Short Title: Upper gastrointestinal dysmotility in diabetes

Oesophageal dysmotility, delayed gastric emptying and gastrointestinal symptoms in patients with diabetes mellitus

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Abstract

Aims: It is known that gastro paresis is a common gastrointestinal complication in diabetes mellitus, whereas dysfunction in the other gastrointestinal organs has been less thoroughly investigated in this entity. Furthermore, it is not known whether there is a relationship in motility or dysmotility between these organs. The aim of this study was to examine whether diabetic patients with gastrointestinal symptoms also have motility disturbances in the oesophagus and stomach, and if so, whether there are any associations between these disturbances.

Methods: In this study 31 patients with diabetes mellitus who complained of gastrointestinal symptoms were asked to complete a questionnaire about their symptoms. They were further investigated with oesophageal manometry and gastric emptying scintigraphy.

Results: Fifty-eight % of the patients had abnormal oesophageal function, and 68 % had delayed gastric emptying. Abdominal fullness was the only symptom that related to any dysfunction, and it was associated with delayed gastric emptying ($p=0.02$). We did not find any relationship in motility or dysmotility between the oesophagus and the stomach.

Conclusion: Oesophageal dysmotility, as well as gastro paresis, are common in patients with diabetes who have gastrointestinal symptoms. It is important to investigate these patients further, to be able to give them an accurate diagnosis and treatment. Our findings indicate that the oesophagus and the stomach function as separate organs and that pathology in one does not necessarily mean pathology in the other.

Introduction

Gastro paresis is a well-known complication in diabetes mellitus [1, 2]. Abnormal oesophageal motility has been described [3], but not to the same extent in connection with diabetes. Usually, oesophageal manometry is performed in patients with primary dysphagia, chest pain without any heart disease [4] or connective tissue abnormalities and dysphagia [5], as these patients are assumed to have oesophageal dysmotility.

We have recently shown that oesophageal dysmotility in diabetics, which is considered to be a rare disorder, may have effects on glucose homeostasis [3]. By addressing this issue we are viewing oesophageal dysmotility from a different perspective. Our aim was to further examine whether patients who suffer from gastrointestinal symptoms also have motility disturbances in the oesophagus and stomach, and if so, whether there are any relationships between the symptoms and disturbances, and between the disturbances in these two organs.

Patients and methods

This study was performed according to the Helsinki Declaration and was approved by the Ethics Committee of Lund University. All subjects gave written, informed consent before entering the study.

Patients

The subjects were all consecutive patients with diabetes mellitus at the Department of Endocrinology at Malmö University Hospital who presented with gastrointestinal symptoms. Patients under treatment with peritoneal dialysis, with other severe diseases or unable to perform oesophageal manometry were excluded. Fourteen of the patients were earlier included in a previously published study [3]. The current study is extended according to the same protocol by a further 17 patients to a total of 31. The patients were asked to participate in this study by undergoing investigations of their symptoms by oesophageal manometry and gastric emptying scintigraphy.

At the same time they completed a questionnaire concerning the symptoms usually present in these patients, namely, loss of appetite, dysphagia, meal-related cough, early satiety, nausea, vomiting, weight loss, abdominal fullness, bloating, regurgitation, constipation, diarrhoea with gas, evacuation incontinence, postprandial glycaemia pitfalls, symptomatic postprandial hypoglycaemia and postprandial perspiration (Table 1).

HbA1c and BMI were checked in conjunction with the investigations. Twenty-four patients had type 1 diabetes and seven had type 2, and all except one had insulin-dependent diabetes. None of the patients were taking any prokinetic drugs. For patient characteristics, see table 2 and 3.

Oesophageal manometry

The manometer was an intraluminal solid-state transducer system (Gaeltec Ltd, Isle of Skye, Scotland). A polygraph A/D converter digitised the analogue signal (Synmed, Stockholm, Sweden). The software was the PolyGram Upper-GI Edition by Gastro Soft Inc./Synmed (Synmed, Stockholm, Sweden). All pressure values were expressed in mmHg. All values are referred to atmospheric pressure. The sampling frequency was 64 Hz. The manometry catheter was introduced through the nose and fluoroscopically positioned initially in the distal oesophagus. The simultaneous video radiography and pharyngeal manometry were performed in an upright-seated position. With the manometry catheter in place, all participants were instructed to swallow 10 ml of barium contrast medium (60% w/v). At least 5 barium swallows were recorded. The lower oesophageal sphincter (LOS) resting pressure was identified and measured during a slow pull-through when the sensor passes from the stomach into the oesophageal-gastric junction. The LOS resting pressure was obtained as a mid-respiratory resting pressure. The video fluoroscopic image and the manometry registration were mixed using a Micro Eye Video Output Card (Digi Hurst Ltd, Roystone, UK). Patients who fulfilled one or more of the following five criteria with abnormal results for the oesophageal manometry were considered to suffer from oesophageal dysmotility: 1/ Absence of peristaltic contractions in the oesophagus (abnormal >0%), 2/ Mean peristaltic contraction amplitude (30-200 mm Hg; abnormal <30 and >200 mm Hg) in the oesophagus, 3/ Percentage of simultaneous, non-propulsive peristaltic waves in the oesophagus (abnormal > 10 %), 4/ Speed of the peristaltic wave (3-6 cm/sec; abnormal <3 or >6 cm/sec) in the distal oesophagus, 5/ Resting pressure in LOS (10-30 mm Hg: abnormal <10 or >30 mm Hg) [3, 4, 6].

Gastric emptying scintigraphy

A test meal was prepared by adding tin colloid labelled with 30-50 Mbq of technetium-99 to an egg, which was whipped in a glass cup in a hot water bath until coagulated. The egg and a slice of toasted white bread were cut into pieces smaller than 1x1 cm and served with 100 ml 37° C water. The meal was eaten within five minutes. Immediately thereafter a large-field gamma camera (Toshiba GCA-901A, Toshiba, Japan) was placed parallel to the upper abdominal wall. The radioactivity was measured continuously (one-minute frames) for 70 minutes starting immediately after meal ingestion. The activity of the first frame was taken as 100% and the gradual decreasing radioactivity, measured as the number of radioactivity decays per minute, (Counts/min), was plotted against time. The time elapsed to reach a 50% decrease in the scintigraphy result (T_{50}) was identified as the point at which this plot crossed the 50% value. The values of the radioactivity measured, were corrected for the half-life of 99Tc, and by using a lateral, one-minute image obtained after ingestion of 3.7 Mbq 99 m Tc-pertechnetate in 150 ml of water according to Collins et al. (7). T_{50} >2 SD for healthy controls (70 min) was considered abnormal (8).

Statistical analyses

The results are expressed as median and interquartile ranges [IQR]. The Mann Whitney U test and Fisher´s exact test were used to calculate differences between groups, and Spearman`s correlation test to evaluate correlations; $p<0.05$ was considered statistically significant.

Results

Only three of the 31 patients examined had normal function in both oesophagus and stomach.

Oesophageal motility

Eighteen of the 31 patients (58%) had abnormal oesophageal function. Of these, 17 showed aperistalsis, six had simultaneous contractions and five had both of these disturbances. The correlation between percent aperistaltic swallowings and percent simultaneous contractions in the oesophagus was approaching statistical significance (R=0.33, p=0.067). There were no differences in patient characteristics between those with and those without oesophageal dysmotility, or in the number of patients with delayed gastric emptying between patients with and without oesophageal dysmotility (Table 2). Seven patients had abnormal manometry but normal gastric emptying. Furthermore, there was no correlation between oesophageal peristaltic speed and T_{50} (R=-0.32, p=0.13).

Gastric motility

Twenty-one of the 31 patients (68%) had delayed gastric emptying. There were no differences on the basis of sex, age, BMI, duration of diabetes or HbA1c between those with and those without pathology (Table 3). T_{50} did neither correlate to HbA1c (R=-0.07, p=0.70) nor with the duration of the diabetes (R=-0.10, p=0.63).

Symptoms

There were no significant differences in the frequency of any of the symptoms between normal oesophageal motility and dysmotility, whereas the only symptom that could be associated with delayed gastric emptying was abdominal fullness (p=0.02). In our investigation of the symptoms (Table1), we found no statistically significant relationship between the various symptoms (data not shown). The patients who suffered from dysphagia

and meal-related cough had often aperistaltic oesophagus, but had fewer simultaneous contractions than those without symptoms (0.00[0.00-0.00] and 10.00[0.00-25.00], p=0.03, and 0.00[0.00-0.00] and 5.00[0.00-22.50], p=0.02, respectively).

Discussion

It is well known that patients with diabetes mellitus often have gastrointestinal motility disorders. However, oesophageal dysmotility has not been seen as a major problem for this population, the focus having been on gastro paresis. As we recently described how oesophageal dysmotility has an impact on the glucose homeostasis, with delayed plasma glucose increase postprandially, the identification of this abnormality may be important [3].

In our study of the 31 diabetic patients with gastrointestinal symptoms we have found that 68% have gastro paresis and 58% have esophageal dysmotility. Only three of the 31 patients had normal function in both oesophagus and stomach. This can be compared to patients without diabetes mellitus where half of those with gastrointestinal symptoms are found to have functional problems without objective findings [9]. Thus, while functional problems are very common in the normal population (10-15%) [10], these disorders may be rare among diabetics and the diagnosis should not be set without a thorough investigation of gastrointestinal motility. According to our previous findings of impaired glucose homeostasis in these patients [3], it is of importance that patients with diabetes who complain of gastrointestinal symptoms should be investigated further with oesophageal manometry and gastric emptying scintigraphy.

After including more patients we could not confirm the earlier observation of a correlation between oesophageal peristaltic speed and gastric emptying [3]. Neither could we find a relationship between oesophageal and gastric dysmotility in this study of diabetes mellitus, as has been described for polymyositis and dermatomyositis [5]. Our findings are in accordance with earlier studies on diabetes which could not show any correlation between oesophageal and gastric transit time [11, 12, 13]. It is interesting that there is no correlation despite their close anatomic relationship, which makes us believe that these organs work

separately and have independent functions. This is in agreement with the earlier findings showing that the stomach and the intestine may be controlled separately [14]. The relationship between disturbances in the oesophagus and the stomach in patients with polymyositis and dermatomyositis may depend on a different aetiology from the dysfunction in these entities [5].

If indeed the oesophagus and the stomach are entirely separate organs it is possible that different factors may cause damage to them. This could explain why some patients suffer from oesophageal dysmotility and others from delayed gastric emptying.

Even though 58% of the patients had oesophageal dysmotility, most could not localize their problems to the oesophagus specifically. The patients often described their problems as if they originated from the stomach. One explanation for abnormal gastrointestinal motility may be damage to the enteric nervous system (ENS) together with the destruction of the interstitial cells of Cajal (ICC) [15, 16]. Another possibility is smooth muscle dysfunction [17] or vagal neuropathy [18]. These dysfunctions may also lead to impairment of perception through afferent pathways [19], and not only to impaired motility, explaining the discrepancy between observed findings and reported symptoms.

Another explanation for the discrepancy between symptoms and findings could be the tendency to correlation between aperistalsis and simultaneous contractions in the oesophagus. The patients with simultaneous contractions had less meal-related cough and dysphagia. Thus, seven of the 14 patients with dysphagia had aperistalsis without simultaneous contractions, whereas only one with dysphagia had simultaneous contractions without aperistalsis. Maybe this means that simultaneous contractions are a compensatory mechanism for the aperistalsis that protects the patient from discomfort. In that case we must redefine what is primarily pathological and what is a compensation in these patients.

In the earlier study with 14 patients there was a significant relationship between abdominal fullness and gastro paresis (p=0.03) [3], and in this larger study we have been able to further confirm this finding (p=0.02).

We could not see a correlation between T_{50} and duration of diabetes mellitus, which is also in accordance with an earlier study [2]. There is a wide variation in complications among newly discovered diabetics, while those whose disease was of long duration have less variation [20]. The reason why duration of diabetes does not predict the degree of complications could be that other factors are of greater importance, for example, periods of hyperglycaemia and type of diabetes. Damage to the autonomous nervous system, which ENS is a part of, has recently been shown to correlate the development of antibody formation [21]. The autoimmunity factor may be stronger in some individuals, which can cause greater damage to cells in the gastrointestinal tract, for example, ICCs.

In conclusion, we have shown that oesophageal dysmotility is very common in diabetic patients with gastrointestinal symptoms. We could not show a relationship between oesophageal dysmotility and delayed gastric emptying. Instead, these findings suggest that these organs work independently of each other. It is also likely that simultaneous contractions in the oesophagus are a kind of compensation by the patient with aperistalsis, as patients with these findings have fewer problems with dysphagia and meal-related cough.

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Conflict of Interest

The authors have no conflict of interest

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Table 1. The prevalence of the different symptoms in the patients (n=31)

Symptoms	**Number of patients with symptom**
Loss of appetite	18
Dysphagia	14
Meal-related cough	8
Early satiety	20
Nausea	21
Vomiting	9
Weight loss	8
Abdominal fullness	25
Bloating	23
Regurgitation	17
Constipation	11
Diarrhoea with gas	11
Evacuation incontinence	8
Postprandial glycaemia pitfalls	13
Symptomatic postprandial hypoglycaemia	12
Postprandial perspiration	6

Elucidation: Abdominal fullness was the only symptom that was associated with any dysmotility, and it was associated with delayed gastric emptying (p=0.02).

Table 2. Distribution of investigated parameters in patients with normal and abnormal oesophageal motility.

Parameters	**Normal oesophageal function (n=13)**	**Abnormal oesophageal function (n=18)**	**p**
Gastric T_{50} (min)	97.0 (58.5-183.5)	129.5 (52.0-231.8)	0.77
Sex female/male	9/4	12/6	0.92
Age (years)	56.0 (52.0-60.5)	52.0 (37.8-56.5)	0.12
BMI	29.0 (23.9-32.2)	24.4 (21.4-29.2)	0.12
Duration of diabetes (years)	30.0 (23.5-47.8)	29.0 (20.0-37.0)	0.56
HbA1c (%)	7.3 (6.6-7.8)	7.2 (6.4-8.0)	0.74
Gastric dysmotility (%)	77	61	0.45

All data are given as the median (interquartile range). n= number. T_{50}= time elapsed to reach a 50% decrease in the gastric emptying scintigraphy result. $P<0.05$ was considered significant.

Table 3. Distribution of investigated parameters in patients with normal and delayed gastric emptying.

Parameters	**Normal gastric emptying (n=10)**	**Delayed gastric emptying (n=21)**	**p**
T_{50} (min)	42.5 (32.2-56.0)	144.0 (106.5-263.0)	0.000
Sex female/male	5/5	16/5	0.25
Age (years)	55.5 (46.0-58.2)	54.0 (42.0-59.0)	0.72
BMI	23.1 (21.2-30.2)	28.2 (23.5-30.7)	0.23
Duration of diabetes (years)	28.5 (27.0-43.5)	31.0 (16.0-41.0)	0.98
HbA1c (%)	7.4 (6.5-8.1)	7.2 (6.6-7.9)	0.57
Oesophageal functions			
Dysmotility (%)	70	52	0.45
Aperistaltic swallowing (%)	25.0 (0.0-90.0)	0.0 (0.0-45.0)	0.29
Mean amplitude contractions (mm Hg)	36.5 (16.2-60.5)	54.0 (27.5-66.0)	0.20
Simultaneous contractions (%)	0.0 (0.0-10.0)	0.0 (0.0-25.0)	0.69
Mean peristaltic speed (cm/s)	5.0 (2.5-6.7)	3.8 (3.4-5.0)	0.42
LOS pressure (mmHg)	12.0 (0.8-20.2)	12.0 (8.0-19.0)	0.83

All data are given as the median (interquartile range). n= number. T_{50}= time elapsed to reach a 50% decrease in the gastric emptying scintigraphy result. LOS = the lower oesophageal sphincter. $P<0.05$ was considered significant.