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Original article

Motilin concentrations in relation to gastro intestinal dysmotility in diabetes mellitus

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ABSTRACT

Aim: Dysmotility in the upper gastro intestinal (GI) tract are common problems in diabetics. Many peptides are involved in the regulation of the motility. The aim of this study was to examine whether plasma levels of motilin were related to dysfunction in the oesophagus and stomach in a well-defined diabetic patient group.
Methods: Nineteen patients with symptoms from the GI tract who had been examined with oesophageal manometry, gastric emptying scintigraphy and deep-breathing test were included. They received a fat-rich meal, after which blood samples were collected and analysed for motilin concentrations.
Results: Symptoms of abdominal fullness and gastro oesophageal reflux significantly associated with delayed gastric emptying, whereas no symptom correlated to oesophageal dysmotility. Plasma levels of motilin were increased after the fat-rich meal ($p=0.000$), with no difference between the groups. Abnormal manometry was characterized by aperistalsis and/or simultaneous contractions. The percentage of simultaneous contractions correlated to basic and peak motilin values ($r_s=0.898$, $p=0.006$ and $r_s=0.842$, $p=0.017$, respectively). Gastric emptying did not influence motilin concentrations.
Conclusion: Plasma motilin concentrations vary with abnormalities of oesophageal motility in diabetics, but not with abnormalities of gastric emptying.

1. Introduction

The gastro intestinal (GI) hormone motilin has for several years been of interest as a regulatory hormone for the motility of the upper GI tract. As early as 1976 Mitznegg et al. [1] showed that stimuli such as fat and acid increased motilin levels in the blood of a group of healthy men. Motilin receptors have been described in the brain and in the entire human GI tract [2,3]. There are several studies that show how motilin induces phase III of inter digestive migrating motor complex (MMC) [4] and has a regulatory effect on the lower oesophageal sphincter (LOS) in man [5].

Motilin has become of interest concerning dysmotility in the upper GI tract and in gastro oesophageal reflux disease (GORD), a condition associated with low LOS pressure. In a study by Perdikis et al. [6] motilin levels significantly correlated with LOS pressure, and patients with poor LOS pressure had significantly lower fasting levels of motilin than patients with normal LOS pressure. Normal physiology of gut peptides can be restored by anti reflux surgery [7]. Motilin agonists, such as erythromycine, have a direct motilin-like effect on the LOS in patients with GORD [8,9] and have been used in the treatment of severe gastro paresis [10].

In diabetic patients with GI symptoms, 58% were found to have oesophageal dysmotility and 68% delayed gastric emptying [11]. The role of motilin in this patient group has not been evaluated. The aim of this study was thus to examine whether blood levels of motilin are related to symptoms and signs of dysfunction in the oesophagus and stomach in a well-defined diabetic patient group.

2. Subjects, material and methods

This study was performed according to the Helsinki declaration and approved by the Ethics Committee of Lund University. Informed written consent was obtained from all subjects.

2.1. Subjects

Consecutive patients at the Diabetes Clinic at Malmo University Hospital, who complained of symptoms from the digestive tract and were supposed to have GI dysmotility, were invited to oesophageal manometry, gastric emptying scintigraphy, deep-breathing test reflecting the autonomic nerve function and continuous glucose monitoring system (CGMS). All examinations were performed in close time relations. Patients with regular use of opiates and other drugs influencing GI motility or hormonal release, or a marked reduced renal

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Table 1
Patient characteristics for patients with normal and abnormal oesophageal manometry, respectively.

Parameter	Normal oesophageal function	Abnormal oesophageal function	*p*
	n = 6	*n* = 7	
Gastric T_{50} (min)	68.0 [32.2–293.8]	178 [42.0–271.0]	0.57
Sex (female/male)	4/2	4/3	1.00
Age (years)	57.0 [48.8–60.0]	49.0 [44.0–56.0]	0.12
Duration of diabetes (years)	47.0 [27.0–50.0]	32.0 [16.0–33.0]	0.28
HbA1c (%)	7.2 [6.0–7.9]	7.0 [6.0–7.6]	0.94
Baseline glucose (mmol/l)	9.0 [7.0–11.6]	6.8 [4.8–10.0]	0.53
Aperistaltic swallowing (%)	0.0 [0.0–0.0]	30.0 [20.0–50.0]	0.00
Mean amplitude contractions (mm Hg)	65.0 [61.5–78.8]	33.0 [19.0–59.0]	0.02
Mean peristaltic speed (cm/s)	5.6 [4.6–7.0]	3.7 [2.9–5.0]	0.04
Simultaneous contractions (%)	0.0 [0.0–0.0]	20.0 [10.0–30.0]	0.00
LOS pressure (mm Hg)	16.0 [0.0–21.0]	11.0 [10.0–15.0]	0.62

Mann Whitney *U* test and Fisher's exact test. $p<0.05$ was considered statistical significant.
The values are given as median [interquartile ranges, IQR].

function were excluded. Twenty patients (10 women) with stable metabolic control were accepted to participate [12].

Standardized oesophageal manometry was performed with an intra luminal solid-state transducer system (Gaeltec Ltd, Ise of Skye, Scotland). Polygraph A/D converter digitized the analogue signal. The software was PolyGram Upper-GI Edition by Gastro soft Inc./Synectics Medical (Medtronic-Synectics, Stockholm, Sweden). All pressure values were expressed in mm Hg and referred to atmospheric pressure. The manometry catheter was introduced through the nose and fluoroscopically positioned in the distal oesophagus with the patient sitting in an upright position, which is the standard method at our laboratory. With the catheter in place, all participants were instructed to swallow 10 ml of a barium contrast medium (60% w/v). At least 5 barium swallows were recorded. The video fluoroscopic image and the manometry registration were mixed using a Micro Eye Video Output Card (Dig Hurst Ltd, Oystone, UK). Patients who fulfilled one or more pathological values in the oesophageal manometry of the following five criteria were considered to suffer from oesophageal dysmotility: 1) Absence of peristaltic contraction in the oesophagus (aperistalsis), 2) Mean peristaltic contraction amplitude <30 or >200 mm Hg in the oesophagus, 3) Percentage of simultaneous, non-propulsive peristaltic waves in the oesophagus >10%, 4) Speed of the peristaltic wave <3 or >6 cm/s in the distal oesophagus, 5) Resting pressure in the LOS <10 or >30 mm Hg. Normal peristaltic activity was defined as propulsive contraction waves with peak amplitudes between 30 and 200 mmHg and a speed between 3 and 6 cm/s [13].

Gastric emptying scintigraphy was performed with the subjects in a semi-recumbent position as described earlier. A test meal was prepared by adding 30–50 Mbq of technetium-99-labelled tin colloid to an egg, which was whipped in a glass cup while being heated in a water bath until coagulated. The scintigraphy half time (T_{50}) was identified from the point at which this tendency line crossed the 50% value. Measurements of radionuclide were corrected for decay according to Collins et al. [14]. T_{50}>2 standard deviation (SD) of healthy controls (=70 min) was considered abnormal [15].

The expiratory/inspiratory (*E*/*I*) ratio was calculated from the mean value of the longest *R*–*R* interval during expiration and the shortest *R*–*R* interval during inspiration. This is an established test of vagal, parasympathetic nerve function [16]. All test results were expressed in age-related values and an age-related value below −1.64 SD was considered abnormal [17].

Using a continuous glucose monitoring system (CGMS) (Mini Med, Sylmar, CA, USA), subcutaneous glucose levels were continuously monitored for 72 h [18].

Out of the 20 patients primarily included for examinations mentioned above, 19 (9 women) were further included in the present study to examine motilin concentrations in relation to GI dysmotility. All patients were insulin-treated; 17 with type 1 and 2 with type 2 diabetes. The 19 patients were all investigated with gastric emptying scintigraphy and CGMS, 17 with a deep-breathing test and 13 with oesophageal manometry. The reason that not all the patients performed all the examinations, depended on that the patients had to perform several different examinations, and thought it was too much to go through everything. Seven out of 13 patients showed dysmotility of the oesophagus in the form of aperistalsis and/or simultaneous contractions (Table 1). Ten patients had delayed gastric emptying of 221.0 [116.0–362.5] min compared to 35.0 [23.5–44.5] min ($p<0.001$) in patients with normal emptying. Nine out of 17 showed abnormal expiration/inspiration (*E*/*I*) quote as a sign of autonomic neuropathy. There was no difference in sex, age, duration of diabetes, HbA1c or glucose levels between the groups (Table 1).

2.2. Experimental procedure for plasma collection

All included subjects were fasted overnight. In the morning they were given a fat-rich meal composed of 150 g cream and 150 g water without any seasoning. This generated 60 g fat and 561 kcal. This meal corresponds to the same content of fat as earlier used to evoke cholecystokinin (CCK) and oxytocin secretion [19]. Blood samples were taken through an intravenous catheter 10 min and immediately before the injection, as well as 10, 20, 30, 45, 60, 90, 120, 150 and 180 min after the injection. All blood samples consisted of 8.0 ml whole blood drawn into iced heparinised tubes. The plasma was separated and frozen at −20 °C immediate after the experiment.

Table 2
The distribution of different symptoms in patients with normal and delayed gastric emptying, respectively.

Symptom/sign	Normal gastric emptying	Delayed gastric emptying	*p*
	n = 9	*n* = 10	
Loss of appetite *n* (%)	3 (33)	7 (70)	0.18
Dysphagia *n* (%)	2 (22)	3 (30)	1.00
Meal related cough *n* (%)	2 (22)	0 (0)	0.21
Early satiety *n* (%)	6 (67)	7 (70)	1.00
Nausea *n* (%)	4 (44)	6 (60)	0.66
Vomiting *n* (%)	2 (22)	2 (20)	1.00
Weight loss *n* (%)	1 (11)	4 (40)	0.30
Abdominal fullness *n* (%)	5 (56)	10 (100)	0.03
Bloating *n* (%)	6 (67)	9 (90)	0.30
Regurgitations *n* (%)	4 (44)	4 (40)	1.00
Constipation *n* (%)	5 (56)	3 (30)	0.37
Diarrhoea *n* (%)	1 (11)	1 (10)	1.00
Gastroesophageal reflux *n* (%)	1 (11)	7 (70)	0.02

Fisher's exact test. $p<0.05$ was considered statistical significant.