Regional gastrointestinal transit times in patients with chronic pancreatitis

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Abstract
The mechanisms behind disrupted gastrointestinal (GI) motor function in patients with chronic pancreatitis (CP) have not been fully elucidated. We compared regional transit times in patients with CP to those in healthy controls, and investigated whether they were associated with diabetes mellitus, exocrine dysfunction, opioid treatment or quality of life. Twenty-eight patients with CP and 28 age- and gender-matched healthy controls were included. Regional GI transit times were determined using the 3D-Transit system, which consists of an ingestible electromagnetic capsule and a detector worn in an abdominal belt for 5 days. Exocrine function was assessed using the fecal elastase-1 test, and quality of life was assessed using the European Organization for Research and Treatment of Cancer questionnaire. Transit times were analyzed for associations with diabetes mellitus, exocrine pancreatic insufficiency (EPI), opioid treatment and quality of life. Compared with healthy controls, patients with CP had prolonged transit times in the small intestine (6.5 ± 1.8 vs 4.8 ± 2.2 hours, \( P = .006 \)), colon (40 ± 23 vs 28 ± 26 hours, \( P = .02 \), and total GI tract (52 ± 26 vs 36 ± 26 hours, \( P = .02 \)). There was no difference in gastric emptying time (4.8 ± 5.2 vs 3.1 ± 1.3 hours, \( P = .9 \)). No associations between transit times and diabetes, EPI, or opioid consumption were found (all \( P > .05 \)). Quality of life and associated functional and symptom subscales were not associated with transit times, except for diarrhea (\( P = .03 \)). Patients with CP have prolonged small intestinal and colonic transit times. However, these alterations do not seem to be mediated by diabetes, EPI, or opioid consumption.

Abbreviations: CP = chronic pancreatitis, EORTC QLQ-C30 = the European organization for research and treatment of cancer quality of life questionnaire, EPI = exocrine pancreatic insufficiency, GI = gastrointestinal, QOL = quality of life.

Keywords: chronic pancreatitis, diabetes mellitus, exocrine pancreatic insufficiency, gastrointestinal transit time, opioids

1. Introduction
Chronic pancreatitis (CP) is an irreversible chronic inflammatory disorder of the pancreas, characterized by fibrotic replacement of the normal pancreatic tissue.\(^{[1]}\) As the disease progresses, endocrine and exocrine pancreatic dysfunction may evolve, leading to development of diabetes and maldigestion. This may manifest as various gastrointestinal (GI) symptoms such as steatorrhea, weight loss, flatulence, and abdominal discomfort. In addition, disturbed pancreatic function may also impact on GI motor function leading to altered gastric and intestinal motility.

GI motor function in the context of CP has been investigated in several pre-clinical studies, in which alterations in the neuronal excitatory capacity of the enteric nervous system have been proposed to play an essential role.\(^{[2]}\) However, the exact underlying cause of disrupted GI motor activity in human CP has rarely been addressed, and several co-factors are also important. Besides endocrine and exocrine pancreatic insufficiency (EPI), autonomic neuropathy associated with diabetes mellitus and/or excessive alcohol consumption, as well as changes in levels of GI hormones, may be potential mechanisms behind CP-related GI dysmotility.\(^{[3]}\) Furthermore, moderate to strong opioids are often necessary to obtain adequate pain relief; these analgesics are known to induce GI dysmotility and prolong transit time.\(^{[4]}\)

Few clinical studies have addressed GI dysfunction and abnormal transit in patients with CP, and data are conflicting and originate from relatively old studies. Originally, Nordgaard et al measured the interval between ingestion of a test meal and the initial increase in the H\(_2\) concentration above 10ppm, and showed delayed mouth-to-cumis transit time in CP patients, while both delayed and accelerated gastric emptying was found.
in patients with alcohol-related CP.[4,5] In contrast, small intestinal- and/or colonic transit has also been shown to be accelerated in CP patients, especially in those with EPI.[6-9] Furthermore, the duration of inter digestive motor cycles using small bowel manometry has been found to be both reduced,[10] or unaffected,[11,12] Finally, the high prevalence of small intestinal bacterial overgrowth points towards prolonged transit.[12]

Methods employed for these studies were scintigraphy, breath tests, and manometry, all of which are well-established and commonly used tools to assess GI motility; however, the possibility of differentiating the various regions of the GI tract is limited. Characterization of regional GI transit times is possible with the 3D-Transit system, which is a minimally invasive and well-validated method for assessment of GI transit time and motility patterns throughout the GI tract, allowing ambulatory study under near normal physiological conditions.[13]

In this study, we hypothesized that patients with CP have prolonged total and regional GI transit times compared to healthy controls, and that this prolongation would be associated with the presence of diabetes mellitus, and/or EPI as well as opioid treatment. Specifically, the aims were to investigate; total and regional GI transit times in patients with CP using the 3D-Transit system (primary endpoint); how alterations in GI transit are influenced by a number of co-factors (CP diagnosis, EPI, opioid use and diabetes); and how GI transit times are associated with patient reported quality of life.

2. Methods
This was a cross-sectional study approved by The North Denmark Region Committee on Health Research Ethics (N-20130030) and the Danish Health and Medicines Authority. It was conducted in compliance with the International conference on Harmonization-Good Clinical Practice principles of the European Union. Experiments were carried out at the research laboratories at Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark from October 2014 to October 2016. The study was part of a larger protocol that evaluated the impact of exogenously administered opioids on GI transit time - the entire protocol is registered at “http://www.clinicaltrialregister.eu” (EudraCT no. 2013-001540-60).

2.1. Study populations
Thirty patients with CP were recruited from the outpatient clinic at Aalborg University Hospital. Inclusion criteria were; men and women above the age of 18, a CP diagnosis based on the Lugner criteria with a score ≥4, ability to read and understand Danish, and if relevant, a stable analgesic treatment regimen for at least 2 weeks prior to study start. Exclusion criteria were, any condition or disease that the investigator found would affect the results, such as neurological disease, cancer, use of nonsteroidal anti-inflammatory drugs and tricyclic antidepressant, expected need of surgical treatment, or change in use of nonsteroidal anti-inflammatory drugs and tricyclic antidepressant, expected need of surgical treatment, or change in use of nonsteroidal anti-inflammatory drugs and tricyclic antidepressant.

Exocrine pancreatic function was characterized by the fecal elastase-1 test, and EPI was defined by a fecal elastase-1 level below 100 µg/g.[13] Information on patient demographics, etiology and duration of CP, diabetes, other concomitant diseases, CP related complications, and use of analgesics were obtained from clinical interviews in the outpatient clinic and reviews of clinical records. Consumption of opioids was converted into daily morphine equivalents (mg). The control group comprised of age- and gender-matched healthy controls, all meeting the following inclusion criteria: no current symptoms or history of GI disease, and signed written informed consent.

2.2. Study design and experimental procedures
2.2.1. Patients. Patients took part in a single 5-day study period. In the morning of day 1, patients arrived at the research unit after an overnight fast. The 3D-Transit system belt was mounted on the abdomen, then the 3D-Transit electromagnetic capsule was swallowed with a glass of water (200 mL) and a standardized meal, consisting of 3 granola bars (“Alpen Bars”) each containing 3.8 g of fat, 21 g of carbohydrate, and 1.9 g of protein, 125 kcal) hereafter, the patients were allowed to leave. They were instructed to fast for an additional 6 hours, after which there were no restrictions on food or liquid intake. While wearing the detector plate throughout the next 4 days, they were asked to refrain from hard physical work or exercise but were otherwise allowed to undertake normal daily activities. The study period ended on day 5, when they returned to the research unit to hand in the 3D-Transit system equipment.

A detailed description of 3D-Transit system data analysis is described elsewhere.[13,14] In short, regional transit times (gastric emptying, small intestinal transit, and colonic transit) were manually determined using dedicated analysis software (MTS2 version 0.4, Motilis Medica SA, Lausanne, Switzerland), by evaluating changes in bowel contraction frequencies as seen on rotation graphs, assessing time-frequency contraction maps, and visualizing the anatomical position of the capsule via 2D images. Whole gut transit time was defined as the time between ingestion and expulsion of the capsule. If the capsule was not expelled by day 5, the time of the last confirmed capsule signal was used as expulsion time.

All patients were asked to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) which has been validated in patients with CP.[17] The questionnaire is used to document patient-reported life quality as well as daily functioning and the presence of several specific symptoms; it is composed of single-item measures and multi-item scales with scores that range from 0 to 100 after linear transformation of the raw score. A high score for a functional scale represents a high level of functioning, as does a high score for the global health status, but a high score for the symptom items represents a high level of symptomatology.

2.3. Healthy volunteers
Transit times from the control group were selected via a large internal database of 3D-Transit recordings obtained at 3 research facilities; Mech-Sense, Aalborg University Hospital, Denmark; Aarhus University Hospital, Denmark; and the Royal London Hospital, Great Britain. Patient data were compared to age and sex-matched healthy volunteers.

2.4. Statistical analysis
All data are presented as means ± 5D unless otherwise indicated. Data were assessed for normality by graphical and numerical methods (histograms and Shapiro-Wilks tests) and handled accordingly. Differences in demographics as well as total and regional GI transit times between patients and controls were investigated using Wilcoxon signed rank sum tests as these data were not normally distributed. Univariate and multivariate nonparametric regression analyses were used to compare transit times between patients with CP and controls, and to analyze the relationship between total and regional transit times and the 4 binary co-variables: CP diagnosis, EPI, opioid use, and diabetes. Univariate nonparametric regression analysis was likewise used to analyze the relationship between total transit time and opioid dose (mg). Differences in EORTC QLQ-C30 data between CP patients stratified by the median whole gut transit time (slower/faster) were analyzed using Wilcoxon
Table 1. Patients had a mean age of 61 ± 7.6 years compared to Larsen et al. • Medicine (2022) 101:41 www.md-journal.com

<table>
<thead>
<tr>
<th>Demographic characteristics of patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean yrs (range)</strong></td>
</tr>
<tr>
<td>61 (47-72)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Women, n (%)</td>
</tr>
<tr>
<td>9 (32)</td>
</tr>
<tr>
<td>Men, n (%)</td>
</tr>
<tr>
<td>19 (68)</td>
</tr>
<tr>
<td><strong>BMI, mean (range)</strong></td>
</tr>
<tr>
<td>23.6 (17.4-31.0)</td>
</tr>
<tr>
<td><strong>Duration of CP, mean yrs (range)</strong></td>
</tr>
<tr>
<td>9 (3-26)</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>Alcoholic, n (%)</td>
</tr>
<tr>
<td>13 (46)</td>
</tr>
<tr>
<td>Idiopathic, n (%)</td>
</tr>
<tr>
<td>12 (43)</td>
</tr>
<tr>
<td>Other, n (%)</td>
</tr>
<tr>
<td>3 (11)</td>
</tr>
<tr>
<td><strong>Pancreatic exocrine insufficiency, n (%)</strong></td>
</tr>
<tr>
<td>17 (61)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, n (%)</strong></td>
</tr>
<tr>
<td>16 (57)</td>
</tr>
<tr>
<td><strong>Analgesics</strong></td>
</tr>
<tr>
<td>Current opioid user, n (%)</td>
</tr>
<tr>
<td>12 (43)</td>
</tr>
<tr>
<td>Daily morphine equivalents, mg (range)*</td>
</tr>
<tr>
<td>41 (1-101)</td>
</tr>
</tbody>
</table>

*Among opioid users.
CP = chronic pancreatitis.

3. Results

Data from a total of 28 patients with CP out of 30, were compared to data from 28 controls. Two recordings from patients with CP were excluded from analysis due to faulty capsule, and premature removal of the MTS-2 belt. Complete dataset was available for the remaining 28 subjects from each group. Clinical and demographic characteristics of patients are presented in Table 1. Patients had an average age of 61 ± 7.6 years compared to 60 ± 9.4 years in the healthy control group (P = .73). The gender distribution was identical for the 2 study populations (9 women and 19 men in each group).

3.1. GI transit time

All participants underwent the 3D-Transit examination without any notable discomforts or adverse events. Capsule retention was observed in 4/28 (14%) of patients on day 5 (the capsules were subsequently expelled over the next 1 or 2 days). Compared to healthy controls, patients had significantly prolonged transit in the whole gut (P = .02), and in the small intestinal- (P = .006) and colonic regions (P = .02), whereas no significant difference was found in gastric emptying time (P = .9) (Fig. 1A). A descriptive summary of the transit time data can be seen in Table 2. Compared with data from healthy subjects with fast versus normal versus slow transit time, distributions of transit times in individual CP patients showed a similar pattern with prolonged transit times in the whole gut (P = .023), the colonic regions (P = .661), and the small intestine (P = .023) although difference were not significant. The same applies for gastric emptying time (P = .051) (Table 3).

Opioid consumption was not associated with total transit time (n = 12, coef. = -0.35, P = .11) on univariate analysis. Binary co-variables opioid treatment (coef. = 4.15, P = .68), diabetes (coef. = -3.18, P = .75), or EPI (coef. = 3.84, P = .70) were also not associated with transit times on univariate analysis (Fig. 1B–D). The lack of association was confirmed in multivariate analysis (Table 4). However, a CP diagnosis remained significantly and independently associated with small intestinal transit time and whole gut transit time when controlling for the aforementioned variables.

3.2. Transit times and life quality

The quality of life analysis was stratified by transit times (faster/slower). The symptom subscales/items showed significant difference for diarrhea where patients with faster total transit times (<45 hours, n = 14) reported more diarrhea compared to their slower transit counterparts (P = .03). Otherwise, no significant differences were seen between the faster and slower transit subgroups for the symptom scales nor in any of the functional scales of the EORTC-C30. The same applies for the global health score, although a trend was seen comparing the faster and slower transit subgroups (P = .51). The QOL functional scales, symptom scales/items and global health scores, are reported in Table 5.

4. Discussion

Using the most advanced equipment for assessment of segmental GI transit time, we demonstrated that patients with CP had prolonged small intestinal- and colonic transit times. Prolonged transit time indicates motility alterations/dysfunction; however, we could not link this to the use of opioid medication, presence of diabetes, or EPI.

4.1. Transit time in CP

We found no significant association of prolonged transit to exocrine insufficiency. However, alterations in digestion and absorption of fats still likely played a role as nutrient exposure of the small intestinal lumen is a major regulatory factor in controlling GI motor function. When nutrients reach the distal ileum, an endogenous feedback mechanism inhibits jejunal pressure wave activity and thereby slows small intestinal transit - a phenomenon known as the ileal brake. This is a physiological regulatory mechanism, however a plausible explanation as to why patients with CP demonstrate prolonged small intestinal transit, as these presumably have an increased load of nutrients in the lower bowel due to malabsorption compared with healthy controls. With regards to colonic transit, the authors are not familiar with previous human studies looking specifically at CP-related motility changes in this region. However, alterations in the neurotransmitter balance of the enteric nervous system have been proposed as an explanation for colonic motor dysfunction in rodents with CP. Also, an aberrant enteric nervous system has been recognized in GI dysmotility associated with acute pancreatitis and neurogenic alterations may influence the prolonged colonic transit time observed in our study. Another plausible explanation for CP-related motility changes in all regions of the GI tract is hormonal changes due to altered endocrine pancreatic function. Thus, it is well known that pancreatic enteroendocrine cells react to luminal content by releasing a variety of GI hormones (e.g., cholecystokinin, gastric inhibitory polypeptide, GLP-1, and GLP-2) that, in part, control GI motility, and CP-related alterations in these hormone levels may contribute to delayed GI transit time.

GI transit time in CP has previously been addressed in only a few studies, with conflicting results. For gastric emptying, all previous studies have reported more rapid transit,[4,6,9] whereas we found no significant changes when compared to healthy controls. This discrepancy is likely a combination of...
several factors. First, varying techniques have been employed, as previous studies used intestinal intubation and scintigraphy, and our study employed the 3D-Transit system. Secondly, differences regarding the number of patients with diabetes and autonomic neuropathy might explain the discrepancy, as diabetic-induced autonomic neuropathy may cause both accelerated and delayed gastric emptying. Accelerated small intestinal transit time was found in a single study, while another, in agreement with our findings, found delayed transit for this region.

Opioids are a mainstay in alleviating pain in CP. These analgesics are often associated with GI dysmotility leading to a slowing of GI transit. In this study, 43% of the patients had varying degrees of opioid consumption, which may have impacted their GI transit time. However, although there was a trend towards longer regional transit times in opioid users, our study implies that opioid medications are not a major contributor to prolonged GI transit in CP patients. A limitation here is the large variation in opioid consumption between patients which may have contributed to the power of the study being too

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Colon</th>
<th>Total GI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Transit time (hours)</td>
<td>P</td>
<td>Transit time (hours)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>28</td>
<td>3.1 ± 1.3</td>
<td>.09</td>
<td>4.8 ± 28.1</td>
</tr>
<tr>
<td>CP patients</td>
<td>28</td>
<td>4.7 ± 5.2</td>
<td>.17</td>
<td>6.5 ± 1.8</td>
</tr>
<tr>
<td>Opioids</td>
<td>12</td>
<td>5.7 ± 5.4</td>
<td>.17</td>
<td>6.5 ± 1.8</td>
</tr>
<tr>
<td>No opioids</td>
<td>16</td>
<td>4.2 ± 5.2</td>
<td>.7</td>
<td>6.4 ± 1.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16</td>
<td>4.7 ± 5.4</td>
<td>.7</td>
<td>6.7 ± 1.8</td>
</tr>
<tr>
<td>No diabetes</td>
<td>12</td>
<td>5.0 ± 5.1</td>
<td>.6</td>
<td>6.8 ± 1.5</td>
</tr>
<tr>
<td>EPI</td>
<td>17</td>
<td>4.7 ± 5.4</td>
<td>.6</td>
<td>6.5 ± 1.5</td>
</tr>
<tr>
<td>No EPI</td>
<td>11</td>
<td>5.0 ± 5.1</td>
<td>.6</td>
<td>6.3 ± 2.2</td>
</tr>
</tbody>
</table>

The P values for the differences between patients with CP and healthy controls; and a sub analysis of patients with CP who: use opioids and no opioids; have diabetes and no diabetes; have EPI and no EPI. Significant findings are marked in bold.

CP = chronic pancreatitis, EPI = exocrine pancreatic insufficiency, GI = gastrointestinal.
low to accurately assess the correlation between transit time and opioid consumption.

Patients with CP have significantly lower QOL independently associated with factors such as constant pain, opioid based pain treatment and alcohol etiology. However, these factors only partly explain the reduced QOL in CP and additional mediators are most likely operative. In the present study no significant differences in QOL, except for diarrhea, were seen between patients with fast and slow transit times, indicating that transit time alone is not an important factor for QOL in CP patients.

Several additional factors that were not investigated in this study, could have influenced GI transit delays. Patients with CP have altered gut microbiota where the diversity of the microbiome is found to be decreased. Abdominal pain is the leading complication in CP patient population and is often worsened by food intake. This can over time lead to malnutrition, and CP patients frequently experience malabsorption and maldigestion. Due to pain and general low QOL, CP patients are less physical active. Reduced physical activity is a common feature that impacts GI motility and other GI associated symptoms.

4.2. Limitations

This study has several limitations. First, it needs to be taken into consideration that power (due to the sample size of 28 CP patients) may be too low to detect significant associations.
When dividing the transit times into previous defined categories of normal/fast/slow, we found that 5 CP patients and none of the healthy controls had slow stomach transit. It cannot be excluded that an increased sample size could have shown larger differences between groups. Second, each participant was only investigated with a single electromagnetic capsule. Though, single capsule magnetic tracking shows valid data on regional GI transit times,[13] it is well-known that transit studies have high intra-subject variation. By including more capsules, for example, ingested at different time-points data variance may have been reduced.[13] Another approach could be to use a method like radiopaque markers. However, this method does not determine gastric emptying, small intestinal and colonic transit times, but provides only whole gut transit time.[16] The wireless Motility capsule could have been used as an alternative method and would most likely have given the same parameters.[17] Third, transit times from the control group were selected via a large internal database, and not all were tested at the same time and location as the patients, although the same protocol was used.[16]

5. Conclusion
In conclusion, we found that GI transit time was prolonged, especially in the small intestine and colon, in patients with CP compared to healthy controls. These alterations in GI motility could not conclusively be linked to opioid treatment, diabetes, or EPI. Further studies are needed to provide detailed knowledge about GI motility in the context of CP.

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Investigation: Asbjørn Mohr Drewes.
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Writing – review & editing: Sidsel Holten-Rossing, Esben Bolvig Mark, Jakob Lykke Poulsen, Klaus Krogh, S. Mark Scott, Sören Schou Olesen, Asbjørn Mohr Drewes.

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