Short title: Diabetic gastrointestinal complications and glucose homeostasis

Oesophageal dysmotility, delayed gastric emptying and autonomic neuropathy correlate to disturbed glucose homeostasis

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Abbreviations: CGMS, Continuous Glucose Monitoring System; E/I, Expiration/Inspiration ratio; SD, standard deviation

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ABSTRACT

Aims/hypothesis: Among diabetic patients, glucose homeostasis may be affected by abnormal gastrointestinal motility and autonomic neuropathy. This study was aimed to dissect whether oesophageal dysmotility, delayed gastric emptying or autonomic neuropathy affect glucose homeostasis.

Methods: Oesophageal manometry, gastric emptying scintigraphy, heart-rate variation during deep breathing (expiration/inspiration [E/I] ratio) and continuous subcutaneous glucose concentrations were monitored in 20 diabetic patients.

Results: Eight of 14 patients had oesophageal dysmotility, 11/20 had delayed gastric emptying (abnormalT_{50}) and 9/18 abnormal E/I. Complaints of abdominal fullness predicted delayed gastric emptying. Low peristaltic speed of oesophagus was associated with impaired T_{50} (r_s=-0.67; p=0.02). One hour after breakfast, subcutaneous glucose levels decreased in patients with delayed gastric emptying but continued to rise in those with normal emptying. Consequently, median glucose level was lower 2.5 hours after breakfast in the former (9.1 [4.2-12.5] vs. 14.3 [11.2-17.7] mmol/l; p<0.05). Glucose fluctuations during the 72 hours were significantly higher in those with abnormal E/I versus those without (coefficient of variation: 41 [46-49] vs. 28 [27-34] %; p=0.008).

Conclusions/interpretation: Abdominal fullness predicted delayed gastric emptying that was associated with diminished glucose uptake after breakfast. Low oesophageal peristaltic speed was associated with slow gastric emptying whereas parasympathetic neuropathy was associated with increased glucose variations.

INTRODUCTION

Albeit, symptoms suggestive of gastrointestinal dysmotility poorly correlate with disturbances [1], gastrointestinal dysmotility is a well-known complication of diabetes mellitus [2]. Gastrointestinal dysmotility is believed to affect glycemic control through unclear mechanisms. An animal model suggests that autonomic neuropathy contributes to impaired glycaemic control [3].

Our hypothesis is that not only delayed gastric emptying but also other gastrointestinal complications impair glycaemic control. This study was aimed to define specific symptoms identifying upper gastrointestinal dysmotility and to evaluate the relationships between oesophageal dysmotility, delayed gastric emptying and autonomic neuropathy versus glucose homeostasis.

MATERIALS AND METHODS

Subjects

This study was performed in a prospective manner according to the Helsinki declaration and was approved by the Ethics Committee of Lund University. All patients gave written informed consent before entering the study.

At the diabetes clinic at Malmö University Hospital, the first 20 consecutive patients complaining of symptoms suggestive of disturbances in the gastrointestinal tract were invited to the current study that comprised 1) a questionnaire with 16 symptom questions (loss of appetite, swallowing disturbances, meal-related cough, early satiety, nausea, vomiting, weight loss, abdominal fullness, bloating, regurgitations, constipation, diarrhoea, evacuation incontinence, postprandial glycaemia pitfalls, symptomatic postprandial hypoglycaemia, postprandial perspiration), 2) gastric emptying scintigraphy (n=20), 3) oesophageal manometry (n=14), 4) autonomic nervous function (n=18) and 5) continuous subcutaneous glucose monitoring during 72 hours (n=20). All patients were insulin-treated (17 with type 1

and 3 with type 2 diabetes). None were on medication affecting intestinal motility or autonomic nervous system.

Examinations

Standardized oesophageal manometry was performed with the patient sitting in the up right position and the peristaltic speed was calculated. Each patient performed ten swallows. The LOS was identified during a slow pull-through in the mid exspiratory phase. Inadequate relaxation of the low oesophageal sphincter, oesophageal uncoordinated contractions or hypo/hypercontractions were considered as oesophageal dysmotility [4].

Gastric emptying (solid food) was assessed [5] and a T_{50} >2 standard deviations (SD) of healthy controls (= 70 minutes) was considered as delayed gastric emptying [6] .

RR interval variation during deep breathing (expiration/inspiration [E/I] ratio) was used as a test of autonomic nerve function and an age-related E/I below –1.64 SD was considered abnormal [7].

Using the Mini Med Continuous Glucose Monitoring System (CGMS) (Mini Med Inc., Sylmar, CA), subcutaneous glucose levels was continuously monitored for 72 hours [8]. Coefficient of variation (CV) of glucose concentration was defined as SD/mean x 100 (%). On the second day, after an overnight fast, the patient took her usual insulin injection at the start of a fibre-rich breakfast and subcutaneous glucose levels could be followed during 4 hours until the lunch meal. The breakfast consisted of oat-meal porridge, cooked from 35 g fibre porridge oats, 150 g 0.1% milk and 17 g mashed apple together with a slice of rye bread containing 9% fibre with 5g, 40% margarine and 10g, 17% cheese.

Statistical analysis

Results are expressed as median and interquartile ranges [IQR]. Mann Whitney U test and Fisher's exact test were used for calculating differences between groups, and Spearman's correlation test to evaluate correlations; $p<0.05$ was considered significant.

RESULTS

Gastrointestinal dysmotility

Eleven of 20 patients had delayed gastric emptying**.** There were no differences in gender, age, disease duration or HbA1c between patients with and without delayed gastric emptying (Table 1). T_{50} was inversely related to age (r_s=-0.46; p=0.05) but did not correlate with HbA1c (r_s =0.00; p=1.00) or duration of the diabetes (r_s=0.18; p=0.60). There was no difference in median T_{50} between 9 patients with an abnormal versus 9 patients with a normal E/I ratio (102 [44-248] vs. 117 [26-240] minutes; p=0.96).

Eight out of 14 patients showed dysmotility of the oesophagus (Table 1). There was no correlation between oesophageal dysmotility versus gastric emptying or the E/I ratio (data not shown). However, there was a negative correlation between mean peristaltic speed of oesophagus and T_{50} (r_s=-0.67; p=0.02).

Symptoms versus gastrointestinal dysmotility

Of the 16 different symptoms in the questionnaire, only abdominal fullness was significantly associated with delayed gastric emptying; found in all (11/11) with delayed gastric emptying compared with 5 out of 9 without (p=0.03). T_{50} was significantly longer in patients with symptoms of abdominal fullness than in patients without (117 [42-255] vs. 31 [19-59] minutes, p=0.04). No symptom was predictable for oesophageal dysmotility (data not shown).

Glucose homeostasis

The HbA1c values indicated fair to good glycaemic control in the patients (Table 1). During the first hour after breakfast, subcutaneous glucose levels rose similarly in patients with and without delayed gastric emptying (Fig 1a). Thereafter, glucose levels decreased in those with delayed gastric emptying while continuing to rise in those without. Accordingly, median glucose level was clearly lower in patients with than in those without delayed gastric

emptying 2.5 hours after breakfast (9.1 [4.2-12.5] vs. 14.3 [11.2-17.7] mmol/l; p <0.05). AUC could not be determined in 7 out of 20 patients due to temporary disconnection of the CGMS equipment after the first 2.5 h. Patients with oesophageal dysmotility showed slow increments in glucose (abnormal vs. normal manometry median glucose level; 11.6 [5.1-14.9] vs. 14.4 [10.3-16.4] mmol/1, 1 hour after breakfast, p=0.16) that continuously increased up to 4 hours after breakfast whereas glucose decreased 2 hours after breakfast in those with normal manometry (Fig 1b). In agreement, the peak for glucose tended to be delayed in patients with abnormal oesophageal manometry vs. those with normal oesophageal manometry (3.5 [1.8-4.9] vs. 1.8 [1.1-2.0] hrs; p=0.08).

There was no association between the E/I ratio and glucose values after breakfast (data not shown). However, the glucose variation during the 72 hours of registration was significantly larger in those with an abnormal E/I ratio versus those without (coefficient of variation: 41 [46-49] vs. 28 [27-34] %; p=0.008).

DISCUSSION

This study showed that a feeling of abdominal fullness is associated with delayed gastric emptying. Patients with delayed gastric emptying showed decreased postprandial subcutaneous glucose concentrations, whereas patients with oesophageal dysmotility showed a tendency to delayed glucose absorption. Parasympathetic neuropathy was not associated with oesophageal dysmotility or abnormal gastric emptying but with increased variation in subcutaneous glucose concentrations.

Albeit it has been shown that variation in gastric emptying rate accounts for approximately 35% of the postprandial variance in glucose concentration in healthy volunteers and in patients with type 2 diabetes with normal gastric emptying [2], our study is the first to directly compare diabetic patients with abnormal gastric emptying versus diabetic patients without.

Found association between disturbed peristaltic oesophageal speed and disturbed gastric emptying is a novel finding, compared with earlier findings [1]. Normal gastrointestinal motor function depends on a delicate balance between extrinsic and enteric nervous systems, smooth muscles and locally released transmitters [2]. Our finding of an obvious association between oesophageal delayed peristalsis and disturbed gastric emptying demonstrates for the first time a generally disturbed oesophageal and gastric motility in diabetic patients. Most likely this defect is local (intrinsic) and not related to autonomic neuropathy. Our study did not provide any evidence for that parasympathetic neuropathy (abnormal E/I ratio) was associated with oesophageal dysmotility, disturbed oesophageal propulsion or disturbed gastric emptying. Our study infers that decreased postprandial subcutaneous glucose concentration is a consequence of proved upper gastrointestinal defect.

In this study, parasympathetic neuropathy was associated with increased variations in subcutaneous glucose levels. As parasympathetic neuropathy lacked associations to oesophageal and gastric functions, it is unlikely that dysfunctions in these organs were involved. Other mechanisms have to be considered to explain disturbed glucose homeostasis in parasympathetic neuropathy. Impaired sensing of the portal venous-hepatic arterial glucose gradient in a rat model suggests that diabetic neuropathy involving intra-hepatic nerves could contribute to postprandial hyperglycaemias [3]. Surgical denervation of liver and pancreas increases the glucagon response to oral glucose delivery in non-diabetic subjects [9]. Moreover, a muscarine cholinergic mechanism decreases hepatic glucose production in humans [10]. Parasympathetic neuropathy with impairment in this cholinergic system may enhance increased glucose production from the liver. Hence, different nervous mechanisms could explain why our diabetic patients with vagal neuropathy had a larger variation in subcutaneous glucose values compared with patients without neuropathy.

In conclusion, this study shows that low speed of oesophageal peristalsis is associated with slow gastric emptying in diabetic patients. This motility disturbance leads to delayed and decreased glucose uptake from the upper gastrointestinal tract. Parasympathetic neuropathy is not associated with this motility disturbance but with increased glucose fluctuations, possibly due to disturbed nervous humoral reflexes.

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Conflicting interests: None of the authors had any conflicting interests in the study.

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Table 1. Distribution of investigated parameters in patients with normal and delayed gastric emptying, respectively.

Parameters	Normal gastric emptying n=9	Delayed gastric emptying n=11	*p*
T_{50} (min)	35.0 (23.5-44.5)	224.5 (116.5-328.3)	<0.001
Sex Female/male	3/6	7/4	0.37
Age (years)	58.0 (47.0-59.5)	51.0 (44.0-56.0	0.20
BMI	23.1 (19.1-28.3)	28.0 (22.3-29.0)	0.41
Duration of diabetes (years)	27.0 (22.0-46.0)	33.0 (24.0-44.0)	0.64
HbA1c (%)	7.6 (6.5-8.4)	6.9 (6.3-7.6)	0.37
E/I ratio (SD from expected)	-1.4 [(-2.2)-(-1.3)]	-1.8 [(-2.1)-(-0.62)]	0.89
Oesophageal functions			
Dysmotility (%)	40	67	0.58
A-peristaltic swallowing (%)	0 (0-55)	20 (0-40)	0.70
Mean amplitude contractions, (mmHg)	60 (26-64)	59 (28-75)	0.80
Simultaneous contractions (%)	0 (0-10)	20 (0-30)	0.15
Mean peristaltic speed (cm/s)	6.5 (5.3-7.6)	3.8 (3.2-4.6)	0.008
LES pressure (mmHg)	5.0 (0-13.8)	15 (7.5-20)	0.15
Continuous Subcutaneous Glucose Registrations			
Baseline glucose (mmol/l)	8.0 (6.7-10.8)	8.7 (3.8-10.0)	0.55
Highest glucose(mmol/l)	17.6 (14.1-18.7)	13.4 (12.5-16.6)	0.20
Lowest glucose(mmol/l)	11.1 (3.7-15.0)	6.8 (4.0-12.7)	0.66
Time to highest glucose (hours)	1.9 (1.2-2.6)	2.1 (1.2-3.5)	0.66
CV of glucose (%)	42.3 (28.8-48.6)	36.4 (30.5-53.4)	0.88

All data are given as median (interquartile range). N = number. $p<0.05$ was considered significant.

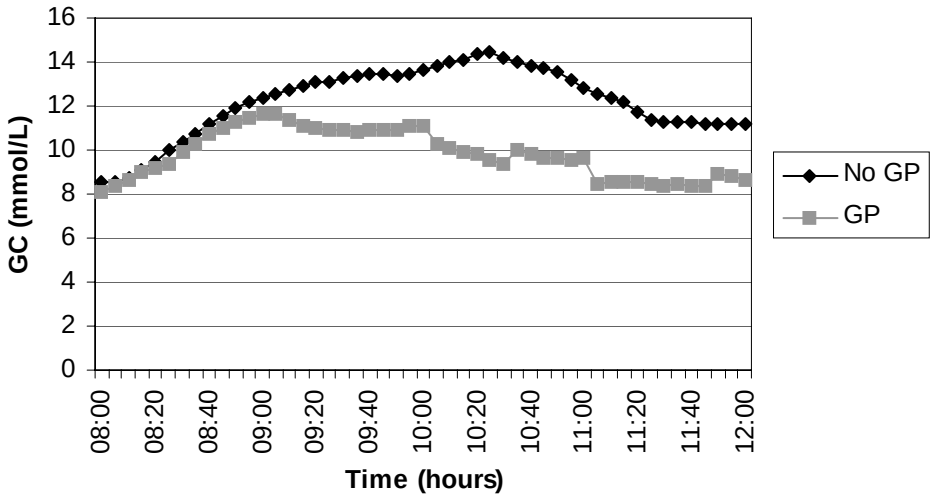
Number of patients investigated with oesophageal manometry was 5 in the group with normal gastric emptying and 9 in the group with delayed gastric emptying.

T_{50}, Gastric emptying half time; BMI, body mass index; LES, Lower Oesophageal Sphincter; CV, coefficient of variation

Legends to figures

Figure 1. Subcutaneous glucose concentrations (GC) after intake of a high fibre breakfast among patients with and without a) delayed gastric emptying and b) oesophageal dysmotility. There was a statistical significant difference in the median value in glucose concentration between patients with delayed vs. normal gastric emptying 2.5 hours ($p<0.05$) after breakfast, and a trend to delay in peak glucose value in patients with oesophageal dysmotility ($p=0.08$). Black is patients with normal function and grey is patients with abnormal function. Seven out of 20 patients had missing values due to temporary disconnection of the CGMS equipment between 2.5h and 4 h after the test meal.

A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GC (mmol/L)
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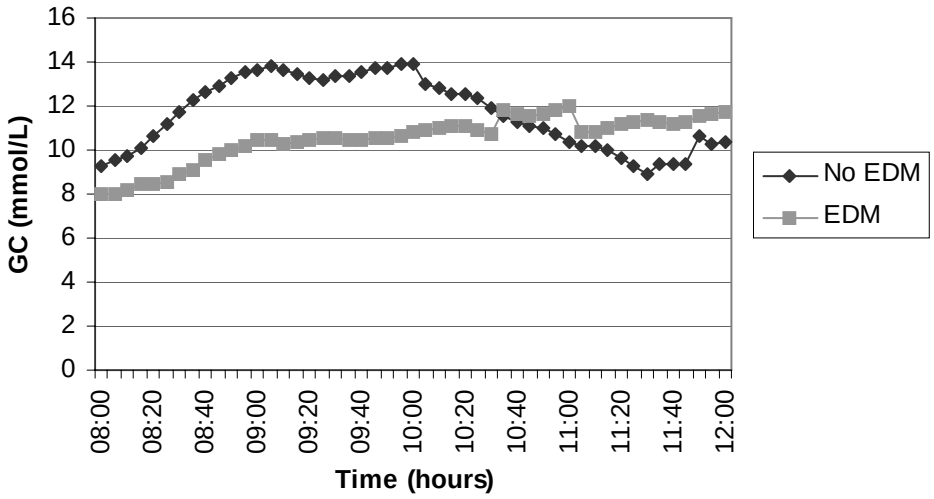
B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