; mean age 58.55 ±4.78). Gastric emptying was assessed using gastric emptying scintigraphy (GES). Dyspeptic symptoms were assesed using Gastroparesis Cardinal Symptom Index (GCSI). Results: 49% reported one or more gastrointestinal symptoms from the scale. From these, 55,5% reported fullness and/or early satiety, 29,6% reported bloating, 14,8% reported vomiting or nausea. 31 patients (56,33%) had abnormal gastric emptying on scintigraphy at 2 hr and 24 patients had normal GES. From subgroup with abnormal GES, only 53,33% reported gastrointestinal symptoms previous to the evaluation, and only 3 from the 9 symptoms of the GCSI had a significant correlation with the severity of the gastric emptying. Conclusion: there was a positive but non significant correlation between symptom score in patients with delayed GE compared to patients with normal GE, except correlation between early satiety and delayed GE.

Keywords: *Gastric emptying scintigraphy • Gastroparesis*

1. Introduction

Diabetic autonomic neuropathy may involve the cardiovascular, genitourinary and the neuro-endocrine system as well as the upper and lower gastrointestinal tract. Abnormalities of gastrointestinal function in diabetics are thought to be interrelated, at least in part, to autonomic neuropathy of the enteric nervous system [1-6]. Gastroparesis is a chronic disorder of gastric motility that is characterized by delayed emptying of either solids or liquids from the stomach in the absence of any mechanical obstruction [5-7]. It is difficult to establish the prevalence of this disorder, because during the first stages the disease is asymptomatic for a long period of time, and the symptoms, when present, are highly non-specific [8,9]. The most frequent etiology is diabetes mellitus. It is estimated that 20% to 40% of patients with diabetes, primarily those with long duration of type 1 diabetes mellitus with other complications, develop gastroparesis [10].

Gastroparesis can also be seen in a variety of conditions: scleroderma and other connective tissue diseases, Norwalk virus and rotavirus, iatrogenic causes (alpha-2-adrenergic agonists, high dosages of Tricyclic antidepressants, subtotal colectomy, intended or accidental injury to the vagus nerves, with Billroth II gastrectomy, fundo-plication, lung or heart transplantation), psychiatric disease, neurologic disease, autoimmune disease; it can also have idiopathic etiology [11,12]. Symptoms may include nausea, vomiting, early satiety, abdominal pain, and bloating [13,14]. Assessment of severity of gastroparesis is important for appropriate management. One assessment method is the Gastro-

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paresis Cardinal Symptom Index (GCSI), which consists of nine symptom severity items that cover the following domains: nausea/vomiting (3 items); fullness/early satiety (4 items); and bloating (2 items).

The most cost-effective, simple, and widely available technique to confirm the presence of postprandial gastric stasis is gastric emptying scintigraphy (GES). Alternatives to scintigraphy are: 13C-octanoic acid breath tests (13C-OBT), magnetic resonance imaging (MRI), gastroduodenal manometry, wireless motility capsule ("SmartPill"), autonomic tests, and single photon emission computed tomography [16,17]. Treatment of gastroparesis may involve prokinetic agents, which could accelerate GE and relieve the gastroparetic symptoms [18].

2. Materials and methods

We included in our study 55 patients with diabetes mellitus (32F/23M; mean age 60.34 ± 4.71 years) and 50 healthy controls (30F/20M; mean age 58.55 ± 4.78 years) who were free of symptoms and any known gastrointestinal disease or diabetes mellitus. The mean duration of disease in diabetic patients was 10.22 (± 9.67) years; 15 (27.27%) patients required insulin treatment; 14 (25.45%) patients were treated with sulfonylurea; 26 (47.27%) patients were treated with biguanids. Gastric emptying was assessed in both controls and diabetic patients using GES. GE was measured at 0, 1, and 2 h after ingestion of a 99mTc sulfur colloid-labeled egg meal. Normal values for the percent remaining in the stomach at the key time points were 37% to 90% at 1 h, 30% to 60% at 2 h.

Dyspeptic symptoms were assessed using the GCSI. Patients in both the study and control groups completed the questionnaire, which covered the following nine symptoms: nausea, retching, vomiting, stomach fullness, not able to finish a normal sized meal, feeling excessively full after meals, loss of appetite, bloating, stomach or belly visibly distended. The GCSI represents a subset of the longer Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM) that also includes symptoms of gastro-esophageal reflux and dyspepsia. The GCSI and PAGI-SYM were designed to assess the severity of patients' symptoms during the previous 2 weeks, and have been used in clinical trials involving patients with gastroparesis [15]. Symptoms were rated by the patients among the choices none (0), very mild (1), mild (2), moderate (3), severe (4), and very severe (5). The GCSI total score equals the sum of the nausea/vomiting, bloating and fullness/early satiety subscales, divided by 3. Mild symptoms are those that are present but do not interfere with daily activities; moderate symptoms are present and interfere with, but do not preclude, daily activities; severe symptoms seriously interfere with daily activities. Very mild and very severe are variations of these symptom descriptions. Patients completed the questionnaire one day before GES.

The diabetic patients also had an upper gastrointestinal endoscopy to exclude any potential obstruction that might explain their complaints or delayed GE. HbA1c was measured in all diabetic patients to establish a correlation between this value and the GE rate. We also measured cholesterol, triglycerides, and plasma glucose in all diabetic patients and controls. Written informed consent was obtained from all patients and the study was conducted according to the Declaration of Helsinki and the local ethic committee.

2.1. Statistical analysis

Continuous variables were expressed as the mean (SD). Differences were tested for significance by an unpaired Student's t test, which is sensitive even for small and numerically unequal groups. Upper and lower 95% confidence intervals for each variable were calculated from the two tails of the Student's t test distribution. We compared the results between the study groups and with the control group. A p value < 0.05 was considered significant. Pearson correlation coefficients were used to explore linear relationships between the study variables. Statistics were performed with SPSS for Windows, version 10.0.

The demographic characteristics of the patients and controls are presented in Table 1.

Table 1. Demographic characteristics of the study group

Parameter	Diabetes mellitus	Control	p
Number (F/M)	55 (32F/23M)	50 (30F/20M)	0.75
Age	60.34 (±4.71)	58.55 (±4.78)	0.66
Disease duration (years)	10.22 (±9.67)	NA	NA
Insulin treatment	15 (27.27%)	NA	NA
Per os treatment (sulfonylurea)	14 (25.45%)	NA	NA
Per os treatment (biguanids)	26 (47.27%)	NA	NA
Cholesterol (mg%)	236.88 (±66.93)	165.21 (±38.91)	0.02
Tryglicerides (mg%)	183.45 (±93.07)	110.33 (±49.21)	0.06
Fasting plasma glucose (mg%)	159.42 (±53.63)	81.02 (±11.33)	0.01
HbA1 (%)	7.20 (±1.59)	4.1 (±2.1)	0.01

Among the 55 patients, 27 (49%) reported one or more gastrointestinal symptoms from the scale, and 28 (51%) of patients were asymptomatic. From those with dyspeptic symptoms, 15 (55.5%) reported fullness and/or early satiety from very mild to severe, 8 (29.6%) reported bloating from very mild to severe, and 4 (14.8%) reported vomiting or nausea ranging from very mild to moderate. All subjects in the control group were asymptomatic, as they answered "none" or "very mild" in all the questions. The symptom distribution and scores for the diabetic patients are summarized in Table 2.

Table 2. Gastroparesis cardinal symptom index results.

Item	Score (mean ± SD)*	Symptomatic patients: number (%)
Fullness/early satiety	4.49 (±1.81)	15 (55.5%)
Nausea/vomiting	2.23 (±1.22)	4 (14.8%)
Bloating	3.49 (±1.47)	8 (29.6%)
Total score	3.81 (±0.91)	27 (100%)

** Total score for all the patients.*
*** 27 patients had symptoms; the percents are calculated from the symptomatic patients.*

In all, 31 patients (56.33%) had abnormal GE on scintigraphy at 2 h, and 24 patients had normal GES. Among the subgroup with abnormal GES, only 53.33% reported gastrointestinal symptoms previous to the evaluation, and only 3 of the 9 symptoms of the GCSI had a significant correlation with the severity of the gastric emptying as evidenced by scintigraphy.

Table 3. GCSI according to scintigraphy (normal or delayed gastric emptying).

Item	Normal scintigraphy (43.67%) Score (mean ± SD)	Abnormal scintigraphy (56.33%) Score (mean ± SD)
Fullness/early satiety	3.77 (±1.85)	5.13 (±1.57)*
Nausea/vomiting	1.96 (±1.38)	2.56 (±1.49)
Bloating	3.21 (±1.46)	3.88 (±1.41)
Total score	3.61 (±0.97)	4.13 (±1.08)

** $p<0.05$*

When analyzed individually, the scores were significantly higher in patients with delayed GE only for nausea (3.13 ± 1.85 versus 2.02 ± 1.77), not being able to finish a normal-sized meal (4.22 ± 1.59 versus 2.66 ± 1.48) and early satiety, (5. 99 ± 1.15 versus 3.21 ± 1.61).

Nausea, not being able to finish a normal sized meal and early satiety significantly correlated with the severity of the GE delay (r = -0.65, r = -0.71, r = -0.58, respectively, with p < 0.05 in all cases).

The total symptom score for diabetic patients with delayed GE was 4.13 (± 1.08), higher than in diabetic patients with normal GE: 3.61 (± 0.97), but it was not statistically significant (p > 0.05).

Early satiety was more frequently present in diabetic patients with delayed GE as compared with those with normal GE (p < 0.05). No significant association was established between vomiting/nausea and bloating and delayed GE (Table 3). There is a positive but non-significant (weak) correlation between disease duration and gastroparesis (r = 0.22, p = 0.02). There are no correlations, in our study, between gender, age, the value of the HbA1, and the severity of gastroparesis (r < 0.20 in all cases).

3. Discussion

Gastroparesis is often suspected through history and physical examination; it can be confirmed by appropriate diagnostic testing. Patients with gastric stasis present with abdominal pain, nausea, vomiting, early satiety, bloating, and weight loss. The vomit may contain "old" food ingested several hours previously. As described in the literature the most frequent complaints are abdominal pain and early satiety [19], which corresponds to our results, but only for the latter, as our questionnaire did not include an abdominal pain evaluation.

Patients with diabetic gastroparesis may be asymptomatic or may develop symptoms that are not directly related to gastroparesis, such as poor glycemic control, particularly in those who are being treated with insulin. A high percentage of patients in our study were asymptomatic.

There is a proposed classification of gastroparesis severity that may be useful in the approach to a diabetes mellitus patient with gastrointestinal symptoms and in treatment decisions, into mild, compensated, and severe (with gastric failure) classes [18]. Diagnostic problems appear in mild and even in compensated forms when the symptoms may not be suggestive of the diagnosis. It is obvious that the diagnosis of diabetic gastroparesis should not be established based upon symptoms alone. Scintigraphy is regarded as the gold standard to measure GE [20], but further discussion remains necessary. For detection of delayed GE (gastroparesis), solid-phase GE is preferable to liquid, since normal GE of liquids is often preserved until there is very severe motor dysfunction of the stomach. The prevalence of delayed GE detected with solid-phase GES at 2 hr is variable, ranging from 12% to 75% [20].

Consensus standards for performing and reporting GES have been published both by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine [21]. The suggested protocol involves

an egg meal containing 99mTc with imaging at 0, 1, 2, and 4 h after meal ingestion. Normal values for the percent remaining in the stomach at the key time points are 37% to 90% at 1 h, 30% to 60% at 2 h and 0 to 10% at 4 h. Therefore, it seems that a 4-hour evaluation is very important for diagnosis; this may be a limitation of our study. In clinical practice, the most useful parameters are gastric retention over 10% at 4 hours, and over 70% at 2 hours. We also used the cut off value of 70% at 2 hrs.

The magnitude of the delay is often modest and not well correlated with symptoms, except possibly with bloating [22,23]. Our data also suggested that the presence or absence of symptoms is not a good indicator for when GES should be performed; we found a significant correlation only with early satiety, but not with bloating or with other symptoms. One possible explanation for the poor correlation between delayed GE and symptoms in diabetes mellitus may be the involvement of the afferent sensory nerve fibers by autonomic neuropathy, thereby decreasing the perception of symptoms [24]. However, increased pain perception in patients with diabetes has also been described. Careful evaluation of diabetics with other "dyspeptic" symptoms such as epigastric pain, nausea, vomiting, early satiety, postprandial fullness, and/or anorexia may reveal other causes (e.g. peptic ulcer or reflux disease), with only a minority of the patients having significant abnormalities of GE [25]. Therefore, the main question still remains: when to suspect gastroparesis and to perform GES.

All patients also require a careful upper endoscopy to exclude mechanical obstruction or mucosal disease as a cause of impaired GE, which we also performed in our study prior to GES. No further testing is necessary if these tests exclude mechanical obstruction and confirm gastric stasis in a patient who has a known etiologic disorder (e.g. diabetes mellitus) [26,27].

4. Conclusion

Regarding the relationship between symptoms and delayed GE, our data was similar to published data; the correlation between symptoms evaluated with GCSI and gastric scintigraphy was significant only for few items from the symptom scales. We can state that GE tests in patients with diabetes mellitus should be performed in those having a history of several years, if they have upper digestive symptoms not explained by upper digestive endoscopy, or if they have unstable diabetes while on insulin or oral therapy. Except for research purposes, we should not perform GE tests in all patients with long history of diabetes, as it wouldn't be cost-effective.

Acknowledgements

Research supported from CNCSIS project number 1277 of Ministry of Education.

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