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The use of magnetic resonance elastography in differentiating autoimmune pancreatitis from pancreatic ductal adenocarcinoma: A preliminary study

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ABSTRACT

Purpose: To assess the value of magnetic resonance elastography (MRE) in patients with autoimmune pancreatitis (AIP) and in the differentiation of AIP from pancreatic ductal adenocarcinoma (PDAC).

Method and materials: This prospective study included 14 AIP patients, 26 PDAC patients, and 14 healthy volunteers. All participants underwent pancreatic MRE (40-Hz; 3 T scanner) at enrollment, and 7 AIP patients underwent a second MRE after initiation of steroid therapy. Pancreatic stiffness values were obtained by MRE and a new logistic regression model (the calculated Rad score) was used to combine pancreatic stiffness and the distribution and shape of high-stiffness areas for differentiation of AIP and PDAC. The area under the curve (AUC) was calculated for all parameters using receiver operating characteristic (ROC) analysis.

Results: Pancreatic stiffness was significantly higher (2.67 kPa [interquartile range, 2.24–3.56 kPa]) in AIP than in healthy pancreas (1.24 kPa [1.18–1.24 kPa]) and significantly lower in AIP than in PDAC (3.78 kPa [3.22–5.11 kPa]; both $P < 0.05$). Diffuse (n = 4 *vs* 1; $P = 0.043$) and multiple (n = 3 *vs* 0; $P = 0.037$) lesions were more common in AIP, while solitary (n = 25 *vs* 7; $P = 0.001$) and nodular lesions (n = 18 *vs* 2; $P = 0.002$) were more frequent in PDAC. Rad scores outperformed individual imaging parameters in distinguishing AIP from PDAC (AUC, 0.948 *vs* 0.607 to 0.782; all $P < 0.05$), with 84.6% specificity and 92.9% sensitivity. Pancreatic stiffness in AIP decreased significantly, from 2.66 kPa [2.29 to 3.05 kPa] to 1.55 kPa [1.43 to 1.67 kPa] ($P = 0.016$), during treatment.

Conclusions: MRE shows promise as a quantitative imaging method for differentiating AIP from PDAC and for monitoring the treatment response in AIP.

1. Introduction

Autoimmune pancreatitis (AIP) is rare condition that ischaracterized by enlargement of the pancreas and irregular narrowing of the main pancreatic duct [1]. AIP may present as painless jaundice and focal enlargement of the pancreas that mimics a pancreatic mass on radiography, and it is therefore sometimes misdiagnosed as a carcinoma. At least 2.5–5% of patients with AIP will undergo unnecessary pancreatectomy because of misdiagnosis as pancreatic cancer [2–4]. AIP responds dramatically to steroid treatment, and as such, correct diagnosis is of the utmost importance to ensure prompt treatment and avoid unnecessary surgery [5,6].

Current diagnostic criteria for AIP are based on clinical, radiologic, and histopathologic findings as well as response to steroid therapy. Histologically, both AIP and pancreatic ductal adenocarcinoma (PDAC) can exhibit dense and extensive fibrosis [7], but PDAC, which accounts for the majority of pancreatic cancers, features dense fibrosis (desmoplasia) that may constitute 90% of the overall tumor volume [8], while AIP is characterized by a swirling storiform fibrosis [9,10] that is centered around ducts and blood vessels. Novel non-invasive magnetic resonance imaging (MRI)-based techniques, such as magnetic resonance elastography (MRE), have shed light on quantifying changes in the mechanical properties associated with fibrosis [11], cell density [12], and inflammation [13]. We hypothesized that AIP and PDAC might cause different elevations in tissue stiffness, and that MRE could be used to facilitate differentiation between AIP and PDAC and to evaluate the

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response to steroid treatment in AIP. No previous study has focused on the usefulness of MRE to aid in the diagnosis of AIP. Hence, the aim of this study is to examine the role of MRE in differentiation of AIP and PDAC and to investigate stiffness changes during steroid treatment of AIP.

2. Materials and methods

2.1. Study participants

This prospective study was approved by the local ethics committee, and all participants gave written informed consent and were enrolled between January 2016 and December 2017. A total of 26 patients with presumptive diagnoses of AIP prospectively underwent full diagnostic pancreatic MRI, including MRE. The diagnosis of AIP was based on the International Consensus Diagnostic Criteria (ICDC) [14–16], which requires one of the following: 1) serum immunoglobulin G-4 (IgG4) level of 1 to 2 times the upper limit of normal; 2) parenchymal imaging findings of focal or diffuse pancreatic enlargement with delayed or rim enhancement in the presence of pancreatic ductal strictures without marked upstream dilation; 3) presence of IgG4-positive plasma cells (type 1) or granulocytes (type 2) at histology; 4) evidence of other organ involvement beyond the pancreas; or 5) a demonstrable clinical response to steroids within 2 weeks, indicated by radiologic improvement or marked clinical resolution of pancreatic and extrapancreatic manifestations. All patients also fulfilled the Asian criteria [17] and the histology, imaging, serology, other organ involvement, and response to therapy (HISORt) criteria [18] for AIP. Eight patients who did not meet the ICDC criteria and 4 with suboptimal imaging quality for validation of tissue stiffness were excluded. Finally, a total of 14 patients with AIP were included, 7 of whom underwent follow-up MRE, with written informed consent, after initiation of steroid therapy. The median interval between the diagnostic MRE and the follow-up MRE was 33 days (range: 29–36 days). Steroid therapy was initiated at doses starting from 40 mg/day for 3–4 weeks and then gradually tapered by 5 mg/week.

Patients with suspected pancreatic cancer were enrolled during the same period and underwent the same imaging protocol. Twenty-six patients with histopatholgically-confirmed PDAC after surgical resection were included, excluding patients with any other histological type of pancreatic cancer and those without definite histological diagnoses. Fourteen healthy volunteers from the nearby community who had no personal or familial history of pancreatic disease and no abnormal laboratory or noncontrast MRI/MRE findings were included as controls. The age and sex distribution of the AIP patients and the healthy volunteers were matched.

2.2. Pancreatic imaging

MRE images were obtained with a 3 T Signa HDX system (GE Healthcare, Milwaukee, WI, USA) with an 8-element torso-phased array coil. All imaging studies were performed with the patients in a supine position, feet first. Mechanical vibrations with a frequency of 40 Hz were generated by an active pneumatic driver system located outside the scan room and were delivered to the upper abdomen *via* a plastic tube terminating in a rectangular soft (19 × 14 cm) or rigid round (19-cm diameter; when BMI > 27 kg/m^2) passive driver [12,19–21] centered at the xiphisternum and secured by an elastic belt. The drivers were developed by the Mayo Clinic (Rochester, MN). A spin-echo echo-planar imaging pulse sequence was used, and the images were acquired at the end of expiration during 4 × 22-s breath-holds and 1 × 11-s breath hold. The imaging parameters for MRE were: repetition time (TR), 1375 ms; echo time (TE), 39.4 ms; field of view (FOV), 350–420 mm; phase offsets, 3; parallel imaging acceleration factor, 3; acquisition matrix, 96 × 96; number of slices, 32; and slice thickness, 3.5 mm. The total MRE acquisition time was approximately 2–3 min. Routine pancreatic MR imaging was performed on the same day on a separate 3 T unit (Ingenia, Philips HealthTech, Best, Netherlands), and included a respiratory-triggered T2-weighted turbo spin echo sequence (T2W TSE, single-shot for each slide) with and without fat suppression (SPAIR) and a T1-weighted (T1W) modified DIXON sequence (mDIXON) to generate high-resolution anatomical in-phase, out-of-phase, water and fat images. Three-dimensional T1W dynamic contrast-enhanced turbo field-echo (TFE) sequence with breath-holds was also used with mDIXON method (Dyn_mDIXON) to measure water-only signal change during contrast administration. The contrast agent, an intravenous bolus of gadodiamide (Omniscan, GE Healthcare, Ireland, which became prohibited by EMA guidelines after 1 February 2018) at a dose of 0.1 mmol/kg (0.2 mL/kg body weight), was infused at a rate of 2 mL/s and immediately followed by a 20-mL saline flush. The dynamic MR sequence included a precontrast phase and 5 postcontrast phases, at 10 s, 40 s, 70 s, and 100 s and 170 s after contrast injection [22,23], with slice thickness of 5 mm and 2.5 mm of negative spacing to enhance the signal-to-noise at each phase. The overall duration of the standard MRI protocol was approximately 15–20 min.

2.3. Image analysis

MRE postprocessing was performed with software integrated with the MRE pulse sequence using the direct inversion algorithm that has been described previously [12,19]. The raw phase data were automatically processed immediately after MRE image acquisition so that maps of tissue stiffness (elastograms) and magnitude images could be generated within 2 min. The elastograms were strictly matched the slices on magnitude images showing the anatomy for region of interest (ROI) selection, and pancreatic shear stiffness values were depicted by quantitative color scale ranging from 0 to 4 kPa [24]. The ROIs were drawn by free-hand on 3 consecutive axial magnitude images (1 ROI/section) to cover as much of the affected parenchyma as possible after identification of lesions on the MRE-magnitude images together with the T1/T2-weighted images. The ROIs were automatically transferred from the magnitude images to the elastograms to obtain the stiffness values in kilopascals (kPa). Care was taken to exclude normal parenchyma, artifacts, vessels, ducts, and surrounding tissues. In patients with multiple or diffuse AIP, stiffness was measured across the largest lesion or across the largest dimension of the pancreas. The stiffness values were determined by averaging across the three ROIs. In order to show all of the high-stiffness areas in the AIP/PDAC patients, the entire pancreas was further segmented on the elastograms and reconstructed using maximal intensity projection to visualize the entire shape of the organ. The imaging parameters of the high-stiffness areas were assessed using the distribution and type of lesions (diffuse or segmental; solitary or multiple of segmental lesions), as well as the shape (nodular or longitudinal) of segmental lesions [25,26]. Lesions were considered segmental when at least one portion of the pancreas appeared normal; otherwise involvement was diffuse. Segmental involvement was further classified as single-segment (solitary) or multiple-segment (multiple), and segmental lesions were described by shape as nodular (irregular or round/oval shape, taller-than-wide, with the long axis perpendicular to the longitudinal axis of the pancreas) or longitudinal (sausage or spindle shape, wider-than-tall, with the long axis parallel to the longitudinal axis of the pancreas). The ROIs for healthy pancreas were placed at the largest dimension of the pancreatic body. The images were interpreted by two radiologists, with 3 and 5 years' experience, respectively, in MRE interpretation. The radiologists were blinded to the clinical diagnoses and pathological results. They reported both the stiffness measurements and their evaluations of the high-stiffness areas in consensus.

2.4. Statistical analysis

Statistical analyses were performed using R statistical computing