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Prevalence of gastroparesis-related symptoms in an unselected cohort of patients with Type 1 diabetes

Kristoffer Kofod-Andersen[a,*], Lise Tarnow[b]

[a] Steno Diabetes Center, Denmark
[b] Head of the Research Unit at Steno Diabetes Center, Denmark

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ABSTRACT

Background: The prevalence of diabetic gastroparesis is not well defined because of discrepancy between objective measurements, i.e. gastric emptying time, and symptoms experienced by patients. Furthermore most studies have been performed on small selected cohorts.
Objective: To determine the prevalence of clinical symptoms of diabetic gastroparesis in a large unselected cohort of out-patients with Type 1 diabetes.
Methods: 1028 patients with Type 1 diabetes attending a specialized diabetes clinic were mailed a validated questionnaire; "patient assessment of upper gastrointestinal disorders-symptom severity index", in which a subset of questions measures symptoms of gastroparesis (GCSI; Gastroparesis Cardinal Symptom Index). Response rate was 74.4% ($n=765$). All patients were classified according to presence or absence of late diabetic complications and clinical and paraclinical data were obtained.
Results: A GCSI Total Score ≥ 1.90 signified definite symptoms of gastroparesis ($n=102$) and patient charts were investigated for concomitant illness and/or medication influencing gastric emptying. In 30 patients an alternative etiology was revealed, leaving 72 (9.8%) patients with symptoms related to diabetic gastroparesis. Only 8 patients were previously diagnosed. HbA_{1c} levels were significantly higher in patients with diabetic gastroparesis (8.4 ± 1.3 vs. 8.2 ± 1.2 respectively, $p=0.02$). Furthermore, patients with diabetic gastroparesis had more retinopathy ($p=0.006$) and peripheral polyneuropathy (16.7% vs. 6.7%, $p<0.001$) and there was a trend for diabetic nephropathy being more common ($p=0.08$).
Conclusions: Symptoms of diabetic gastroparesis affect approximately 10% of patients with Type 1 diabetes in a specialized diabetes clinic and are associated with poor glycemic control and other late diabetic complications.

1. Introduction

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach. Patients experience symptoms such as nausea, early satiety, bloating and abdominal pain with a substantial fluctuation over time. The etiology of symptoms is diverse but one third of cases diagnosed with gastroparesis have diabetes where it often coexists with other longstanding complications such as peripheral polyneuropathy, retinopathy and diabetic nephropathy (Haans & Masclee, 2007), and may be associated with anxiety and depression (Quan, Talley, Jones, Spies, & Horowitz, 2008).

Aside from the obvious discomfort related to symptoms, the consequences of delayed gastric emptying can be severe including impaired glucose regulation, hypoglycemia, poor drug absorption, malnutrition and wasting, a high rate of hospitalizations and poor quality of life (Bell, Jones-Vessey, & Summerson, 2002; Gallar, Oliet, Vigil, Ortega, & Guijo, 1993; Horowitz, Jones, Rayner, & Read, 2006).

It is generally accepted that in patients with diabetes, gastrointestinal symptoms occur more frequently than in the general population but the precise prevalence of diabetic gastroparesis is not well described. By using scintigraphic radioisotopic techniques several studies have quantified delayed gastric empting to occur in 30%–50% of patients with longstanding Type 1 diabetes (Jones et al., 2001; Keshavarzian, Iber, & Vaeth, 1987; Kong, Horowitz, Jones, Wishart, & Harding, 1999; Ziegler et al., 1996) but many of the patients with signs of gastroparesis are asymptomatic and conversely, patients with symptoms may have normal gastric emptying (De Block et al., 2002). Furthermore, while consensus of delayed gastric emptying rates around 30%–50% has been established, symptoms attributable to gastroparesis are reported at a great range from 5% to 83% and most studies were performed on small cohorts (Haans & Masclee, 2007; Jones et al., 2001; Parkman et al., 2010).

* Corresponding author. Steno Diabetes Center, Niels Steensens Vej 2, 2820 Gentofte, Denmark. Tel.: +45 29651979.
E-mail address: kka1982@gmail.com (K. Kofod-Andersen).

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Therefore, the aim of this study was to determine the prevalence of clinical symptoms of diabetic gastroparesis in a large unselected cohort of patients with Type 1 diabetes by application of a validated questionnaire (Revicki et al., 2003) and furthermore to explore the clinical characteristics of patients with symptoms of gastroparesis.

2. Methods

A survey was performed in 1028 unselected patients with Type 1 diabetes attending the Steno Diabetes Center (a specialized diabetes clinic, attended by the majority of patients with type 1 diabetes in the Copenhagen area) by sending out the self-report questionnaire PAGI-SYM ("patient assessment of upper gastrointestinal disorders-symptom severity index") (Revicki et al., 2003). The questionnaire was sent out twice to all the patients born on the 1st through the 9th day of each month, no additional selection criteria were applied, with an accompanying letter with the explanation that this was an attempt to determine the prevalence of symptoms of gastroparesis. The total reply rate was 74.4% ($n=765$). Non-responders were 5.7 years younger, had 4.2 years shorter duration of diabetes mellitus and poorer glycemic control ($HbA_{1c}=8.5\%$) but were otherwise comparable to responders. PAGI-SYM is a comprehensive 20-item symptom severity measure for gastroesophageal reflux disease, dyspepsia and gastroparesis. A subset of the PAGI-SYM is the Gastroparesis Cardinal Symptom Index (GCSI) which was developed as a patient reported outcome measure of gastroparetic symptoms. It consists of nine symptoms covering three areas; nausea/vomiting (3 items), fullness/early satiety (4 items), and bloating (2 items). All symptoms are rated from none (0) to very severe (5) based on the prior two weeks and GCSI Total Score is calculated as the mean of the three subtotals.

Patients' GCSI Total Scores were entered into a database and values ≥ 1.90 were chosen as having definite symptoms of gastroparesis. The cutoff at 1.90 was chosen in accordance with inclusion criteria for a clinical intervention study on symptomatic diabetic gastroparesis (NCT 00889496) and data from Revicki et al., 2003 ($n=169$).

In patients scoring ≥ 1.90 in GCSI Total Score ($n=102$) a thorough search in their medical charts was performed in order to reveal concomitant illness as underlying cause of chronic gastric stasis, such as Parkinson's disease, systemic lupus erythematosus, liver disease, anorexia nervosa, or central nervous system disease.

Other alternative etiologies of gastroparetic symptoms include mechanical outlet obstruction, peptic ulcer disease, gastroesophageal reflux disease, gastritis, pancreatitis, postoperative ileus, or metabolic abnormalities such as uremia, hypercalcemia, hypokalaemia, hypomagnesaemia, hypocortisolaemia, hypothyroidism or critical illness. Patient charts were reviewed for concomitant illness. Several medications may also slow gastric emptying. Hence, the patients' medication was registered with a focus on anticholinergics, antidepressants, calcium channel blockers, sedatives, beta-adrenergic agonists, opiates, antipsychotics, nicotine, and dopaminergic drugs (Horowitz et al., 2002).

Furthermore, all patients were classified according to presence or absence of late diabetic complications: Diabetic nephropathy was defined as persistent macroalbuminuria, i.e. more than 300 mg per day, in at least two of three consecutive 24 h urine collections, in the presence of diabetic retinopathy and in the absence of other kidney or urinary tract disease.

Diabetic retinopathy was assessed in all patients by fundus photography after pupillary dilatation and graded as nil, simplex or proliferative.

Peripheral polyneuropathy was considered present in patients with loss of vibration perception (>50) measured by biothesiometry.

Data on body mass index (BMI), blood pressure, smoking and laboratory parameters were obtained from patients' last routine visit to the outpatient clinic.

2.1. Statistical analysis

Nominal values are presented as number of cases with percentages. Continuous data are presented as mean ± SD for normally distributed variables, and as median [range] for non-normally distributions. A Chi-square test was used to compare non-continuous variables. A Student's *t* test was used to compare normally distributed clinical variables and Mann–Whitney test for non-normally distributed parameters. A two-tailed p-value<0.05 was considered statistically significant. All calculations were performed with a commercially available program (SPSS for Windows, version 14.0).

3. Results

A total of 102 out of 765 patients reported a GCSI Total Score ≥ 1.90. Hereof, 30 patients had concomitant causes of gastrointestinal symptoms like pregnancy ($n=2$), coeliaci ($n=7$), uremia ($n=5$), upper gastrointestinal disease ($n=4$), colitis ($n=5$), alcoholism ($n=3$) or CNS disease ($n=4$). These 30 patients were excluded from further analyses. Thus, 72 patients (9.8%) had symptoms compatible with diabetic gastroparesis without any other plausible explanations. Clinical data on patients with and without diabetic gastroparesis are presented in Table 1. The distribution of GCSI scores is skewed as shown in Fig. 1. Median GCSI score is 0.71 (range: 0.0 to 4.36).

The two groups were similar concerning sex, age, duration of diabetes and BMI. HbA_{1c} levels were significantly higher in patients with diabetic gastroparesis than without, $p=0.02$. Furthermore, patients with diabetic gastroparesis had more frequent retinopathy ($p=0.006$), more severe retinopathy ($p=0.003$) and peripheral polyneuropathy ($p<0.001$). There was a trend for nephropathy being more common in patients with diabetic gastroparesis ($p=0.08$). Smoking was more common in patients with diabetic gastroparesis ($p=0.05$).

In 433 patients data on hypoglycemia were available: Patients with gastroparesis ($n=39$) had experienced significantly more episodes of severe hypoglycemia as compared with non-gastroparesis patients (2.2 ± 0.7 (SE) versus 1.5 ± 0.4 episodes per year, $p=0.01$). Mild hypoglycemic episodes were not more frequent in patients with gastroparesis (2.5 ± 0.4 versus 2.5 ± 0.1 episodes per week).

Only 8 of the patients with GCSI Total Score ≥ 1.90 were previously diagnosed with gastroparesis in the routine clinic. In addition, some patients had signs or symptoms of other types of diabetic

Table 1
Clinical characteristics of type 1 diabetic patients with and without symptoms of diabetic gastroparesis.

Variable	Diabetic gastroparesis	Not diabetic gastroparesis	*P* value
n	72	663	
Men (%)	50.0	50.4	0.9
Age (years)	50.4 ± 15.0	51.1 ± 15.5	0.7
Duration of diabetes (years)	28.3 ± 14.8	26.0 ± 14.4	0.2
BMI (kg/m^2)	25.1 ± 4.2	25.5 ± 4.2	0.4
P-creatinine (μmol/l)*	72 (34 - 177)	71 (34 - 476)	0.9
Haemoglobin (mmol/l)	8.6 ± 0.8	8.7 ± 0.9	0.9
Total cholesterol (mmol/l)	4.7 ± 1	4.7 ± 0.9	0.3
BP systolic (mmHg)	134 ± 17	135 ± 17	0.8
BP diastolic (mmHg)	76 ± 10	77 ± 10	0.4
HbA_{1c} (%)	8.4 ± 1.3	8.2 ± 1.2	0.02
Nephropathy (normo/micro/macro %)	58 / 35 / 7	73 / 22 / 5	0.08
Retinopathy (nil/simplex/proliferative%)	17 / 54 / 29	35 / 49 / 16	0.006
Vibration perception (absent %)	16.7	6.5	<0.001
Vibration perception threshold*	26 (5-50)	17 (5-50)	<0.001
Smoking (no/previous/current %)	62 / 3 / 35	72 / 7 / 21	0.05

Data are *n* (%), mean (SD) or *median (range).