Original papers

The size of the spleen by magnetic resonance imaging in patients with cystic fibrosis; with and without diabetes—a novel observational study

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Summary

Background: Magnetic resonance imaging (MRI) has been shown to be a useful tool to evaluate the volume of the pancreas. There is currently no information about the size of the spleen in cystic fibrosis (CF) patients.

Patients and methods: We investigated 51 adult volunteers: 28 pancreatic insufficient CF patients [13 with CF-related diabetes (CFRD) and 15 non-diabetic] and 23 male non-CF patients [12 with type 1 diabetes mellitus (T1DM) and 11 healthy control subjects]. Patients with known liver cirrhosis or portal hypertension were excluded. The size of the spleen was measured in all subjects by an investigator unaware of patients’ clinical status. For comparison of spleen size in the four study groups only male CF patients were included. For CF patients, spleen size was compared with forced expiratory volume in 1 s (FEV₁), body mass index (BMI), total number of days of intravenous (IV) antibiotic treatment for pulmonary exacerbations in year previous to study, levels of circulating white blood cells, glycosylated haemoglobin A1c (HbA1c), and exocrine function of the pancreas, as assessed by daily requirement of oral lipase.

Results: Amongst the four study groups, spleen size was greatest in the male non-diabetic CF patients (P=0.01). For CF patients, spleen size was greater in male compared to female patients (P=0.012). For patients with CFRD, there was an inverse correlation between the spleen size and HbA1c (r=−0.59, P=0.04) and the daily intake of supplementary lipase (r=−0.63, P=0.02). The size of the spleen in patients with CFRD, but not in CF patients without CFRD, inversely correlated with the days of IV antibiotic treatment received in the year previous to the study (r=−0.67, P=0.012). There was no correlation between spleen size and BMI, FEV1 and white blood cell counts in any group.

Conclusions: On MRI, the spleen size was greatest in male non-diabetic CF patients in comparison with other groups. The size of the spleen in CFRD patients was smaller when diabetes was poorly controlled, when exocrine pancreatic function was greatly impaired and in those with greater need for IV antibiotics in the year prior to the study.
Introduction

Despite the increased propensity of cystic fibrosis (CF) patients to have repeated pulmonary exacerbations (PExs) due to chronic bacterial infection, the role of the spleen in CF has not been systematically investigated. In CF patients, an enlarged spleen is known to occur in those with CF related liver disease and portal hypertension.

Magnetic resonance imaging (MRI) has been proven to be a useful tool to assess the volume of the pancreas in patients with type 1 diabetes mellitus (T1DM).1 We have extended the study to investigate abdominal organs in a cohort of adult patients with CF.

We have assessed the architecture of the liver and the size of the spleen in adult CF patients. We noticed that the size of the spleen differed between those with CF-related diabetes (CFRD) compared with those without CFRD. To our knowledge, there have been no studies that looked specifically at the size of the spleen in CF patients relating this to their diabetes status.

This research aims to identify by MRI the difference in the size of the spleen in CF patients with and without CFRD and to compare spleen size with patients with long standing T1DM (without CF) and healthy control subjects. We also aim to correlate spleen size in CF patients with lung disease severity as determined by spirometry values, body mass index (BMI), parameters related to clinical infection such as number of circulating white cells at the time of the MRI and requirement of intravenous (IV) antibiotic treatment during year previous to study, and measures of endocrine and exocrine function of the pancreas.

Patients and methods

A total of 55 subjects were enrolled to the study (32 CF patients and 24 non-CF participants). Four patients with CF were excluded from the analysis (two were pancreatic sufficient and two had known portal hypertension) leaving 28 patients out of whom 13 had CFRD. For the non-CF group, one patient was excluded for insufficient data leaving 23 patients 12 of whom had T1DM.

Our Ethics Committee had allowed only male patients to be included in the study which compared the volume of the pancreas in patients with T1DM and healthy control1 Table 1 shows the demographic data for the four groups. Due to the fact that non-CF patients were all male, we have separated out the demographics for male CF patients.

Diabetes in CF patients was regarded to be present if patients met the criteria identified by the UK CF Trust guidelines. 2 In short, diabetes was considered to be present and needed treatment if any of the following criteria was met: (i) 120 min random plasma glucose level of >11.1 mmol/l on two occasions during disease stability away from pulmonary exacerbations; (ii) when there was an impaired glucose tolerance test (120 min plasma levels of 7.9–11 mmol/l) with weight loss and deteriorating clinical condition; (iii) when patients had transient hyperglycaemia on regular daily glucose monitoring with weight loss or clinical deterioration.

In the study population, all patients with CFRD were prescribed insulin. To rule out those with borderline diabetes, all non-diabetic CF patients underwent an oral glucose tolerance test (OGTT) as recommended by the WHO criteria. 3 Those with OGTT within the normal range (120 min glucose of <7.8 mmol/l) were included in the study. We planned to exclude patients with impaired OGTT, but as it happened, none fell into this category.

The daily intake of oral lipase was calculated upon entry to the study as total units of lipase per body weight in kilograms. This was pragmatically

Table 1  Demographic data for the study groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Type 1 DM</th>
<th>CF no diabetes (all patients)</th>
<th>CFRD (all patients)</th>
<th>CF no diabetes (male only)</th>
<th>CFRD (male only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>11</td>
<td>12</td>
<td>15</td>
<td>13</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (years) (SD)</td>
<td>27.5 (3.8)</td>
<td>29.2 (4.2)</td>
<td>25.6 (6.5)</td>
<td>25.9 (7.0)</td>
<td>26.9 (8.8)</td>
<td>29.4 (6.5)</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>24.8 (2.1)</td>
<td>24.6 (2.2)</td>
<td>22.03 (2.7)</td>
<td>23.6 (3.8)</td>
<td>21.9 (3.3)</td>
<td>23.3 (2.6)</td>
</tr>
<tr>
<td>Spleen size (cm)*4, mean (SD)</td>
<td>10.1 (1.5)</td>
<td>9.9 (1.5)</td>
<td>11.6 (1.4)</td>
<td>10.3 (1.2)</td>
<td>12.5 (1.4)</td>
<td>10.9 (1.1)</td>
</tr>
</tbody>
</table>

Type 1 DM: type 1 diabetes mellitus, CFRD: CF-related diabetes.

*P=0.016 (analysis of variance for all study groups).

1P=0.01 (analysis of variance for male patients only).
regarded to represent the marker of the degree of exocrine pancreatic insufficiency.

The spleen was measured in all four groups by MRI. MRI scans were performed using a Siemens 1.5 Tesla scanner. Two scan sequences were used for analysis—volumetric interpolated breath-hold examination (VIBE) and T1 weighted breath-hold with fat suppression (T1BHFS). No contrast media was administered. Images were analysed and the size of the spleen was measured by one consultant radiologist (M.C.) who was unaware of patients’ group. The size of the spleen was measured on longitudinal scans as the largest splenic length, defined as the maximum distance between the dome of the spleen and the spleen tip\(^4\) as seen in Figure 1.

At the time of the study, all CF patients were at least 14 days away from any PEx. The number of days of IV antibiotic treatment for PExs during the year of the study was obtained from patients’ medical records. Forced expiratory volume in one second (FEV\(_1\)), forced vital capacity (FVC), BMI, HbA1c and the number of circulating white cell counts were measured at entry to the study. The values of FEV\(_1\) and FVC were expressed as percentage of predicted values.

### Statistical analysis

Statistical analysis was done with the help of the Department of Medical Statistics of the Bristol Royal Infirmary. Variables regarded to be normally distributed—age, gender, BMI, spleen size and white cell counts were compared using Student’s \(t\)-test when comparing two groups, and using one way analysis of variance (ANOVA) when comparing more than two groups.

Comparison between the number of days of IV antibiotics requirement for CF patients with and without DM was made using the Mann–Whitney U-test, as these variables were not normally distributed.

Correlation between the size of the spleen and FEV\(_1\), FVC, BMI, lipase intake, HbA1C and white cell counts was done using a simple regression analysis. Correlation with the number of days of IV antibiotics requirement was made using Spearman’s correlation test. Differences were considered statistically significant if \(P\)-values were <0.05.

### Results

Demographic data and summary of comparison of groups are shown in Tables 1 and 2.

The mean age for CF patients was 25.9 years compared with 28.4 years for the non-CF subjects, but this did not reach statistical significance. The number of days of IV antibiotics required by CFRD patients was greater than that for CF patients without diabetes; median 42 days (range 0–84) for CFRD and median 28 days (range 0–84) for CF without diabetes. This difference did not reach statistical significance; \(P=0.43\) (Mann–Whitney U-test).

The size of the spleen for CF patients was greater in the males compared with females, \(P=0.012\) (Figure 2).

Table 1 and Figure 3 show spleen size in the four study groups—the size of the spleen was greatest in the male CF patients without diabetes, and smallest in the control group.

For patients with CFRD but not for those with CF without diabetes, the size of the spleen inversely correlated with HbA1C \((r=-0.59, P=0.04)\) and the daily intake of lipase/kg of body weight \((r=-0.63, P=0.02)\) (Figure 4). The size of the spleen in patients...
with CFRD, but not in those CF patients without diabetes, correlated with the number of days of IV antibiotics in the study year \((P=0.012, \text{Spearman’s test})\) (Figure 5).

Neither circulating white cell counts nor neutrophil counts correlated with the size of the spleen in the two CF groups. For non-CF patients, there was no correlation between the size of the spleen and age, BMI or HbA1c. For either group of CF patients there was no correlation between the size of the spleen and age, FEV\(_1\), FVC or BMI.

**Discussion**

The non-CF subjects were previously investigated by MRI in a study aimed at assessing the volume of the pancreas\(^1\). Solely male subjects were included in that study to satisfy the local research ethics committee.

To our knowledge, there are no published human or animal longitudinal data on the size of spleen in response to diabetic treatment in type I diabetic non-CF patients. Given the results of this study, this is an area for future research.

When comparing the four study groups but excluding female patients, those with the largest spleen size were CF patients without diabetes. We postulate that the larger sized spleen in CF patients could be due to the chronic lung infection that these individuals suffer.

In previous studies on normal population, gender did not seem to significantly influence variation in spleen size in adults\(^5,6\). In our study, male CF patients had larger spleen than female patients. The smaller sized spleen found in female CF patients compared to male CF patients could not be explained by differences in age or BMI between males and females, as these were similar. This difference could simply be a true structural anatomical difference between genders in CF patients. Its significance is not immediately obvious, although this finding may be another reason to explain the poor disease course described in females compared with male CF patients\(^7,8\).

The spleen size was found to be larger in CF patients without diabetes compared to CFRD patients. In order to explain this difference, we examined the incidence of pulmonary exacerbations needing IV antibiotic treatment during the year previous to the study for the CF groups. The number of days of IV antibiotic treatment was fewer in the CF patients without diabetes, although in this small group, this did not reach statistical significance.

**Figure 2.** The size of the spleen in male and female CF patients (open shapes are diabetic and closed shapes are non-diabetic).

**Figure 3.** The size of the spleen in the four study groups. The size of the spleen is displayed for male CF patients (A) and for all CF patients (B) for comparison with the non-CF groups who were all male.
There were no correlations between the size of the spleen in CF patients and the circulating white blood counts or circulating neutrophil counts. This may be, in part, due to the fact that patients were included during disease stability away from periods of pulmonary exacerbations. Other inflammatory markers such as CRP and serum ferritin or iron stores were not measured.

There was an inverse correlation between the size of the spleen in patients with CFRD and the number of days of IV antibiotic treatment. Once again, the reasons for this can only be speculative. The difference may represent an inability of the spleen to respond to infections by increasing its size in patients with CFRD. Conversely, it may be that those CF patients without diabetes are able to mount more effective immune responses, shown by a larger spleen size and hence requiring fewer days of IV antibiotics. Another possibility is that the pancreas as an organ and insulin as a hormone may be important for the growth of the spleen and its effectiveness against infections. This theory is supported by the fact that the size of the spleen was smaller in those with poorly controlled diabetes, as identified by higher HbA1c levels, and in patients with higher requirements of lipase which we used as a marker of the impaired exocrine pancreatic function.

Adherence to treatment (including insulin) is problematic area in the CF population. The raised Hb A1c (Figure 4) is an indicator of this fact. Given the inverse correlation with the spleen size, variability in adherence to treatment (indicated by the level of HB A1c) would have played a part in the size of the spleen on MRI scan.

We acknowledge the study’s limitation including the relatively small size of study populations. We do not have a reference spleen size for healthy, non-CF female patients. There are no specific investigations for the evaluation of the function of the spleen as opposed to its anatomical size. We also, acknowledge that we are merely reflecting on a relatively small, albeit significant, difference in the size of the spleen, rather than its function.

Although the multisystem nature of CF is known, the role of the spleen in CF has never been evaluated. Short of inspection of the spleen on autopsy samples, the size of the spleen on images obtained...
by modern MRI scanner is a reasonable alternative to study this organ.

Whether the difference in the size of the spleen described in this study may represent a difference in response to chronic infection amongst study groups remains unclear. The role this difference plays in the defence system for study group is also unknown.

There is no precedent to this study. The authors felt that the research findings were sufficiently consistent that it would be worth reporting. The spleen was small in diabetic CF patients compared to non-diabetic CF patients. The spleen size inversely correlated with HbA1c levels and the requirement of oral lipase in patients with CFRD. These indicate that, at least in this group, the spleen may be affected by the diabetic status in CF patients.

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References


