Increased prevalence of symptoms of gastroesophageal reflux diseases in type 2 diabetics with neuropathy

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Abstract

AIM: To analyze the prevalence of gastroesophageal reflux disease (GERD) related symptoms in patients with diabetes mellitus (DM) and to find out the relationship between diabetic neuropathy and the prevalence of GERD symptoms.

METHODS: In this prospective questionnaire study, 150 consecutive type 2 diabetic patients attending the endocrine clinic were enrolled. A junior physician helped the patients to understand the questions. Patients were asked about the presence of five most frequent symptoms of GERD that included heartburn (at least 1/wk), regurgitation, chest pain, hoarseness of voice and chronic cough. Patients with past medical history of angina, COPD, asthma, cough due to ACEI or preexisting GERD prior to onset of diabetes and apparent psychiatric disorders were excluded from the survey. We further divided the patients into two groups based on presence or absence of peripheral neuropathy. Out of 150 patients, 46 had neuropathy, whereas 104 patients did not have neuropathy. Data are expressed as mean $\pm$ SD, and number of patients in each category and percentage of total patients in that group. Normal distributions between groups were compared with Student *t* test and the prevalence rates between groups were compared with Chi-square tests for significance.

RESULTS: The average duration of diabetes were 12 ± 9.2 years and the average HbA1c level of this group was $7.7\% \pm 2.0\%$. The mean weight and BMI were 198 ± 54 lbs. and 32 ± 7.2 kg/m². Forty percent (61/150) patients reported having at least one of the symptoms of GERD and thirty percent (45/150) reported having heartburn at least once a week. The prevalence of GERD symptoms is

higher in patients with neuropathy than patients without neuropathy (58.7% vs 32.7%, $P < 0.01$). The prevalence of heartburn, chest pain and chronic cough are also higher in patients with neuropathy than in patients without neuropathy (43.5% vs 24%; 10.9% vs 4.8% and 17.8% vs 6.7% respectively, $P < 0.05$).

CONCLUSION: The prevalence of GERD symptoms in type 2 DM is higher than in the general population. Our data suggest that DM neuropathy may be an important associated factor for developing GERD symptoms.

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Key words: Diabetes; Neuropathy; Gastroesophageal reflux disease; Symptom; Heart burn

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INTRODUCTION

The prevalence of gastrointestinal (GI) symptoms is reported to be higher in patients with diabetes mellitus (DM)^[1] than the general population. Although not generally considered as important causes of morbidity or mortality in DM patients, these symptoms can influence health related quality of life (HRQOL) and affect productivity and employment status^[2,3]. GI symptoms can be encountered in up to 75% of diabetic outpatients evaluated in tertiary care referral centers^[4,5]. Many patients with GI disorders remain undiagnosed and untreated. The underlying mechanisms of the high prevalence of gastrointestinal symptoms in type 2 DM are poorly defined and controversy exists at the present time. The association of GI symptoms in DM to glycemic control is debated and controversy exists^[6,7]. Many of the gastrointestinal symptoms in diabetics suggest motor dysfunction, and a neuropathic basis to those dysfunctions would be a reasonable explanation. A recent study by Bytzer *et al* suggests that GI symptoms in DM were associated with complications of DM, particularly peripheral neuropathy^[6]. Some studies even suggest that gastrointestinal symptoms in

diabetic patients were poorly related to diabetic neuropathy, instead were related with psychiatric illness^[8,9]. The duration of DM was also an important factor for GI symptoms in type 2 DM patients since longer duration tends to have more complications^[1,10].

In the pathophysiology of gastroesophageal reflux disease (GERD), a major mechanism that promotes reflux of gastric contents into esophagus is delayed gastric emptying, a frequent complication of diabetes with neuropathy. The most common symptoms of GERD are heartburn and regurgitation^[11] and GERD may also responsible for other symptoms such as hoarseness, asthma (chronic cough) and chest pain. The aim of this study is to analyze the prevalence of GERD symptoms in patients with diabetes and to find out the relationship between the duration of diabetes, BMI, HbA1c, diabetic neuropathy and the prevalence of GERD symptoms. We especially focus on the role of DM neuropathy in the development of symptoms of GERD in type 2 diabetes.

MATERIALS AND METHODS

In this cross-sectional study, 150 type 2 diabetic patients were enrolled. This was comprised of 150 consecutive type 2 diabetic patients attending the endocrine clinic in a major University diabetic center. This was elicited based on a questionnaire distributed to patients.

A junior physician helped the patients to understand the questions. Patients were asked about the presence of five most frequent symptoms of GERD that included heartburn, regurgitation, chest pain, hoarseness of voice and chronic cough^[11]. To maximize the specificity of symptoms of GERD for our analysis, we considered only participants with frequent symptoms and excluded patients with less frequent than weekly. Patients' weight, height, BMI, BP, duration of diabetes, medications, HgbA1c and complications of diabetes including neuropathy were obtained within 6 wk of eliciting the answers to the questionnaire. Patients with past medical history of angina, COPD, asthma, cough due to ACEI or preexisting GERD prior to onset of diabetes and apparent psychiatric disorders were excluded from the survey.

We further divided the patients into two groups based on presence or absence of peripheral neuropathy. Out of 150 patients, 46 had neuropathy, whereas 104 patients did not have neuropathy. Presence of neuropathy was determined by past change in neuropathy and positive sensory symptoms including: limbs numbness, prickling sensation, aching pain, burning pain and at least one of the positive neurological examination findings including: (1) decreased pressure or pain sensation: positive monofilament test; (2) decrease of light touch sensation: positive cottonwool swab test; (3) decreased tendon reflexes.

Data are expressed as mean $\pm$ SD, and number of patients in each category and percentage of total patients in that group. Normal distributions between groups were compared with Student *t* test and the prevalence rates between groups were compared with Chi-square tests for significance. $P < 0.05$ is selected as significant level.

Table 1 Prevalence of GERD symptoms in DM patients with and without neuropathy

	DM 150	DM w Neuro 46	DM w/o Neuro 104	P value
Age (yr)	54 $\pm$ 15	56 $\pm$ 13	53 $\pm$ 16	> 0.10
DM Duration (yr)	12 $\pm$ 9.2	14.8 $\pm$ 9.1	10.7 $\pm$ 9.0	> 0.10
Weight (lbs)	198 $\pm$ 54	207 $\pm$ 42	194 $\pm$ 58	> 0.10
BMI	32 $\pm$ 7.2	33.9 $\pm$ 6.9	31.2 $\pm$ 7.2	> 0.10
HbA1c (%)	7.7 $\pm$ 2.0	7.9 $\pm$ 1.8	7.7 $\pm$ 1.2	> 0.10
Metformin	87/150 (58%)	26/46 (56.5%)	61/104 (58.6%)	> 0.10
GERD	61/150 (40.7%)	27/46 (58.7%)	34/104 (32.7%)	< 0.01
Heartburn	45/150 (30%)	20/46 (43.5%)	25/104 (24%)	< 0.05
Chest pain	10/150 (6.6%)	5/46 (10.9%)	5/104 (4.8%)	< 0.05
Chronic cough	14/150 (9.4%)	8/46 (17.8%)	7/104 (6.7%)	< 0.05
Regurgitation	19/150 (12.8%)	7/46 (15.6%)	12/104 (11.5%)	> 0.10
Hoarseness	5/150 (3.3%)	2/46 (4.4%)	3/104 (2.9%)	> 0.10

GERD: Presence of one or more of the five symptoms. Prevalence of heartburn in US adults is 14% weekly^[11].

RESULTS

The mean age $\pm$ SD of the group was 54 $\pm$ 15; the mean weight and BMI were 198 $\pm$ 54 lbs. and 32 $\pm$ 7.2 kg/m². Eighty-seven (58%) of the patients were women. Ninety two (61%) patients were Caucasians, twenty-five (16.7%) of the patients were African Americans, seventeen (11.3%) of the patients were Asia Americans and twenty-one (14%) patients were from the other ethnic groups. The average duration of diabetes was 12 $\pm$ 9.2 years and the average HbA1c level of this group was 7.7% $\pm$ 2.0%. All patients took multiple medications including eighty-seven patients (56.5%) took metformin for their DM control.

Forty percent (61/150) patients reported having at least one of the symptoms of GERD and 30% (45/150) reported having heartburn at least once a week (Table 1).

There is no difference in age, body weight, BMI, duration of DM, and combination therapy with metformin between patients with neuropathy and patients without neuropathy ($P > 0.05$). The prevalence of GERD symptoms is higher in patients with neuropathy than patients without neuropathy ($P < 0.01$). The prevalence of heartburn, chest pain and chronic cough are also higher in patients with neuropathy than patients without neuropathy ($P < 0.05$) (Table 1).

DISCUSSION

Gastrointestinal symptoms are frequently encountered in patients with DM. Although not generally considered important causes of mortality in DM patients, these symptoms can influence Health Related Quality of Life (HRQOL)^[2,3] and be encountered in up to 75% of diabetic outpatients^[4,5]. Our data showed that the overall prevalence of GERD symptoms in diabetics is 40.7% and is greater than in general population (14%) reported in the literature^[12]. In a study by Nebel *et al* they reported 7% had daily heartburn and 14% had weekly symptoms^[12]. In those with neuropathy, the presence of heartburn (43.5%) was significantly higher than in the group without neuropathy (24%; $P < 0.05$). The mechanisms of the high

prevalence of gastrointestinal symptoms in type 2 DM are poorly defined and controversy at present time. The proposal mechanisms include: over weight and obesity, blood glucose levels at the time of presentation, DM medications, duration of DM and DM complications.

Over weight and obesity are risk factors for symptoms of GERD^[13-15], and recent study by Jacobson *et al* found BMI is associated with symptoms of GERD in both normal-weight and overweight women^[16]. Most of our type 2 diabetes patients are over weight or obesity with average BMI of 32, so over weight might be explained part of high frequent symptoms of GERD in type 2 diabetes patients. However, there was no difference in BMI between patient with or without neuropathy, over weight or obesity might not associate with the high frequency of GERD symptoms of type 2 DM patients with neuropathy. Acute hyperglycemia (> 200 mg/dL) is a contributory factor for the GI symptoms that can slow gastric motor function and delay gastric empty. Bytzer and colleagues reported that gastrointestinal symptoms were associated with DM complications but not with current glycemia control measured by blood glucose and glycosylated hemoglobin levels and a later study from the same group suggested that GI symptoms were associated with both poor glycemic control and DM complications^[1]. Our data indicate that the symptoms of GERD were not associated with recent HbA1c levels. DM medications, especially metformin induce many gastrointestinal symptoms including nausea, vomiting, diarrhea, flatulence, chest discomfort and abdomen discomfort but not heartburn. Since there was no difference in medications usage between patients with neuropathy and without neuropathy, medications might not associate with the high prevalence of GERD symptoms in type 2 DM patients with neuropathy.

In our study, we focused on the symptoms of GERD and found that the prevalence of GERD symptoms is higher in patients with neuropathy (58.7%) than in those without neuropathy (32.7%). Heartburn is noted in 42% of patients with neuropathy *versus* 24% patients without neuropathy. Since experience of heartburn is likely to be blunted by neuropathy, the actual incidence of GERD may even be higher. Our data thus suggest that neuropathy is an important associate factor of the symptoms of GERD in type 2 DM. Delayed gastric emptying is a well-known mechanism promoting gastric retention and reflux. In type 1 DM, peripheral neuropathy is present in the majority of patients with enteropathy and GI symptoms are associated with DM peripheral neuropathy^[1]. Two recent reports suggest that the pacemaker cells in the wall of the upper digestive tract are abnormal in experimental diabetes and in a single DM patient^[17,18]. It is generally believed that gastroparesis of some degree complicates diabetes of > 10 years in duration when accompanied by peripheral and autonomic neuropathy. Type 2 diabetics with GI symptoms most commonly presented with gastroesophageal reflux disease whereas type 1 diabetics had bloating fullness and satiety^[7].

Ideally all patients above the age of 50 and those with alarm symptoms (dysphagia, weight loss, anemia, history of cigarette smoking and alcoholism) with GERD symptoms should undergo esophago gastro duodenoscopy, and gastric

emptying studies. However we did not perform these studies since our goal is not to identify a pathogenic mechanism but first to note whether neuropathy contributed to GERD symptoms. Several studies have been published that the validity and reliability these symptoms in identify cases of GERD^[13,14]. Furthermore, to improve our specificity for GERD, we restricted our primary analysis to patients who reported at least weekly symptoms.

In summary, the prevalence of GERD symptoms in type 2 DM is higher than in general population and the prevalence of GERD symptoms is higher in patients with neuropathy than patients without neuropathy. Our data suggest that DM neuropathy is an important associated factor for developing GERD symptoms. Patients with DM and neuropathy should be presumed to have GI abnormalities until proven otherwise. The work up should start with thorough patients' history, physical examination, appropriate laboratory test and possible endoscopy examination. Appropriate therapy including dietary manipulation and pharmacological therapy should be given to patients with GERD symptoms to improve health related quality of life.

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COMMENTS

Background

Many investigators have reported that the prevalence of gastrointestinal (GI) symptoms is higher in patients with diabetes mellitus (DM) than the general population. Although not generally considered as important causes of morbidity or mortality in DM patients, these symptoms can influence health related quality of life and affect productivity and employment status. The underlying mechanisms of the high prevalence of gastrointestinal symptoms in type 2 DM are poorly defined. The proposal mechanisms include: over weight and obesity, blood glucose levels at the time of presentation, DM medications, duration of DM and DM complications. The association between diabetes peripheral neuropathy and GERD symptoms is controversy at present time. In the present study, we focus on the association of DM neuropathy and the symptoms of gastroesophageal reflux disease (GERD) in type 2 diabetes.

Research frontiers

To analyze the prevalence of GERD symptoms in patients with diabetes and to find out the relationship between the duration of diabetes, BMI, HbA1c, diabetic neuropathy and the prevalence of GERD symptoms. We especially focus on the association between DM neuropathy and symptoms of GERD in type 2 diabetes.

Innovations and breakthroughs

In our study, we found in first time that the prevalence of GERD symptoms is higher in patients with neuropathy (58.7%) than in those without neuropathy (32.7%). Heartburn is noted in 42% of patients with neuropathy *versus* 24% patients without neuropathy. Since experience of heartburn is likely to be blunted by neuropathy the actual incidence of GERD may even be higher.

Applications

Our data suggest that DM neuropathy is an important associated factor for developing GERD symptoms. Patients with DM and neuropathy should be presumed to have GI abnormalities until proven otherwise. The work up should start and appropriate therapy should be given to patients with GERD symptoms to improve health related quality of life.

Peer review

This is a very good study. Much more solid and valid conclusions could be drawn if more appropriate statistical analysis were done.

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