CLINICAL STUDY

Does diabetic autonomic neuropathy influence the clinical manifestations of reflux esophagitis?

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Abstract

Diabetic autonomic neuropathy is a common complication of diabetes mellitus and affects every segment of the gastrointestinal tract. Gastrointestinal problems tend to be more common and severe in diabetics compared with the nondiabetic population. In the literature, the prevalence of reflux esophagitis is not known.

The aim of this study was to analyze esophagoscopic findings, compare them with esophageal symptoms, and evaluate reflux esophagitis in relationship with autonomic neuropathy. We examined 54 diabetics (15 type I, 39 type II), 28 males and 26 females, average age 55.4 (95 % confidence intervals 52.1–58.8), with duration of diabetes more than 5 (average 15.0; 12.4–17.6) years. All patients completed a structured questionnaire. After overnight fasting, gastroesophageal endoscopy was performed in the morning to establish the presence of reflux esophagitis, using the Los Angeles classification. Cardiovascular autonomic neuropathy was diagnosed with the help of cardiovascular autonomic reflexes (deep breathing, active orthostasis, Valsalva's maneuver) and spectral analysis of heart rate variation.

Endoscopic esophagitis was present in 22 (40.7 %) diabetics and 10 of them (45 %) also complained of reflux symptoms. Sensitivity of symptoms was 45.5 % and specificity was 72 %. We found the presence of symptoms of reflux esophagitis in 21 (38.9 %) diabetics, but of this group only 10 (47.6 %) had endoscopic changes. Autonomic neuropathy was present in 29 patients, 16 (55 %) of them had reflux esophagitis and 18 (62 %) were positive for reflux symptoms. In the diabetics without autonomic neuropathy, esophagitis was noted in 6 (24 %), which reflects a significant difference ($p<0.05$). Reflux symptoms were present in 10 (40 %) diabetics without autonomic neuropathy, and in comparison with patients who had autonomic neuropathy, the difference was not statistically significant.

Thus, reflux eosophagitis is common in diabetic patients, with a prevalence of 40.7 %. Reflux symptoms do not have a great diagnostic value in establishing reflux esophagitis. We confirmed a relationship between autonomic neuropathy and the clinical manifestations of reflux esophagitis, but no association with accompanying reflux symptoms. ***(Tab. 2, Ref. 27.)***

Key words: diabetes mellitus, reflux esophagitis, autonomic neuropathy.

Diabetic autonomic neuropathy is a common complication of diabetes mellitus, and in the gastrointestinal tract it can manifest in 20–60 % patients (1). It is generally known, that autonomic neuropathy affects every segment of the gastrointestinal tract. However, this is not usually manifest within the first five years of the diagnosis of diabetes. Development of gastrointestinal disease tends to be more common and severe in diabetics compared with nondiabetics (2, 3, 4).

Esophageal dysmotility resulting from autonomic neuropathy can lead to hypotonia and incompetence of the lower esophageal sphincter, causing stagnation of food in the esophagus due to diminished peristaltic activity (5). These mechanisms together with diabetic gastroparesis and transient lower esophageal sphincter relaxation can precipitate pathological gastroesophageal reflux and consequent reflux esophagitis (6, 7).

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In the literature, the prevalence of reflux esophagitis is not known. The aim of this study was to analyze esophagoscopic findings, compare them with esophageal symptoms, and evaluate the clinical manifestation of reflux esophagitis in relationship with autonomic neuropathy.

Material and methods

Between 1998–2001 we examined 54 diabetics (15 type I, 39 type II), 28 males and 26 females, average age 55.4 (95 % confidence intervals 52.1–58.8), with a duration of diabetes more than 5 (average 15.0; 12.4–17.6) years. Metabolic compensation of diabetes was determined by fasting blood glucose and glycosylated hemoglobin (HbA1c).

Questionnaire

All patients were interviewed regarding their esophageal symptoms and completed a structured questionnaire. The following symptoms, which may indicate the presence of reflux esophagitis, were reviewed; retrosternal pain, heartburn, acidic regurgitation and dysphagia. Extraesophageal reflux symptoms included chronic night cough.

All interviews were performed by a single experienced clinician and patients completed the questionnaire after everything was carefully explained. None of the patients had any other disease or surgery involving the esophagus. This methodology is generally accepted (8, 9).

Esophagoscopy

Patients were examined in the morning after overnight fasting for at least 6 hours. The presence of esophagitis proximal to the Z line was noted and evaluated according to the Los Angeles classification, Grade A; one or more isolated mucosal breaks confined to the mucosal folds, each no longer than 5 mm, Grade B; one or more isolated mucosal breaks more than 5 mm long confined to the mucosal folds, Grade C; at least one mucosal break continuous between the tops of two or more mucosal folds but not circumferential, and Grade D; circumferential mucosal break (10).

Endoscopy was performed by an experienced endoscopist using a flexible fibreoptic equipment, Olympus Q-20 (Japan). In order to avoid any influence on the evaluation of endoscopic findings, the endoscopist was not made aware of the results of the questionnaire or cardiovascular autonomic tests.

Cardiovascular autonomic tests

We examined the cardiovascular reflexes (variation of heart rate during deep breathing, active orthostasis and Valsalva's maneuver) and spectral analysis of heart rate using an apparatus with telemetric transmission of the electrocardiographic signals, VariaPulse TF3 (Sima Media, Czech Republic). This method of evaluation is generally known (1).

Patients with unfavorable lifestyle, as well as those using medication that affects the lower esophageal sphincter were withdrawn from the study.

Tab. 1. Parameters of diabetes in patients with endoscopic proven reflux esophagitis.

	Reflux esophagitis		p
	Present n=22	Absent n=32	
Age (years)	56.3 (51.3–61.3)	54.9 (50.2–59.2)	NS
Length of duration of diabetes (years)	17.2 (12.0–22.3)	13.5 (10.8–16.3)	NS
Fasting glycemia (mmol/l)	9.8 (8.3–11.3)	10.3 (8.8–11.8)	NS
HbA1c (%)	8.9 (8.0–9.9)	8.1 (7.6–8.7)	NS

Data is expressed in mean values and 95 % confidence intervals.

Statistical analysis

In determining the importance of reflux symptoms in the diagnosis of reflux esophagitis, sensitivity, specificity, and positive and negative predictive values were calculated. Sensitivity was defined as the proportion of patients with reflux symptoms who had positive endoscopic findings. Specificity was defined as the proportion of patients without reflux symptoms who had no endoscopic findings. The positive predictive value was defined as the probability of the presence of reflux symptoms in patients with positive endoscopic findings. The negative predictive value was defined as the probability of the absence of reflux symptoms in patients with no endoscopic findings.

Individual parameters in the groups were tested using the nonparametric Student's t-test. Chi^2-test was used to evaluate qualitative parameters.

Results

Endoscopic esophagitis (grades A to D according to the Los Angeles classification) was present in 22 (40.7 %) diabetics. Of this 10 (45.5 %) described reflux symptoms in the questionnaire. We did not find any difference in the metabolic compensation of diabetes, patient age and duration of diabetes between the groups with and without reflux esophagitis (Tab. 1).

Sensitivity of reflux symptoms was 45.5 %, and specificity 72 %. The positive and negative predictive value for symptoms was 52.6 % and 65.7 % respectively.

In all 21 (38.9 %) patients had reflux symptoms indicative of the possible presence of esophageal disease. The commonest symptom was heartburn. Macroscopic endoscopic changes in the esophageal mucosa were present in 10 (47.6 %) of these patients. There was a significantly longer duration of diabetes in patients who developed reflux symptoms (Tab. 2).

Autonomic neuropathy was proven in 29 diabetics, endoscopic esophagitis was present in 16 (55 %) of them, and 18 (62 %) had reflux symptoms. In the group without autonomic neuropathy, 6 (24 %) patients had eosophagitis and this prevalence was significantly lower ($p<0.05$). Reflux symptoms were present in 10 (40 %) patients without autonomic neuropathy. The difference between the two groups was not statistically remarkable. Thus, we proved that autonomic neuropathy has an

Tab. 2. Parameters of diabetes in patients with reflux symptoms indicative of possible reflux esophagitis.

	Symptoms		p
	Present n=20	Absent n=34	
Age (years)	54.8 (48.5–61.1)	55.8 (51.8–54.9)	NS
Length of duration of diabetes (years)	19.1 (13.1–25.1)	12.6 (10.6–14.7)	<0.02
Fasting glycemia (mmol/l)	9.5 (7.6–11.4)	10.4 (9.1–11.8)	NS
HbA1c (%)	8.3 (7.3–9.4)	8.6 (8.0–9.1)	NS

Data is expressed in mean values and 95 % confidence intervals.

influence on the development of endoscopic esophagitis, however not on reflux symptoms.

Discussion

Endoscopy is an important method for assessing the degree of inflammatory changes in the esophagus (11). We found a high prevalence of macroscopic changes in about 41 % of diabetics, which in most cases do not produce symptoms. This finding is higher compared with that of Petersen et al in the nondiabetic population, where the prevalence of reflux esophagitis was about 15 % (12). Thus the prevalence of endoscopic reflux esophagitis in diabetics appears to be more than twice that of nondiabetics. Recently Lluch et al found a high prevalence (28 %) of abnormal gastroesophageal reflux in diabetic patients compared with the nondiabetic population (13).

The metabolic compensation of diabetes, age of the patient and the duration of diabetes do not influence the prevalence of endoscopic reflux esophagitis, although we noted a tendency for reflux esophagitis to occur in those with older age, longer duration of diabetes and poor metabolic compensation.

Endoscopic, roentgenographic, manometric and scintigrafic methods are all important in the diagnosis of gastrointestinal autonomic neuropathy, though in practice some of them are hardly accessible (1). In general, examination of cardiovascular reflexes is used in diagnosing autonomic neuropathy, though it is possible to admit its lower specificity in determining the presence of gastrointestinal autonomic neuropathy. However, with this less specific examination, we succeeded in establishing a significant relationship between autonomic neuropathy and a high prevalence of reflux esophagitis in our diabetic patients. We confirmed the possible role of impaired autonomic nervous system regulation in the development of reflux esophagitis. Jackson et al (2000) also found pathological changes in the function of the autonomic nervous system in patients with gastroesophageal reflux disease (14).

Impaired gastric emptying resulting from diabetic gastroparesis can contribute to the development of reflux esophagitis. It appears that there is a close link between reduction of the interstitial cells of Cajal, which are responsible for gastric motility, and diminished neurotransmission (15).

Nitric oxide (NO) seems to play a critical role in gastrointestinal motility and in diabetic mice with diabetic gastropathy, NO synthase was found to be decreased in the myenteric neurons (16). Decreased NO-synthase in esophageal neurons is closely connected with impaired autonomic regulation leading to lower esophageal sphincter dysfunction, and in extreme cases achalasia can occur (17, 18).

In the literature, the prevalence of esophageal symptoms in diabetics varies from 2–27 % (19). The presence of upper gastrointestinal symptoms is more common in diabetics than nondiabetics (44.3 % vs 24.6 %) (20). A more recent study has confirmed this occurrence in diabetics compared with nondiabetics (21). 38.9 % of our patients complained of symptoms of esophageal origin. Heartburn and regurgitation are considered to be specific symptoms of reflux esophagitis (22, 23). Heartburn was confirmed to indeed be the most common symptom among our patients. However, reflux symptoms weakly predict the presence of endoscopic changes and are often present in more than half of diabetics who do not have evident macroscopic causes. Of relevance, we only noted an association between symptoms of esophageal dysfunction and the duration of diabetes. This is consistent with recent reports, that the duration of diabetes is the most important factor, which influences the manifestation of gastrointestinal symptoms, independent of metabolic compensation (20).

It is remarkable, that the feelings of discomfort, which originate most probably from the upper gastrointestinal tract without evident macroscopic cause, increase with the duration of hyperglycemia. Nonspecific esophageal motor dysfunction is the most probable cause of these unpleasant feelings. This is a clinical problem, which has not been precisely defined, involving intermittent delayed food transit, which is associated with retrosternal discomfort of varying intensity. The pathogenesis of this manifestation is not clear, because the myenteric plexus and the esophageal musculature appear intact (24). It has been recently proven that patients with the poorly compensated diabetes, determined by values of glycosylated hemoglobin, have significantly more symptoms than those with good metabolic control (25). We could not confirm the influence of metabolic compensation of diabetes in the development of upper gastrointestinal symptoms in our patients.

It is unlikely, that autonomic neuropathy is related to symptoms from the gastrointestinal tract. Symptoms developing from impaired autonomic function were not associated with a higher occurrence of gastrointestinal symptoms (26). Patients with autonomic neuropathy did not have an increase in any gastrointestinal symptom (27), and in our study, the prevalence of esophageal symptoms was not found to be high.

Our results show that reflux esophagitis is a common condition in diabetics, with a prevalence of 40.7 %. Reflux symptoms do not have a great diagnostic value in establishing reflux esophagitis, in fact they are present in only a third of patients with positive endoscopic findings, and only about half of symptomatic diabetics have reflux esophagitis**.** Their low sensitivity and specificity also confirms this observation.

In this study, we established a relationship between autonomic neuropathy and the endoscopic reflux esophagitis.

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