Secretin-enhanced Magnetic Resonance Cholangiopancreatography in Pancreatic Insufficient and Pancreatic Sufficient Cystic Fibrosis Patients

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INTRODUCTION

Cystic fibrosis (CF) is a recessive genetic disease in which disruption of ion transport across cellular membranes [1] leads to an increase in viscosity of the mucus secreted by various glands throughout the body. The detrimental impact of this phenomenon on individual organs was first described in the pancreas [2]. Exocrine pancreatic insufficiency has wide-ranging consequences for the long-term survival and disability in CF patients. This is due to the impaired fat digestion and absorption which lead to the poor nutritional status that readily translates to increased susceptibility of the respiratory system to CF-related insults [3, 4]. Reduced bicarbonate secretion to the lumen of the pancreatic ductal system is at the focus of our current understanding of pathophysiology of pancreatic involvement in CF [5]. It leads to protein precipitation, which blocks the flow of the pancreatic juice and thus triggers self-digestion.

The application of available biochemical tests to distinguish between pancreatic insufficient (PI) and pancreatic sufficient (PS) patients remains a current clinical challenge in CF care [5]. It was shown that between 10% and 28% of CF patients are PS [6–9] and this phenotypic property is not readily predicted by the genotype [10]. Only PS CF patients may be affected by pancreatitis, which may lead to insufficiency in the long term [8]. New approaches are needed to identify such patients at an early stage.

ABSTRACT

Background & Aims: Although indirect methods of assessment of the exocrine pancreatic function have become the standard of care in the monitoring of pancreatic status, it still remains a current clinical challenge. Our aim was to compare the width of the pancreatic duct in pancreatic insufficient (PI) and pancreatic sufficient (PS) cystic fibrosis (CF) patients using secretin-enhanced magnetic resonance cholangiopancreatography (SE-MRCP).

Methods: Thirty-seven CF patients were enrolled for this cross-sectional study, including 21 PI and 16 PS, all of whom underwent SE-MRCP. Measurement of the diameter of the pancreatic duct was performed in the head, body, and the tail of the pancreas at the baseline and after 1, 2, 3, 5, and 10 minutes after secretin administration.

Results: The diameter of the pancreatic duct in the head of the pancreas after 5 and 10 minutes of secretin injection was greater in PI than in PS patients (median = 2.0 mm [interquartile range: 1.6-3.0] vs. 2.0 mm [1.0-2.0] and 2.0 mm [1.4-2.0] vs 1.0 mm [1.0-2.0], p=0.047 and p=0.040, respectively). Areas under ROC curves for discriminating between PI and PS patients were 0.693 (95% CI 0.521-0.866) and 0.698 (95% CI 0.528-0.868), respectively. No other differences in the width of the duct were identified at the baseline or during SE-MRCP.

Conclusions: The measurement of the diameter of the pancreatic duct during secretin stimulation does not allow for differentiating between PS and PI status in CF patients.

Key words: pancreatitis – fecal elastase – Wirsung duct – CFTR.

Abbreviations: CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; ELISA: enzyme-linked immunosorbent assay; ERCP: endoscopic retrograde cholangiopancreatography; E1: elastase-1; MRI: magnetic resonance imaging; PI: pancreatic insufficient; PS: pancreatic sufficient; SCT gene: secretin gene; SE-MRCP: secretin-enhanced magnetic resonance cholangiopancreatography; T: tesla; TR: repetition time; TE: echo time.
Secretin is a gastrointestinal hormone that is produced by a subclass of duodenal cells in response to acidic pH, which stimulates bicarbonate secretion by the pancreas [11]. It was shown in an animal model that secretin stimulation fails to increase the volume of the pancreatic fluid and to render it more alkaline when CFTR function is not preserved [12]. Secretin-enhanced magnetic resonance cholangiopancreatography (SE-MRCP) is a functional imaging method first described in 1990 [13], which allows for improved visualization of the pancreatic duct.

This study aimed to compare the diameter of the pancreatic duct during SE-MRCP in PI and PS CF patients in order to understand whether this particular measurement could be useful in discriminating between the two groups of patients in a clinical setting (1) and to further our knowledge of pathophysiology of the pancreas in CF (2).

**METHOD**

Thirty-seven CF patients were enrolled in the study, including 21 PI and 16 who were PS (Table I). The median age [interquartile range] was 18.7 years [17.7-24.7] in the PI CF group and 24.0 years [22.1-29.4] in the PS CF group (p = 0.006; Mann-Whitney U-test). Cystic fibrosis was diagnosed based on Cystic Fibrosis Foundation Guidelines [14], i.e. clinical manifestations, abnormal sweat chloride concentration, and also supplemented by identification of CFTR gene mutations. The PI CF patients were recruited on the basis of steatorrhea in past medical history, increased stool fat content as measured with the Van de Kamer method [15], and decreased elastase 1 (E1) fecal concentration (<100 µg/g) as determined with an ELISA assay (ScheBo Biotech AG, Giessen, Germany) [16, 17]. The inclusion criteria for the PS CF group were: normal fecal fat excretion [18] and E1 concentration (>200 µg/g). All the patients taking part in the study provided informed, written consent. The study adhered to the tenets of the revised Declaration of Helsinki and was approved by the Bioethical Committee of the Poznan University of Medical Sciences, Poznan, Poland (211/04).

Magnetic resonance imaging (MRI) was carried out employing a 1.5 T Optima system by General Electrics (Little Chalfont, United Kingdom). It provided high-performance gradients and utilized a phased-array coil for excitation and reception. Peristaltic artifacts were minimized with gradients and utilized a phased-array coil for excitation and reception. Peristaltic artifacts were minimized with secretin stimulation fails to increase the volume of the pancreatic fluid and to render it more alkaline when CFTR function is not preserved [12].

Dynamic MR pancreatography employed a T2-weighted fast spin-echo, breath-hold, single-shot, thick-slab sequence with the effective TE of 1052 ms, section thickness of 2.0 mm, field of view of 35-45 cm, and the matrix size of 256x256 px in the coronal oblique plane, taking 1-2 s to acquire every image. Secretin (Secretrelux, Sanochemia Diagnostics Deutschland GmbH, Neuss, Germany) was injected intravenously (1 cU/kg of body weight) over 2 minutes before single-slice imaging was repeated after 1, 2, 3, 5, and 10 min.

A radiologist with experience in pancreatic imaging in CF (K.K.K.) who was blinded to information describing the patients assessed the images. This was done in one session for the native images, another for SE-MRCP, and in the random order. The widest diameter of the pancreatic duct was searched for on T2 axial scans.

**RESULTS**

Pancreatic insufficient CF patients presented with the following genotypes: F508del/F508del (n=12), F508del/unknown (n=4), F508del/2143delT (n=1), dele2,3/dele2,3 (n=1), N1303K/G551D (n=1), N1303K/IVS21(+3insT) (n=1), G542X/R553X (n=1). Pancreatic sufficient CF patients had the following genotypes: F508del/3849+10-kbC>T (n=11), 2143delT/3849+10kbC:T (n=1), F508del/R334W (n=1), F508del/674T-G (n=1), C225W/unknown (n=1), unknown/unknown (n=1) (Table I).

Fecal concentrations of E1 were <30 µg/g of stool in all PI CF patients (9 µg [6-11] and >200 µg/g of stool in all PS CF patients (530 µg [356-815]). The stool fat excretion in PI CF patients was abnormal (39.9 g/day [32.5-48.8]; 12.8 g/day minimum) and in PS CF patients it was below the upper limit of the reference range (4.30 g/day [2.98-5.23]; 5.5 g/day maximum).
At the baseline, no differences between the groups with regard to the diameter of the pancreatic duct in the head, body, and tail of the pancreas were stated. The pancreas in PI CF patients was narrower than in PS CF patients when measured at the level of the head, the body, and the tail. It was found that in 5th and 10th minutes of SE-MRCP the pancreatic duct was wider in the head of the pancreas in PI CF patients than in PS CF patients (Table II, Fig. 1). Apart from this, no other differences were identified with regard to the diameter of the pancreatic duct in SE-MRCP in the two groups of patients.

Areas under receiver operating curves (AUROCs) for discriminating between PI and PS CF patients are presented in Table III. AUROCs’ values for the best discriminating minutes after stimulation were not better than for pancreatic size.
DISCUSSION

A difference was identified between PI and PS CF patients in the diameter of the pancreatic duct in the head of the pancreas at the end of the period of action of secretin. The smaller diameter of the pancreatic duct in PS CF patients could be explained by a stronger contraction of the smooth muscle in the wall of the duct in reaction to pancreatic juice secreted minutes earlier. It is possible that in PI CF patients this would not occur due to the damage to the pancreatic parenchyma. Another possible explanation is that fibrosis of the pancreatic tissue renders it more resistant mechanically and thus prevents changes in the diameter of the pancreatic duct located within it. However, no significant differences in the diameter of the pancreatic duct were found between the two groups at baseline or in the body or the tail of the pancreas.

The clear difference in the size of the pancreas is in accordance with earlier observations [19]. The size of the pancreas in PS CF patients matched that of healthy persons and atrophy in PI CF group was not as severe as described by Soyer et al. [19]. It highlights the extent of damage to the pancreatic parenchyma that may be caused by CF. It should be stressed that the relationship between the CF-related atrophy of the pancreas seen on MRI and the function of the organ is not direct and does not provide the required clinical value [20]. However, as documented in the present study the width of non-stimulated and secretin-stimulated pancreatic duct was less useful in the differentiation between PI and PS CF subjects. In fact, none of the parameters studied could serve to predict PS-PI turnover.

The CF-related morphological changes of the pancreas can be visualized using ultrasonography, endoscopic retrograde cholangiopancreatography (ERCP) [21], computed tomography, and MRI. Different morphological patterns of CF-related pancreatic damage were identified by various authors and include: diffuse hyperintensity with and without lobular pattern or areas of sparing, with organ enlargement or atrophy [22], and also pancreatic atrophy without signs of fatty tissue replacement [23]. Other changes may include cyst formation, fibrosis, and

Table II. The width of the pancreatic duct in pancreatic-insufficient and pancreatic-sufficient patients with cystic fibrosis during SE-MRCP. The width of the pancreas in the two groups is also presented. Median values and interquartile ranges are reported.

<table>
<thead>
<tr>
<th>Time, min</th>
<th>PI, mm</th>
<th>PS, mm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas – head</td>
<td>0</td>
<td>15.0 [13.0-22.0]</td>
<td>23.5 [19.0-26.5]</td>
</tr>
<tr>
<td>Pancreas – body</td>
<td>0</td>
<td>12.0 [9.0-17.0]</td>
<td>20.0 [15.0-25.0]</td>
</tr>
<tr>
<td>Pancreas – tail</td>
<td>0</td>
<td>9.0 [7.0-12.0]</td>
<td>19.0 [9.5-26.0]</td>
</tr>
<tr>
<td>Pancreatic duct – head</td>
<td>0</td>
<td>2.0 [1.0-3.0]</td>
<td>1.0 [1.0-2.0]</td>
</tr>
<tr>
<td>Pancreatic duct – body</td>
<td>0</td>
<td>2.0 [1.0-3.0]</td>
<td>1.0 [1.0-2.0]</td>
</tr>
<tr>
<td>Pancreatic duct – tail</td>
<td>0</td>
<td>1.0 [0.0-1.0]</td>
<td>1.0 [0.0-1.0]</td>
</tr>
</tbody>
</table>

PI: pancreatic insufficient; PS pancreatic sufficient.

Table III. Areas under receiver operating characteristic curves (AUROCs) for discriminating between pancreatic insufficient and pancreatic sufficient cystic fibrosis patients using the five parameters that differed between the two groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUROC (95% CI)</th>
<th>p-value</th>
<th>Optimal cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas – head</td>
<td>0.717 (0.549-0.886)</td>
<td>0.0114</td>
<td>17 mm</td>
</tr>
<tr>
<td>Pancreas – body</td>
<td>0.771 (0.619-0.923)</td>
<td>0.0005</td>
<td>19 mm</td>
</tr>
<tr>
<td>Pancreas – tail</td>
<td>0.722 (0.554-0.889)</td>
<td>0.0094</td>
<td>18 mm</td>
</tr>
<tr>
<td>Pancreatic duct – head – 5th minute</td>
<td>0.693 (0.521-0.866)</td>
<td>0.0279</td>
<td>3.0 mm</td>
</tr>
<tr>
<td>Pancreatic duct – head – 10th minute</td>
<td>0.698 (0.528-0.868)</td>
<td>0.0228</td>
<td>1.4 mm</td>
</tr>
</tbody>
</table>
pancreatic duct abnormalities [24]. Similar morphological changes were also reported on computed tomography [25]. The main advantage that SE-MRCP holds over other imaging methods is improved visualization of the pancreatic ductal system [26]. This increases its diagnostic potential in early and mild pancreatitis [27], as well as in congenital abnormalities, such as the pancreas divisum [28]. Different teams elaborated protocols in which SE-MRCP is used to assess the pancreatic fluid volume [29–33], which provides additional information on exocrine pancreatic function.

Among current biochemical approaches to pancreatic function, measurement of fecal E1 concentration, which was used in this study, is the one that established itself as the standard of care in CF. Assessment of E1 levels is most sensitive and specific in identifying moderate and severe exocrine pancreatic insufficiency, and is less useful in patients with mild disease [34]. Fecal chymotrypsin is another indirect pancreatic function test, which has a lower sensitivity than E1 in CF patients [35]. Fecal lipase is not widely used, and it was shown that the diagnostic value of E1 is superior [36]. The classical Van de Kamer method of total stool fat content measurement is more cumbersome in application [15]. In contrast, acid steatocrit assessment takes less time to accomplish, and yet it offers sensitivity and specificity that in some studies matched that of the 72-hour stool fat collection [37]. However, acid steatocrit was shown to be less useful than E1 in infants with CF [38]. Previously, we reported a smaller increase in serum lipase concentrations in PS CF patients compared with healthy controls and virtually none in PI CF patients [39]. Invasive tests of pancreatic function include the secretin stimulation test, the CCK stimulation test, and the secretin-CCK stimulation test [40].

The study is limited by its design: it focuses uniquely on measuring the diameter of the pancreatic duct during SE-MRCP. The intentional simplicity of statistical analysis reflects the aim of the research. Although it was not powered to compare relative changes in the width of the pancreatic duct between the two groups, which would require significantly larger numbers of patients, such additional analyses were performed and did not yield informative results.

Pancreatic sufficient CF patients were older than those PI because of the shorter survival of PI patients, which influenced the age structure of the patient population from which study participants were recruited. Given that mild pancreatitis might be present in PS CF patients and be contributing to changes in morphology, the older age of PS CF patients should only reduce the eventual differences between the two studied groups.

CONCLUSION

The measurement of the diameter of the pancreatic duct during secretin stimulation does not allow for discrimination between pancreatic sufficient and pancreatic insufficient status in patients with cystic fibrosis.

Conflicts of interest. The authors have no conflicts of interest.


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