Abstract

MRI plays an important role in the clinical management of pancreatic disorders and interpretation is reliant on qualitative assessment of anatomy. Conventional sequences capturing pancreatic structure can however be adapted to yield quantitative measures which provide more diagnostic information, with a view to increasing diagnostic accuracy, improving patient stratification, providing robust non-invasive outcome measures for therapeutic trials and ultimately personalising patient care.

In this review, we evaluate the use of established techniques such as secretin-enhanced MRCP, diffusion-weighted imaging, T1, T2* and fat fraction mapping, but also more experimental methods such as MR elastography and arterial spin labelling, and their application to the assessment of diffuse pancreatic disease (including chronic, acute and autoimmune pancreatitis/IgG4 disease, metabolic disease and iron deposition disorders) and cystic/solid focal pancreatic masses. Finally, we explore some of the broader challenges to their implementation and future directions in this promising area.

Introduction

Pancreatic MR protocols employed in clinical practice are generally optimised for anatomical imaging[1]. High native T1 signal of normal pancreatic parenchyma, high T2 signal of the main pancreatic duct, pancreatic secretions and cystic pancreatic lesions, use of fat suppressed T2 weighted imaging for the assessment of regional inflammation, avid pancreatic parenchymal contrast enhancement (compared to low T1/hypoenhancement of pancreatic adenocarcinoma) and increased conspicuity of many pancreatic lesions on diffusion-weighted imaging (DWI)[2] have all rendered widespread use of pancreatic MRI in routine clinical pancreatico-biliary practice[3].

Many of the signal changes underpinning structural pancreatic MR are amenable to quantification (supplementary material, table 1). MR sequences designed to quantify these signal changes can complement anatomical imaging, improve diagnostic accuracy and enable the development of new quantitative biomarkers, with the broader objective of better stratifying patients and developing more personalised treatment regimens. In this review we define this potential, appraise current evidence and discuss how methods could be used to expand the utility of MR evaluation of (a) chronic pancreatitis, (b) acute pancreatitis and pancreatic/peripancreatic collections, (c) autoimmune pancreatitis and IgG4 disease, (d) non-alcoholic fatty pancreatic disease and metabolic disease, (e) iron deposition disorders involving the pancreas, and (f) cystic and solid focal pancreatic lesions. As this review is pathology focussed, we have included a brief glossary of MR methods referenced in the text as supplementary material.

DIFFUSE PANCREATIC DISEASE

Chronic pancreatitis

Chronic pancreatitis (CP) is driven by recurrent pancreatic inflammation causing irreversible pancreatic structural damage and progressive endocrine/exocrine dysfunction. Proposed pathophysiological mechanisms include stagnant pancreatic juice forming protein plugs that undergo eventual calcification and cause ductal obstruction, ectasia, chronic inflammation, and periductal fibrosis/scarring. Toxic metabolites and reactive oxygen species are also thought to induce cellular inflammation eventually leading to fibrosis[4].

MR assessment of CP typically involves assessment of pancreatic morphology, parenchymal T1 signal (as a marker of fibrosis) and where indicated, secretin-enhanced MR cholangio-pancreatography (sMRCP). Unfortunately, qualitative assessment is not particularly sensitive for early disease or assessment of disease severity[5].

Several quantitative MR studies have developed methods for quantification of post-secretin fluid release[6,7], specifically measuring pancreatic flow rate (ml/minute), total excreted volume (mls) or time to peak fluid released (minutes). Quantification has been shown to have good inter-observer agreement and measurements are robust to differing doses of secretin[8–10]. Validation studies have typically been based on phantom studies, but correlations between faecal elastase and pancreatic flow rate (r=0.79)[11] and total excreted volume at 10 minutes (r=0.573, p<0.001)[12] have been encouraging. Correlation with invasive endoscopic post-secretin maximal bicarbonate concentration has been less convincing[13].

In patients with severe CP, pancreatic flow rates (5.3±2.4 ml/min) are lower relative to those with moderate chronic pancreatitis (7.0±3.0 ml/min, p=0.03) or normal controls (7.4±2.9 ml/min, p=0.018)[14] and time to peak fluid release increases with progressive disease severity (normal controls 5.8±1.7 mins vs mild CP 7.7±2.6 mins vs moderate CP 9.1±3.0 mins vs severe CP 12.3±1.6 mins, p=0.0001)[11]. Following endotherapy (sphincterotomy/stone extraction/stenting) in patients with CP, increases in pancreatic flow output and total excreted volume have been demonstrated[10].

Applications to other conditions associated with pancreatic insufficiency such as cystic fibrosis have found limited value in the use of post-secretin main pancreatic duct diameter as a marker of disease severity[15], but demonstrated qualitatively reduced post-secretin excreted volume

in patients with more advanced disease[16]. Quantitative MRCP studies in this cohort have not been reported.

As an alternative, a carefully positioned spatially selective inversion-recovery slab followed by high temporal resolution single-shot MRCP imaging can be used to derive a 'cine' loop of signal refilling the distal pancreatic duct. This has been used to develop a five point grading system that correlates with Cambridge CP scores (r=-0.698, P<0.001)[17].

The use of secretin MRCP is unfortunately limited by supply shortages and its significant cost[18]. While a number of quantitative metrics have been proposed, a consensus around methodology, metrics and cut off levels is lacking, and will need to be defined for multicentre formal evaluation studies and more widespread adoption.

DWI signal reflects water movement within tissue, driven by random (thermal) motion but also water diffusion between tissue compartments across cell membranes (supplementary material, table 2). Water diffusion between the intracellular, intravascular, interstitial and intraductal compartments present in normal pancreatic tissue are each likely to be influenced by ductal stagnation/obstruction, and fibrosis/scarring occurring in CP.

Reduced and delayed increases in pancreatic apparent diffusion coefficient (ADC) following secretin have been described with more severe CP[19], although findings have not been reproduced[20]. Baseline ADC values have also been reported to be lower in CP and correlate strongly with endoscopic post-secretin maximal bicarbonate concentration (r=0.771, p<0.0001)[20,21].

Intravoxel incoherent motion (IVIM), an extension of DWI (supplementary material, table 2) has been applied to CP to show that perfusion fractions tend to be higher in CP, relative to pancreatic adenocarcinoma[23]. In a study including 165 patients, patients with moderate and severe pancreatic fibrosis tended to have lower parenchymal pseudodiffusion coefficient (D*) and perfusion fraction compared to those with mild or no fibrosis[24]. Interestingly, intra-operative measurements of pancreatic hardness were not correlated with pancreatic ADC values[25].

DWI and IVIM are promising approaches, but much like in other areas of the body the lack of consensus on which and how many b-values to use and the approach to modelling ADC/IVIM parameters continue to hamper the development of DWI-derived biomarkers.

Reduction in pancreatic parenchymal T1 signal has been linked with pancreatic fibrosis[24] (figure 1). T1 mapping refers to the formal quantification of T1 signal (supplementary material, table 3). Increasing T1 with progressive disease has been demonstrated using both multi-flip angle (normal controls 1099 ms vs mild CP 979 ms, p<0.0001)[26] and modified Look-Locker inversion recovery methods (normal controls 865±220 ms vs mild CP 1075±221 ms vs severe CP 1350±139 ms, p<0.0001)[27].

<Figure 1>

MR elastography (MRE, supplementary material table 4) has shown increasing pancreatic parenchymal stiffness with progressive disease, and was superior to T1 mapping in the diagnosis of moderate and severe CP[27]. Pancreatic perfusion measured using Dynamic Contrast Enhanced (DCE) MRI (reliant on intravenous gadolinium-based contrast agent, supplementary material table 5) and arterial spin labelling (supplementary material, table 5) have both been used to measure increases in pancreatic perfusion post-secretin in normal volunteers, albeit both with poor repeatability[28,29].

Acute pancreatitis
Although diagnosis is based on clinical parameters, CT in the subacute phase is used to exclude acute complications, provide alternative diagnoses and give an early assessment of classification into 'interstitial' or 'necrotising' morphologies (as per the 2012 Revised Atlanta Classification)[30]. Latent cross-sectional imaging in the early/late phase (before/after 4 weeks respectively) can subsequently

be used to assess fluid collections, necrosis and formation of pseudocysts/walled-off necrosis. For patients who are able to tolerate MR imaging, better characterisation of fluid/solid/haemorrhagic components of collections, identification of aetiology (such as gallstones) and the potential to derive prognostic information from quantitative imaging sequences justify its use over CT[31].

Pancreatic parenchymal based phenomena such as acinar cell death, leucocytic infiltration, interstitial fibrin deposition and microvascular thrombosis each have the potential to affect the diffusion of water molecules. DWI has comparable sensitivity to CT for the detection of acute pancreatic inflammation[32], with significantly lower parenchymal ADC values and diffusion tensor imaging derived fractional anisotropic measures (supplementary material, table 2) relative to normal controls[33,34], both of which have been correlated with MR severity index scores (r=-0.63 and r=-0.65, p<0.01)[34]. Histogram analysis of pancreatic parenchymal ADC maps have linked reduced skewness and higher kurtosis (supplementary material, tables 1 and 2) with increased risk of future complications, although overall sensitivity was low (AUC=0.784)[35]. Parenchymal T2* measurements can increase in acute pancreatitis (the cause of this is uncertain, but may be secondary to increased perfusion), although these reduce in the presence of superadded haemorrhage[36]. Finally, DWI can also be useful in the evaluation of pancreatic/peripancreatic collections, as lower ADC values (as a result of cellular debris) can be indicative of superadded infection[32,37].

Quantification of T2 signal using T2 mapping (supplementary material, table 3) in acute pancreatitis has not been reported to date, but typically increased pancreatic/peri-pancreatic T2 signal (figure 2) has the potential to yield useful quantitative markers.

<Figure 2>

Autoimmune pancreatitis and IgG4 disease
Pathological phenomena in autoimmune pancreatitis (AIP) including acute inflammation, infiltration with IgG4 positive plasma cells, fibrosis and obliterative phlebitis all have the potential to influence quantitative MR parameters[38]. Published data has focussed on DWI, where pancreatic parenchymal ADC values in AIP have been shown to be lower than in CP[39,40], pancreatic adenocarcinoma or normal pancreatic tissue[41,42]. Pancreatic ADC values have also been significantly correlated with serum IgG4 levels (r=-0.8, p<0.05)[39], shown to be significantly lower in patients with symptoms[43] and have been reported to increase following steroid treatment[39]. Association of low pancreatic parenchymal T1 signal with AIP[44] (figure 3) underscores the potential for T1 mapping, which to date has not been reported.

<Figure 3>

Non-Alcoholic Fatty Pancreas Disease and Metabolic Disease
Non-alcoholic fatty pancreas disease (NAFPD) refers to pancreatic steatosis in association with obesity and the metabolic syndrome. Eventual sequelae of intracellular lipid accumulation and proliferation of pancreatic adipocytes include inflammation, pancreatitis, malignancy and the development of type 2 diabetes mellitus[45]. Fatty infiltration and pancreatic atrophy are common morphological findings, but changes in intralobular, interlobular and extralobular fat and their significance are poorly understood[46].

MR spectroscopy (MRS, supplementary material table 4) is the gold standard approach to fat quantification but is technically challenging in the pancreas because of organ size and respiratory motion artefact. Increased pancreatic fat in obesity, diabetes[47] and impaired glucose tolerance have been reported but correlation with measures of beta-cell function have been less clear[48,49].

Anatomical imaging methods such as the multipoint Dixon sequences have limitations, but have reported increased pancreatic fat in type 2 diabetes mellitus[50,51] and associations with age[52], obesity, hypertriglyceridaemia and insulin resistance[53,54], with reported reductions in pancreatic fat following low calorie diet regimes in diabetic patients[55]. Proton density fat fraction (PDFF,

supplementary material table 4) mapping methods are currently the most robust method for pancreatic fat quantification but have to date been optimised for the liver and not the pancreas[56](figure 4). There is conflicting data on the association between pancreatic PDFF fat and diabetes, with some reporting pancreatic fat increases[57,58] or no relationship[59,60] . Association with insulin resistance has been suggested[61].

MRE has been shown to be repeatable in the pancreas, with increasing stiffness with age[62] Reductions in pancreatic stiffness have also been reported in obese patients following glycaemic stress[63]. Post-glycaemic load changes in pancreatic blood-oxygen level dependent (BOLD, supplementary material table 5) MRI based T2* measurements have also been shown in normal volunteers[64].

<Figure 4 >

Iron deposition disorders involving the Pancreas
Iron deposition in the pancreas remains poorly understood but occurs alongside atrophy and fibrosis and is associated with impaired exocrine/endocrine function. It is thought to account for the high rates of diabetes seen in patients with thalassaemia major[65].

T2*/R2* mapping (supplementary material, table 3) is sensitive to parenchymal iron content, although formal invasive validation studies have not been published. Quantitative studies have focussed on thalassaemia major, but reports of correlations between cardiac, liver and pancreatic T2*/R2* have been conflicting[66–68]. Correlations between logarithmic pancreatic T2* values and beta-cell function[69] , together with differences in pancreatic T2* between those with normal and abnormal (impaired glucose tolerance/diabetes) glucose metabolism are promising[70]. Pancreatic R2* cut-off values for HFE gene positivity in hereditary haemochromatosis also raise the possibility of applications in other iron deposition disorders[71].

Segmentation, particularly in the presence of fatty infiltration/parenchymal atrophy and errors introduced by multi-echo measurements in the presence of low iron concentrations[72] pose important challenges.

FOCAL PANCREATIC MASSES
Cystic pancreatic lesions
T2-weighted tissue contrast from fluid content within pancreatic cystic lesions enables differentiation from solid lesions using standard MRI. Improvements in MR and CT image quality, increasing obesity, diabetes and an aging population have resulted in a 19.6% rise in the prevalence of incidental indeterminate non-pseudocyst pancreatic cystic lesions on cross-sectional imaging[73]. Cystic pathology can range from non-neoplastic cysts to pancreatic ductal adenocarcinomas, therefore there is a genuine need for imaging methods that can distinguish between malignant and benign pathology (figure 5).

The most common potentially malignant cystic pancreatic lesions - intraductal mucinous neoplasms (IPMNs) – can range from slow-growing indolent to aggressive forms, committing patients to extended follow-up regimes with significant resource implications[74]. Several DWI studies have demonstrated that aggressive IPMNs tend to have lower ADC values than more benign lesions, supporting the use of DWI as a predictor malignant risk[75–77]. Malignant IPMNs have also been associated with lower IVIM D_{slow} and higher D_{fast} values relative to more benign IPMNs[78].

Current prognostication guidelines are based entirely on anatomical features – distinction between mucinous content and serous content (and therefore differentiation between mucinous cystic neoplasms and benign serous cystadenomas) would significantly aid diagnosis and prognostication.

Simple cysts tend to have higher ADC values due to T2 shine through[79], while the presence of mucin tends to lower ADC values[80]. Small scale studies have also demonstrated that ADC values of abscess tend to be lower than neoplastic cysts[81].

Finally, genetic characterisation of excised pancreatic cystic lesions have suggested hyperpolarised ^{13}C-pyruvate MRS maybe useful in the distinction between malignant and benign cysts[82].

<Figure 5 >

Solid pancreatic lesions

Unlike their cystic counterparts, solid pancreatic lesions are more commonly malignant (i.e. pancreatic ductal adenocarcinoma or neuroendocrine tumours, NETs; figure 6). Important benign differentials include solid inflammatory masses such as focal/mass-forming pancreatitis, which can be difficult to exclude without extended follow-up, often at the expense of a worsened prognosis if malignancy is eventually diagnosed. Improved diagnostic sensitivity, better characterisation, early exclusion of benign differentials and prognostic/therapeutic stratification are therefore important areas where quantitative MRI has the potential to improve patient outcomes.

Limited differences between lesion and pancreatic parenchymal T1/T2 signal intensity, gland atrophy and fatty infiltration can make the detection of small solid pancreatic lesions difficult. B-value optimised DWI can be used to increase lesion conspicuity[83] and sensitivity for small NETs[84].

Pancreatic malignancy is associated with reduced ADC[85–88] and reduced fractional anisotropy[85] relative to adjacent normal pancreatic tissue (supplementary material, table 2). Studies using DWI to distinguish inflammatory and malignant solid pancreatic lesions, have been less conclusive with some demonstrating lower ADC in malignancy[89–93] and others showing no difference[79,94–96]. IVIM studies (supplementary material, table 2) have shown lower perfusion fractions and D_{fast} in adenocarcinoma[97], and that differences in D_{slow} could be used to separate pancreatic ductal adenocarcinoma and NETs[78].

Evaluation of NETs has been more promising with tumour differentiation linked to ADC values, although correlations with mitotic counts and Ki-67 have been poor[98]. Whole lesion segmentation and measures of ADC entropy and kurtosis (supplementary material, table 1) are associated with more advanced NETs[99]. ADC values of normal pancreatic tissue upstream to infiltrated tissue are also an independent prognostic factor in overall patient survival[100].

Quantitative DCE MRI (supplementary material, table 5), using Tofts pharmacokinetic modelling to T1-corrected enhancement data has demonstrated lower K_{trans} and higher extracellular volume in pancreatic ductal adenocarcinoma compared with normal pancreas[101,102], with enhancement patterns differing between inflammatory and malignant masses[93]. Combining DCE and ADC data, sensitivity and specificity levels of 97% and 94% have been reported[93], but lesion DCE parameter variability is high and repeatability is poor[103].

Finally, a small study has demonstrated altered pancreatic adenocarcinoma T2* relative to normal pancreas, potentially explained by altered oxygenation (and vascularity) within the lesion[103].

<Figure 6 >

Challenges and future directions

Adoption of quantitative pancreatic MR methods within the wider clinical community requires validation against robust gold-standards, which are currently lacking. Percutaneous biopsy, with the attendant risks of haemorrhage and visceral damage is seldom justified, and histological characterisation of diffuse pancreatic disease or solid pancreatic masses is only likely if endoscopic ultrasound (EUS) guided or intraoperative aspiration/biopsy/excision takes place[104]. Assessment of secretory function requires endoscopy and the method is prone to inaccuracies, particularly in early disease[105]. Markers such as faecal elastase can be useful for validation but represent a competing biomarker – justifying the use of MRI given cost and patient convenience in this setting can be difficult.

Many of the quantitative MRI methods that have been applied in the pancreas have been developed and optimised for other organs (e.g. fat quantification using PDFF, T2*/R2* mapping for iron quantification). This is challenging because signal changes in the pancreas though measurable are small[46]. Dedicated studies optimising methods such as DWI may have utility, but a lack of consensus in standardising acquisition parameters (e.g. number of b-values and modelling methods for ADC/IVIM[106]) remain a major barrier to deriving diagnostic quantitative cut-off values that can be applied across different sites and scanners[107]. The lack of standardised protocols is a common barrier for methods such as T1 mapping (where different methods can yield small but significant differences in quantification) and DCE MRI. Finally, quantitative MR sequences must be time-efficient to enable them to be included within normal anatomical imaging protocols.

Delivery of quantitative imaging to the end-user radiologist is also a challenge. Automated generation of parametric maps that are amenable to simple region-of-interest analysis on standard PACS systems is essential to the acceptance of quantitative techniques within the wider radiological community. Creative methods of displaying quantitative data, such as overlay of colour-rendered DWI on anatomical images have the potential to improve diagnostic utility[84]. Improvements in image registration methods can address motion and misregistration artefacts particularly where co-registered acquisitions are needed[108]. Additionally, extraction of quantitative data relies on image segmentation which remains cumbersome and controversial. For example, in the presence of diffuse disease, the pancreas becomes atrophic and irregular – little is known about the differing pathological implications of intralobular, interlobular and extralobular portions of the pancreas[46]. The application of new machine-learning based segmentation methods promises to help address some of these challenges[109].

This review has also highlighted methods which have theoretical potential but as yet have not been investigated – the role of T1 mapping in autoimmune pancreatitis or T2 mapping in acute pancreatitis are ripe for well-designed imaging-outcome based studies.

Finally, the advent of new quantitative MRI methods in the pancreas has delivered a number of measures for which the pathological implications are either undefined or better defined in other organs. In combination with validation studies, development of hypotheses for mechanistic studies will help define a clear role for pancreatic quantitative MR and ultimately deliver robust non-invasive biomarkers that can be used as primary outcome measures in much-needed therapeutic trials.

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Figure legends:

Figure 1:

Axial T1 weighted images of the pancreas (white dashed line) in a normal volunteer (a) and patient with chronic pancreatitis (b). Chronic inflammation and fibrosis are thought to account for low parenchymal T1 and reduced volume in (b). Also note the presence of high T1 signal dependent pigment gallstones (solid white arrow) in (b).

Figure 2:

Axial T2 fat saturated image through the pancreas in a patient with acute pancreatitis. Note the presence of high peripancreatic T2 signal (solid white arrows) indicative of peripancreatic free fluid and the presence of patchy areas of increased pancreatic parenchymal T2 signal (clear white arrow) indicative of acute interstitial oedema. Perihepatic and perisplenic high T2 signal free fluid is also noted.

Figure 3:

Axial T1 weighted image through the pancreas of a patient with a flare of autoimmune pancreatitis. The pancreas is bulky, with a rind of low T1 signal (solid white arrows) and there is diffusely reduced pancreatic parenchymal signal with patchy areas of further reductions in T1 signal (clear white arrow) likely secondary to acute inflammation.

Figure 4:

Axial proton-density fat fraction image of the pancreas (black dashed line). Preserved pancreatic parenchyma is low signal but the gland is irregular and there is interlobular fatty infiltration suggestive of pancreatic steatosis.

Figure 5:

Axial T2 weighted image through the pancreas. The lobulated cystic lesion in the pancreatic tail (solid white arrow), demonstrated some concerning features (e.g. 2.7 cm size, thickened internal septations) but also some reassuring features (such as no associated main pancreatic ductal dilatation or enhancing components). Endoscopic US guided fine needle aspiration confirmed an intraductal papillary mucinous neoplasm.

Figure 6:

Coronal (a) and axial (b) T1 weighted fat saturated post-contrast images of the pancreas in two different patients. The hypervascular lesion in the superior head of pancreas (a), is associated with two large ill-defined right-sided hepatic metastases (solid white arrows) and was later confirmed as a neuroendocrine tumour. The irregular hypovascular mass in the head of the pancreas (b), was later confirmed to be a pancreatic ductal adenocarcinoma.