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Evaluation of gastric and small bowel transit times in coeliac disease with the small bowel PillCam®: a single centre study in a non gluten-free diet adult italian population with coeliac disease

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Abstract. – **BACKGROUND:** The mechanisms underlying bowel disturbances in coeliac disease are still relatively unclear. Past reports suggested that small bowel motor abnormalities may be involved in this pathological condition; there are no studies addressing small bowel transit in coeliac disease before and after a gluten-free diet.

AIM: The objective of this study was to determine whether capsule endoscopy (CE) could serve as a test for measurement of gastric and small bowel transit times in a group of symptomatic or asymptomatic coeliac patients at the time of diagnosis with respect to a control group.

PATIENTS AND METHODS: Thirty coeliac untreated patients and 30 age-, sex- and BMI-matched healthy controls underwent CE assessment of whole gut transit times.

RESULTS: All subjects completed the study per protocol and experienced natural passage of the pill. No statistical significant differences between gastric emptying and small bowel transit times both in coeliac and control group were found ($p = 0.1842$ and $p = 0.7134$; C.I. 95%, respectively). No correlation was found in coeliac patients and control group between transit times and age, sex and BMI. By using the Pearson's correlation test, significant correlation emerged between gastric emptying time and small bowel transit times in coeliac disease ($r = 0.1706$).

CONCLUSIONS: CE reveals unrecognized gender differences and may be a novel outpatient technique for gut transit times' assessment without exposure to radiation and for the evaluation of upper gut dysfunction in healthy patients suffering from constipation without evidence of intestinal malabsorption. Nevertheless, CE does not seem to be the most suitable method for studying gut transit times in untreated coeliac patients; this might be ascribed to the fact that CE consists of inert (non-digestible, non-absorbable) substances.

Key Words:
Capsule endoscopy, Small bowel transit times, Coeliac disease.

Introduction

Coeliac disease (CD) is the most common severe food intolerance in the Western World[1]. The disease is characterized by a clinical syndrome of intestinal malabsorption of nutrients due to the damage of the lining of the small intestine consisting in total, subtotal or partial small bowel villous atrophy. Many reports suggest that 30 to 60% of untreated coeliac patients are affected by motility disorders of the oesophagus, stomach, small bowel and colon[2-6].

Studies of small bowel transit in CD are scarce; however, one study of orocaecal transit described a delayed orocaecal transit time in untreated patients with CD[6] which has been considered to be a non-specific compensatory response to fat malabsorption. Another work revealed the normalization of orocaecal transit in patients with CD after starting a gluten-free diet[4].

Wireless capsule motility shows promise as a useful diagnostic test to evaluate patients for GI transit disorders and to analyse the effect of prokinetic agents on GI transit. Aim of our investigation was to measure and evaluate gastric and small bowel transit times during capsule endoscopy (CE) in a group of symptomatic or asymptomatic coeliac patients at the time of diagnosis with respect to a control group and furthermore the effect of Body Mass Index (BMI) on transit times.

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Patients and Methods

This is a retrospective, case-control study including 30 consecutive patients with a clear diagnosis of CD but still following a normal unrestricted diet. Each coeliac patient was matched with a healthy non-coeliac outpatient control. Therefore, 30 sex-, age- and BMI-matched controls were selected from CE examinations performed at our Department. CE was performed making use of the Given PillCam® (Given Imaging Ltd, Yoqneam, Israel). All patients underwent a bowel cleansing consisting of two litres of a polyethylene glycol (PEG) electrolyte lavage solution the day before the procedure and had been fasting since midnight[7]. On the examination day, two hours after capsule ingestion patients were allowed to drink and four hours after capsule ingestion they were permitted to eat a light meal. At the end of the examination, eight hours later, data were downloaded to the workstation. Transit times were calculated by RAPID 4 Software®. Thirty patients [9 males and 21 females, median age 38.4 years; range 21-64 years] recently diagnosed with CD were enrolled.

The diagnosis of CD was based on positive serological test results relying on detection of anti-endomysial antibodies (EMA) and anti-tissutal transglutaminase antibodies (tTG). Endoscopic predictive signs of malabsorption at traditional upper endoscopy and CE (i.e. disappearance or an evident decrease of Kerkring's folds, atrophic or mosaic-like mucosa) were independently assessed by two experienced observers. Finally, histological findings from duodenal biopsy specimens were evaluated and the severity and extent of villous atrophy was graded according to the modified Marsh criteria[8].

None of the patients in both groups did suffer from conditions known to cause delayed gastric emptying or any other reason for prolonged capsule transit times nor presented with a clinical suspicion of gastrointestinal obstruction.

At CE examination the anatomic marks were used as described by Barkay et al[9]: entrance in the duodenum was defined as the passage of the capsule through the pylorus and entrance in the colon after the passage of the capsule through the ileocaecal valve. The prominent folds and high narrow villi characterize the jejunum. The presence of the capsule in the ileum was deduced by the appearance of fewer folds and shorter villi.

Control Group

Among the procedures performed at our Endoscopic Unit, we reviewed 30 patients with negative CE examinations carried out for obscure-occult gastrointestinal bleeding including chronic iron deficiency anaemia or for chronic abdominal pain after negative upper and lower gastrointestinal endoscopy. All the patients had undergone negative serological testing for CD. The patients were age-, sex- and BMI-matched with CD patients.

Gastric Emptying and Small Bowel Transit

Gastric emptying was defined as the time elapsed between the first gastric image and the first duodenal image; small bowel transit time was determined as the time from the first duodenal image to the first caecal image. Transit and emptying times were calculated by RAPID 4 Software〉 and all the examinations were independently assessed by 2 experienced observers[10]. The interobserver difference in interpretation was < 5% and was resolved by reexamination whether subsisting.

Body Mass Index

Body Mass Index (BMI) is a number combining a person's weight and height. BMI provides a fairly reliable indicator of body fatness for people. BMI does not measure body fat directly but correlates to direct measures of body fat, such as underwater weighing and dual energy x-ray absorptiometry (DXA)[11,12]. Therefore BMI can be considered an alternative for direct measures of body fat. The correlation between the BMI number and body fatness is fairly strong; however the correlation varies according to sex, race and age. For adults aged 20 and older, BMI is interpreted using standard weight status categories that are the same for all ages and for both men and women[13] (Table I). BMI was calculated for both CD patients and control group patients. Only a few published studies to date have addressed the issue of changes of BMI on small bowel transit depicting an inverse relation between BMI and transit times[14,15].

Statistical Analysis

Statistics were performed using the Epi Info™ (version 3.5) software package. Continuous variables, reported as mean plus-minus standard de-

Table I. Characteristics of the patients.

	Range (Min-Max)	Mean ± SD
Coeliac patients		
Age (years)	21-64	38.4 ± 21.9
BMI (kg/m^2)	17-27	20.9 ± 2.4
Gastric transit time	4-81	30.4 ± 21.9
Small bowel transit time	76-361	252.2 ± 67.4
Control group		
Age (years)	21-64	38.4 ± 21.9
BMI (kg/m^2)	17-27	20.9 ± 2.4
Gastric transit time	3-215	43.6 ± 48.8
Small bowel transit time	50-443	244.7 ± 88.4

viation (SD), were compared using the Student's *t*-test. Categorical variables were analyzed using Pearson's Correlation coefficient. Correlations were calculated to determine the degree of variance in a dependent variable explained by an independent variable. Statistical analysis was performed for sex group and BMI.

Results

In the coeliac patients the mean age was 38.4 years (range 21-64 years). Patients pertaining to the healthy control group were exactly age-matched. In both groups (30 coeliac disease patients and 30 healthy controls) the median BMI was 20.9 kg/m^2 (range 17-27 kg/m^2). A female predominance (21 females and 9 males) was observed.

Coeliac group: mean ± standard deviation of gastric emptying time (GTT) was 30.4 ± 21.9 minutes (range: 4-81 minutes), while small bowel transit time (SBTT) was 252.2 ± 67.4 minutes (range: 76-361 minutes).

Control group: mean ± standard deviation of gastric emptying time was 43.6 ± 48.8 minutes (range: 3-215 minutes), while small bowel transit time was 244.7 ± 88.4 minutes (range: 50-443 minutes). Descriptive statistics are shown in Table I.

No statistical significant differences between gastric emptying and small bowel transit times both in coeliac and control group were found (p = 0.1842 and p = 0.7134; C.I. 95%, respectively). However, using Pearson's correlation in coeliac patients a significant correlation was observed between gastric emptying time and small bowel transit times in CD patients (r = 0.1706). Furthermore, the time (from the pylorus) for the capsule to reach the ileocecal valve, was significantly higher in patients where CE quickly reached the duodenum than in those in which more minutes were taken to pass through the stomach.

No significant relationship was found in both groups between gastric and intestinal transit times and age, sex and BMI (Table II).

Table II. Correlation between BMI and SBTT.

	r	GTT	SBTT
Coeliac patients			
Age	Pearson's correlation	–0.116	–0.0534
BMI (kg/m^2)	Pearson's correlation	0.07404	0.04907
Gastric transit time	Pearson's correlation	1	0.1706
Small bowel transit time	Pearson's correlation	0.1706	1
Control group			
Age	Pearson's correlation	–0.2445	0.0441
BMI (kg/m^2)	Pearson's correlation	–0.0301	0.0538
Gastric transit time	Pearson's correlation	1	–0.4755
Small bowel transit time	Pearson's correlation	–0.4755	1

Discussion

The assessment of transit times with CE has been of interest to capsule users since the approval of the technology. Gastric and small bowel transit times are of crucial relevance in case of small bowel investigation with wireless capsules. Even though many aspects about motility disorders in CD still need clarification, so far data available from the literature suggest an altered gastrointestinal motility, especially of the esophagus[2], stomach[3], small bowel[4], colon[5] and gallbladder[16] in untreated CD patients. Some Authors[17] postulated that in untreated coeliac patients delayed gastric emptying and slow orocaecal transit may be explained by an abnormal exposure of small bowel to unabsorbed starch and fats which is proportional to the extent of the small bowel affected by reduced absorptive capacity and surface. Unabsorbed starch has been shown to delay gastric emptying, to reduce gastric tone and to prolong orocaecal transit time[18].

Small bowel transit is rather influenced by contractile activity of the gut and intestinal secretion[19,20]. In CD intestinal contractile dysfunction may be so severe as to mimic pseudo-obstruction[21]. Probably this might be due to the fact that the damage of the lining of the small intestine in untreated coeliac disease may alter the gut-hormone profile and its secretory activity and subsequently affect the contractile upper gut activity because of neuroimmunomodulation and hormonal deregulation[22,23]. In particular, in subjects with untreated or undetected CD postprandial cholecystokinin (CCK) levels are low resulting in consequent gallbladder inertia and impairment of small bowel transit[24]. Peptide YY (PYY) and neurotensin lead to a similar effect on gastrointestinal motility. PYY level in untreated CD is higher[25]; this hormone inhibits gastric emptying and gastrointestinal motility[26] and in malabsorption syndromes is likely involved in a compensatory mechanism reaction when the passage of nutrients is accelerated[27]. Neurotensin has analogue effects of PYY and its levels are high in malabsorption syndromes[28]. All alterations of hormonal secretion disappear after starting a gluten-free diet.

Gut motility disorders have been reported in animals sensitized to specific antigens[29] and adverse reactions to food in human beings might be linked to a significantly prolonged mouth-to-caecum transit time and intestinal dysmotilities[30].

A large body of literature shows the role of BMI and other variables on gastric emptying and small bowel transit time. Madsen[31] assessed separately the effects of gender, age, and BMI on gastric emptying, small intestinal transit, and colonic transit times of a meal containing ^{99m}Tc-labeled cellulose fiber and 2- to 3-mm ^{111}In-labeled plastic particles. His study revealed an inverse association between BMI and mean gastric emptying time of radiolabeled cellulose fiber but BMI had no influence on other transit variables. On the contrary, other investigations found an accelerated small bowel transit time in healthy overweight women[32] and in overweight men and women with idiopathic bile acid malabsorption[33], whereas a delayed transit time was observed in patients with portal hypertension and chronic liver disease[34] and in primary anorexia[35].

Transit times seem to be accelerated in overweight patients and delayed, probably as a result of adaptative mechanisms, in people affected by malnutrition and/or malabsorption syndromes.

Chiarioni et al[36] studied the mouth-to-caecum transit time of a caloric liquid meal in a homogeneous group of coeliac patients presenting with clinical and biochemical evidence of malabsorption and complaining of diarrhoea. At the time of diagnosis, mouth-to-caecum transit time was significantly prolonged in untreated coeliac disease patients compared to healthy controls. Intestinal transit was brought back to normal value after an adequate gluten-free period. Similarly, Rana et al[37] showed that orocaecal transit time in coeliac patients was significantly delayed being 180±10.6 minutes (Mean ± SD) as compared to 105±12.4 minutes in healthy controls.

Sadik et al[38] studied gut transit and BMI in patients with coeliac disease before and after treatment. They showed that in untreated male patients BMI was significantly reduced compared to healthy males and small bowel transit times was significantly longer compared with healthy males. In women, BMI did not significantly differ between untreated patients and healthy subjects and 31% of the female patients were overweight. Small bowel transit was significantly faster in overweight untreated female patients compared with lean female patients.

Velayos Jimenez et al[39] analyzed in 89 patients gastric and intestinal transit times through the images obtained with CE and evaluated the influence of age, sex, BMI and abdominal perimeter on these times. Gastric transit times ranged from 0.7 to 171 minutes while small intestine transit times ranged from 91 to 416 minutes. No significant associations were found between gastric and intestinal transit times with age, sex, BMI, abdominal perimeter or nutritional status. The investigated parameters did not seem to influence intestinal kinetics. Up to the time of capsule endoscopy gastrointestinal transit times were indirectly measured by hydrogen breath tests[40,41] or evaluated from contrast radiographic techniques[42,43]. Recently, two studies[44,45] assessed the gastrointestinal transit time by means of a new method approved for evaluation of gastric emptying that is wireless capsule motility using the SmartPill® (SP) GI monitoring system (SmartPill Corporation, Buffalo, NY, USA). The SP system consists of an ingestible capsule, a receiver, a receiver docking station, and display software. The SP houses sensors for pH, temperature, and pressure and has the ability to transmit the sensed data at 434 MHz to a receiver worn by the subject. SP shape and dimensions (cylindrical, 26.8 mm long by 13 mm in diameter) are nearly identical to those of the capsule used for capsule endoscopy from Given Imaging Ltd. (Duluth, GA, USA). Both the above mentioned studies demonstrated that SmartPill® capsule measurement of gastric emptying and whole gut transit compares favorably with that of scintigraphy.

The results of our study showed that at the time of diagnosis, mouth-to-caecum CE transit time is not significantly prolonged in untreated coeliac disease patients compared to healthy controls; no significant associations were found between gastric and intestinal transit times with age and sex, BMI, or nutritional status and these variables do not seem to influence intestinal kinetics. However, according to Fireman et al[46] gastric emptying may indirectly influence capsule transit time.

Conclusions

It is quite frequent to run into coeliac patients who show gastrointestinal motor abnormalities in clinical practice. These findings are related to the complex interactions among reduced absorption of food constituent (in particular fat), neurologic alteration and hormonal derangement. Our data suggest that CE does not seem to be the most suitable method for studying gut transit time in untreated coeliac patients and this might reasonably be ascribed to the fact that CE consists of non-absorbable inert substances.

These results still need further validation on a larger sample size. CE reveals hitherto unrecognized gender differences and may be a novel outpatient device for assessment of regional (gastric, small bowel, colonic) and whole gut transit times without exposure to radiation and for investigation of upper gut dysfunction healthy subjects suffering from without evidence of intestinal malabsorption.

Conflict of Interest

None declared.

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