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Dyspeptic symptoms in patients with type 1 diabetes: endoscopic findings, *Helicobacter pylori* infection, and associations with metabolic control, mood disorders and nutritional factors

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ABSTRACT

Objectives: To evaluate, in a group of patients with long-standing type 1 diabetes (DM1), an association of dyspepsia symptoms with: changes in the gastroduodenal mucosa, infection by *Helicobacter pylori,* glycemic control, and psychological and nutritional factors. **Subjects and methods:** A total of 32 patient with DM1 were studied (age: 38 ± 9 years; females: 25; diabetes duration: 22 ± 5 years). All patients answered a standardized questionnaire for the evaluation of gastrointestinal symptoms and underwent upper gastrointestinal endoscopy, with gastric biopsies for the evaluation of *Helicobacter pylori* infection. The presence of anxiety and depression was evaluated by the HAD scale. Nutritional parameters were BMI, arm and waist circumference, skinfold measurement, and body fat percentage. **Results:** Upper endoscopy detected lesions in the gastric mucosa in 34.4% of the patients, with similar frequency in those with (n = 21) and without dyspepsia (n = 11). The patients with dyspepsia complaints showed greater frequency of depression (60% *vs.* 0%; p = 0.001), higher values for HbA1c (9.6 ± 1.7 *vs.* 8.2 ± 1.3%; p = 0.01) and lower values for BMI (24.3 ± 4.1 *vs.* 27.2 ± 2.6 kg/m^2; p = 0.02), body fat percentage (26.6 ± 6.2 *vs.* 30.8 ± 7.7%; p = 0.04), and waist circumference (78.7 ± 8 *vs.* 85.8 ± 8.1 cm; p = 0.02). No association was found between the symptoms and the presence of *Helicobacter pylori.* **Conclusions:** Dyspepsia symptoms in patients with long-standing DM1 were associated with glycemic control and depression, and they seem to negatively influence the nutritional status of these patients. Arch Endocrinol Metab. 2015;59(2):129-36

Keywords

Type 1 diabetes; dyspepsia; anxiety; nutrition

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INTRODUCTION

Recent studies indicate that the prevalence of gastrointestinal symptoms in patients with type 1 diabetes (DM1) is greater than that observed in the overall population (1-3). It was also demonstrated that this clinical picture has a negative impact in the quality of life of these patients (4). However, the mechanisms responsible for digestive manifestations in diabetes have not been elucidated, yet (5).

Few authors have used upper digestive endoscopy (UDE) to analyze the presence of mucosal lesions that could explain the esophageal and dyspeptic complaints in diabetic patients. In one study, endoscopic evaluation showed that the lesions in the esophagogastric mucosa were more frequent in diabetic patients (most of them with type 2 diabetes) than in non-diabetic controls. However, no relationship was observed between the lesions found and the presence of digestive symptoms (6). On the other hand, some authors observed a similar frequency of endoscopic lesions in diabetic and non-diabetic control patients (7).

Studies that investigated the relationship between digestive symptoms and *Helicobacter pylori* infection (8), glycemic control (1,9), and abnormal autonomic function (5) in diabetes also showed contradictory results. Besides, no direct relationship was demonstrated between diabetic gastroparesis and specific digestive symptoms (10,11).

The association between gastrointestinal symptoms and psychological factors, particularly anxiety and depression, is growingly recognized in the literature since the studies which were carried out in patients with functional diseases, such as functional dyspepsia and irritable bowel syndrome (12). There is evidence of increased prevalence of anxiety and depression in diabetic patients (13,14), but the relationship between these disorders and the presence of gastrointestinal symptoms have seldom been investigated in diabetes. An Australian study that evaluated both type 1 and type 2 diabetes patients demonstrated that digestive symptoms were twice more frequent in those patients that showed anxiety and/or depression (15). This information indicates the need for new studies to confirm this relationship in patients with DM1. Besides, there are no studies involving the possible influence of dyspeptic symptoms in the nutritional picture of patients with DM1.

Therefore, the objectives of this study were to evaluate, in a group of patients with long-term DM1, the relationship between dyspeptic symptoms with the following factors: changes in the gastroduodenal mucosa; infection by *Helicobacter pylori*; glycemic control; and psychological and nutritional factors.

SUBJECTS AND METHODS

A total of 32 patients with DM1 were seen at the DM1 outpatient clinic of the Endocrinology Division at the Hospital das Clínicas da Unicamp (HC-Unicamp). Mean age of the participants in the study was 38 ± 9 years, with 25 (78.1%) female patients and 7 (21.9%) male ones. DM1 diagnosis was determined by the criteria of the American Diabetes Association (ADA) (16).

Inclusion criteria were: patients had to be older than 18 years of age, diabetes diagnosis should have been established more than 10 years before, written consent for upper digestive endoscopy (UDE). Exclusion criteria were: pregnancy, previous gastrointestinal tract surgery, renal failure with dialysis, concurrent diseases that may cause changes in gastrointestinal motility.

The control group for the presence of gastrointestinal symptoms was made up by 50 healthy volunteers (30 women and 20 men, aged 33 ± 8 years) recruited among employees and students at the HC and Gastrocentro-Unicamp. The control group was matched to the patient group based on age, sex and BMI. None of the volunteers had cardiac or gastrointestinal disease, arterial hypertension, diabetes or previous abdominal surgery.

This study was approved by the Research Ethics Committee at Unicamp. All participants signed a written informed consent term.

Clinical and laboratory assessment

Factors related to DM1, including duration of the disease, chronic complications (retinopathy, peripheral neuropathy, and diabetic nephropathy), and laboratory parameters, including fasting glucose, urea, creatinine, creatinine clearance, and TSH were obtained from patient records. Glycemic control was analyzed by means of glycated hemoglobin (HbA1c) obtained by high efficiency liquid chromatography. Levels above 7% were considered inadequate glycemic control.

Diabetic retinopathy was diagnosed by fundoscopy carried out by an ophthalmologist at HC-Unicamp. Diabetic nephropathy was evaluated by means of microalbuminuria in a morning urine sample; nephropathy was considered when two values observed on two different days were above the normal value (up to 30 mg/g creatinine), in the absence of urinary infection. The diagnosis of peripheral neuropathy was determined using a 10 g-monofilament for pain sensation, 128 Hz tuning fork for vibration perception, assessment of achilles and patellar reflexes, as well as palpation of dorsalis pedis and posterior tibial pulses.

Gastrointestinal symptoms

Gastrointestinal symptoms were analyzed in patients and controls using a standardized questionnaire that was previously validated (17). The following esophageal symptoms were analyzed: dysphagia, heartburn and regurgitation. Dyspeptic symptoms included pain or epigastric burning, postprandial bloating, nausea, and vomiting. Intestinal symptoms analyzed were: abdominal distention, abdominal pain, constipation, diarrhea, and fecal incontinence. Each symptom received a score from 0 to 4, according to the intensity, as follows: 0 = no symptom, 1 = mild (symptoms can be ignored), 2 = moderate (symptoms cannot be ignored, but do not influence daily activities), 3 = severe (symptoms influence daily activities). Only moderate or severe symptoms that occurred more than once a week were considered in the analysis of the data.

Upper digestive endoscopy

Upper digestive endoscopy was carried out in order to diagnose gastroduodenal lesions responsible for gastro-

intestinal symptoms. Besides, gastric biopsy fragments were collected for *H. pylori* analysis (body and antrum) and fragments of the bulb and postbulbar portion (distal to the duodenal papilla) were collected to the analysis of celiac disease.

Analysis of H. pylori infection

Analysis of *H. pylori* was carried out by the urease test and histological examination of fragments collected in the endoscopy. Infection was considered to be negative when both tests were negative.

Diagnosis of celiac disease

Considering the increased prevalence of celiac disease in DM1 (18), and the possible nutritional changes caused by this comorbidity, the presence of celiac disease in the patient group was analyzed by means of histological examination of duodenal biopsies.

Assessment of mood disturbances by the HAD scale

The presence of anxiety and depression was evaluated using the Portuguese version of the HAD (Hospital Anxiety and Depression) scale, which was validated in Brazil (19). This scale is divided into subscales for anxiety and depression, and values over 8 in each subscale indicate anxiety or depression.

Assessment of nutritional status

Nutritional status of the patients was assessed according to standardized protocols (20) that yielded the following anthropometric indices: body mass index (BMI), calculated as weight (kg)/height^2 (m); arm circumference (AC); corrected arm muscle area (cAMA); waist circumference (WC); and skinfold measurements: tricipital (TSF), bicipital (BSF), subscapular (SSSF) and suprailiac (SISF). Body fat percentage was calculated based on these indices. Measurement of arm and waist circumferences were carried out with an inextensible tape, and skinfolds were measured with a Lange caliper (Cambridge Scientific Industries Cambridge, MA) with 0.2 mm accuracy.

Statistical analysis

Results were expressed as means ± SD. Statistical analysis was carried out using the Mann-Whitney, Chi-Square and Fischer Exact Test, as necessary. The comparison between multiple variables was carried out by the analysis of variance (ANOVA) and Tukey test. Correlation analysis was carried out using Spearman correlation coefficient. Statistical significance was set at $p < 0.05$.

RESULTS

Clinical and demographic characteristics of the patients

Table 1 shows the main demographic and clinical characteristics of the 32 patients with DM1. Mean time from diagnosis was 22 ± 5 years.

All patients used insulin, and none of them was under treatment with metformin. Peripheral neuropathy was found in 46.9% of the participants. Mean HbA1c was 9.1 ± 1.7%, indicating that the group of patients studied had inadequate glycemic control. Only one patient (3%) showed good control, with HbA1c < 7%. There were no significant differences ($p > 0.05$) between men and women in relation to the clinical parameters.

Gastrointestinal symptoms

Table 2 shows the frequency of the different gastrointestinal symptoms reported by diabetic patients and the control group. Compared with the control group, diabetic patients presented significantly greater frequencies of dysphagia, heartburn, regurgitation, postprandial bloating, nausea, vomiting, and intestinal symptoms (constipation, diarrhea, abdominal distention, and fecal incontinence).

Considering the group of symptoms, it was observed that 21 (65.6%) of the patients showed dyspepsia. The main dyspepsia complaint was postprandial fullness more than three times a week in all cases. In patients with dyspepsia, 7 (33.3%) presented symptoms associated with gastroesophageal reflux (heartburn and/or regurgitation) and 18 (85.7%) showed associated intestinal complaints, such as constipation, diarrhea, pain or abdominal distention. None of the patients presented with exclusively reflux symptoms, and none of them used gastric acid secretion inhibitors or prokinetic drugs in the treatment of the symptoms.

Nineteen (90.5%) of the patients with dyspepsia symptoms related the onset or worsening of the gastrointestinal symptoms with the ingestion of specific foods. The most common foods reported were: milk, bread and pasta, fried foods, red meat, banana and coffee.

Table 1. Demographic and clinical characteristics of patients with DM1. Comparison of patients with and without dyspepsia

Variables	Total (n = 32)	Patients with dyspepsia (n = 21)	Patients without dyspepsia (n = 11)	p
Age (years)	38 ± 9	37 ± 9	41 ± 7	0.18
Sex:				1
Female (n %)	25 (78.1)	16 (76.2)	9 (81.8)	
Male (n %)	7 (21.9)	5 (23.8)	2 (18.2)	
Time since diabetes diagnosis (years)	22 ± 5	25 ± 6	21 ± 5	0.06
Peripheral neuropathy n (%)	15 (46.9)	10 (47.6)	5 (45.4)	1
Retinopathy (%)	28 (87.5)	17 (81)	11 (100)	0.27
Diabetic nephropathy n (%)	22 (68.7)	16 (76.2)	6 (54.5)	0.25
Smoking n (%)	4 (12.5)	4 (19)	0 (0)	0.27
HbA1c (%)	9.1 ± 1.7	9.6 ± 1.7	8.2 ± 1.3	0.01

Table 2. Frequency of gastrointestinal symptoms in patients with DM1 and in the control group

Symptoms	DM1 patients (n = 32)	Controls (n = 50)	p
Dysphagia	6 (18.7%)	1 (2%)	0.01
Heartburn and/or regurgitation	7 (21.9%)	3 (6%)	0.04
Postprandial fullness	15 (46.9%)	5 (10%)	0.001
Epigastralgia	9 (28.1%)	11 (22%)	0.60
Nausea/vomiting	7 (21.9%)	3 (6%)	0.04
Abdominal distention	13 (40.6%)	8 (16%)	0.02
Constipation	9 (28.1%)	5 (10%)	0.04
Diarrhea	6 (18.7%)	0 (0%)	0.002
Abdominal pain	3 (9.4%)	1 (2%)	0.29
Fecal incontinence	5 (15.6%)	0 (0%)	0.01

Association between dyspeptic symptoms, glycemic control and diabetes complications

Comparisons between diabetic patients with and without dyspepsia are shown in tables 1 and 3-5. Table 1 shows that diabetic patients with dyspepsia presented significantly higher levels of HbA1c when compared with diabetic patients without dyspepsia, indicating that this subgroup had worse glycemic control.

There was no statistical association (p > 0.05) between dyspepsia symptoms and diabetes complications (peripheral neuropathy, retinopathy, nephropathy), or with any of the other parameters analyzed: sex, age, fasting glucose, creatinine values, creatinine clearance, and TSH.

Upper digestive endoscopy findings

UDE analysis showed that most of the patients with DM1 (65.6%) did not present relevant changes in the mucosa of the digestive system. The most important findings were severe erosive gastritis in two patients and a healing gastric ulcer in a patient. The comparison of patients with and without dyspepsia did not show significant differences in the frequency of endoscopic lesions.

Helicobacter pylori infection

H. pylori infection was found in eleven patients (34.4%). The urease test and histological examination were in agreement in all cases. None of the patients reported previous treatment of the infection. There were no statistical differences between dyspeptic and asymptomatic patients as for the presence of the bacteria (Table 3).

Presence of celiac disease

Histological examination of the duodenal biopsies confirmed the diagnosis of celiac disease in one patient.

Presence of anxiety and depression

Thirty patients completed the HAD scale. According with the scores, 19 patients (63.3%) presented some kind of mood alteration. Ten patients (33.3%) presented anxiety associated with depression, 7 (23.3%) showed only anxiety, and two (6.7%) presented only depression.

There was no significant correlation (p > 0,05) between the scores for anxiety and depression, HbA1c values and any other biochemical parameter. No statistically significant association was observed with gender, age, or diabetes complications, either.

Table 4 shows that 60% of the dyspeptic patients and 50% of the diabetic patients without symptoms of

dyspepsia presented anxiety (p > 0.05). On the other hand, depression was identified in 60% of the patients with dyspeptic complaints, whereas none of the diabetic without dyspepsia presented this disorder (p = 0.001). In accordance with these data, the score in the depression subscale was significantly greater in patients with dyspeptic symptoms.

Association between dyspeptic symptoms and nutritional parameters

Mean values of anthropometric parameters are presented in table 5. For the analysis of the results, the patient diagnosed with celiac disease was excluded, once she was malnourished. According to the BMI, 13 patients (43.3%) were overweight and one (3.3%) was obese.

When compared with patients without dyspeptic complaints, patients with dyspepsia presented significantly decreased values (p < 0.05) for the following

parameters: BMI, waist circumference, and fat percentage.

There was no association between anthropometric data and any of the other clinical and laboratorial parameters analyzed. Besides, there was no statistical association between nutritional factors, anxiety and depression (p > 0.05).

DISCUSSION

Most of the studies that investigated gastrointestinal symptoms in DM1 were carried out in groups that were mostly made up by patients with DM2 (3). Besides, the analysis of different study groups shows wide variability in terms of clinical and laboratory characteristics and length of the disease in patients with DM1. The advantage of the present study was to analyze dyspeptic symptoms in a homogenous group of patients with

Table 3. Lesions observed in upper digestive endoscopy and *H. pylori* infection in patients with type 1 diabetes and without dyspepsia

Endoscopic alterations	Total n = 32	Patients with dyspepsia (n = 20)	Patients without dyspepsia (n = 11)	p
Erosive lesions/peptic ulcer	11 (34.4%)	8 (38.1)	3 (27.3%)	0.70
Mild erosive gastritis	7	5	2	
Mild erosive gastritis + erosive esophagitis	1	1	0	
Severe erosive gastritis				
Gastric ulcer	2	1	1	
	1	1	0	
H. pylori infection	11 (34.4%)	6 (28.6%)	5 (45.4%)	0.44

Table 4. Anxiety and depression in patients with DM1 according to the HAD scale. Comparison between diabetic patients with and without dyspeptic symptoms

Mood alterations	Total (n = 30)	Patients with dyspepsia (n = 20)	Patients without dyspepsia (n = 11)	p
Anxiety	17 (56.7%)	12 (60%)	5 (50%)	0.70
Anxiety score	8.3 ± 4.7	9.1 ± 5	6.4 ± 4.4	0.20
Depression	12 (40%)	12 (60%)	0 (0%)	0.001
Depression score	6.9 ± 4.3	8.3 ± 4.2	4.0 ± 3.0	0.005

Table 5. Anthropometric data of diabetic patients according to the presence or absence of dyspeptic symptoms

Anthropometric data	Total (n = 31*)	Patients with dyspepsia (n = 20)	Patients without dyspepsia (n = 11)	p
BMI (kg/m²)	25.3 ± 3.8	24.3 ± 4.1	27.2 ± 2.6	0.02
Body fat (%)	28.3 ± 7.1	26.6 ± 6.2	30.8 ± 7.7	0.04
Waist circumference (cm)	81.5 ± 8.6	78.7 ± 8	85.8 ± 8.1	0.02
Arm circumference (cm)	29.7 ± 3.8	28.4 ± 3.8	31.5 ± 3	0.08
Tricipital skinfold (mm)	15.9 ± 5.7	14.6 ± 5.9	17.6 ± 5.2	0.14
Corrected arm muscle area (cm²)	42.7 ± 12	39.1 ± 12.3	47.8 ± 10	0.06

* Patient with celiac disease excluded from the statistical analysis.

DM1 in relation to the length of the disease, the presence of diabetes complications, and even in terms of inadequate glycemic control.

Patients were characterized by the high frequency of gastrointestinal symptoms, which was significantly greater than that in the control group, confirming the results of previous studies that demonstrated that digestive symptoms are more frequent in diabetic patients compared with non-diabetic controls (1-3). However, it is important to observe that the prevalence of dyspeptic complaints observed in the present cases was higher than that reported in population studies, and cannot be generalized to the whole population of DM1 patients. This may be due to the fact that the study protocol required upper endoscopy to be carried out. Therefore, it is possible that diabetic patients with dyspeptic complaints had more interest in taking part in the study, what may have increased the frequency of changes in the group studied. Similarly, the predominance of female patients may also be related with greater interest in taking part in the study, once previous observations demonstrated that gastrointestinal symptoms are more frequent in women than in men with DM1 (2). Considering this possible bias, all statistical analyses considered a possible gender effect.

Upper endoscopy showed that a large number of the diabetic patients with dyspeptic symptoms did not show gastroduodenal lesions that could explain the clinical picture, indicating that other factors may be responsible for the digestive complaints in these patients.

Results presented here indicate that *H. pylori* infection is not related to the presence of dyspeptic symptoms, confirming recent literature data (8,21). The infection was found in 34.4% of the patients, similar to another Brazilian study with DM1 adolescent patients (22). However, this prevalence is lower than the one reported in a Brazilian population study involving blood donors, which was 65-70% for individuals in the same age group (23). It is also lower than that observed in patients with functional dyspepsia in a previous study carried out by our group, which demonstrated the presence of the bacterium in 65% of the cases (24). Data on the prevalence of *H. pylori* infection in DM1 are contradictory. Some studies show greater prevalence than the one found in the controls, and others show similar prevalence (8). On the other hand, some authors reported lower frequency of infection in those patients that had the disease for a longer time, due to the repeated use of antibiotics (25). This may be the

explanation for the relatively low proportion of infections by *H. pylori* in the group of diabetic patients in the present study: they may have been treated countless times with antibiotics during the prolonged course of their disease.

A large number of patients with DM1 presented anxiety and/or depression disorders, confirming literature results (13,14). Besides, an association between depression and dyspeptic symptoms in these patients was demonstrated. The relationship of gastrointestinal symptoms with anxiety and depression was already described in groups of DM1 and DM2 patients (15). This association was also documented in the follow-up of a mixed group of patients with DM1 and DM2 during a period of two years. It was observed that the onset of depression symptoms increased three times the risk of gastrointestinal symptoms, no matter the type of diabetes (26).

The mechanisms responsible for the relationship between gastrointestinal symptoms and psychological factors have not been elucidated in diabetes, yet. One of the mechanisms proposed to explain this association in functional dyspepsia is visceral hypersensitivity, that is, an increased perception of gastrointestinal sensations (27,28). It was demonstrated that anxiety and depression may influence the central processing of visceral stimuli, increasing the perception of gastrointestinal sensations (29). Gastrointestinal symptoms, on their turn, may increase the levels of anxiety and depression, leading to a vicious cycle. Once the studies on diabetes already demonstrated abnormalities in the perception of visceral sensations in different parts of the gastrointestinal tract (30), it may be inferred that, similar to what was observed in functional diseases, the relationship between psychological factors and gastrointestinal symptoms in diabetes may be explained, at least in part, by visceral hypersensitivity (15). This hypothesis still needs to be confirmed by new studies.

In spite of the fact that almost all diabetic patients in the study presented inadequate glycemic control, the levels of HbA1c were significantly higher in dyspeptic patients than in those without dyspepsia, suggesting a role of glycemic control in the production of dyspeptic symptoms in DM1. These results are in agreement with the observations of other authors (2,31). Laboratory studies in which patients were submitted to gastric distention by means of the insufflation of intragastric balloons showed that severe hyperglycemia increases the perception of nausea and bloating (30-32), suggesting that visceral hypersensitivity may also be involved

in the relationship between glycemic control and dyspeptic symptoms in DM1. New studies are necessary to explore this hypothesis.

According to the data presented here, there was no association between digestive symptoms and peripheral neuropathy or other diabetes complications. However, these results do not enable us to rule out the participation of autonomic neuropathy in the pathogenesis of dyspeptic symptoms, once the appropriate tests to investigate this change were not used in the present study. It is important to mention, however, that previous studies did not evidence good correlations between digestive symptoms and diabetic autonomic neuropathy, suggesting a multifactorial physiopathology for dyspepsia in these patients (5,30). The results of the present study seem to fit the current view that digestive symptoms in DM1 are result of a complex relationship between psychological changes, glycemic control, visceral hypersensitivity, and autonomic neuropathy (15,33).

The evaluation of data on BMI in the studied group evidences a high percentage of overweight patients, confirming recent studies on DM1 (34,35). However, the values for nutritional parameters in dyspeptic patients were reduced compared with those observed in patients without dyspepsia, suggesting that digestive symptoms may influence the nutritional status of DM1 patients. As patients related their digestive complaints with the ingestion of different foods, it is possible that food intake in these patients was reduced due to the severity of the symptoms, leading to the changes in nutritional status. This possible relationship should be adequately investigated in future studies.

In conclusion, dyspeptic symptoms may be associated with worse glycemic control and presence of depression, in most of the patients with DM1. Besides, dyspepsia seems to negatively affect the nutritional status of the diabetic patients. Therefore, it is important that the endocrinologist considers these symptoms and recognize that adequate treatment of digestive complaints also depends on the effective approach of psychosocial factors involved.

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