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doi: 10.53388/ghr2021-03-030

REVIEW

Research progress in the imaging diagnosis of non-alcoholic fatty pancreas disease

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Abstract: Currently, imaging modalities such as ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) are considered the method of choice for diagnosing non-alcoholic fatty pancreas disease. In addition, imaging-based clinical examination methods such as B-scan ultrasonography, transient elastography, and MRI-proton density fat fraction are the most widely used and have a high diagnostic value. Endoscopic ultrasonography is more accurate than CT and MRI in diagnosing pancreatic steatosis. MRI is a sensitive, non-invasive, and safe inspection method and also the best imaging technique to assess pancreatic steatosis. However, no clear consensus has been reached on diagnostic methodology for pancreatic fat.

Key words: non-alcoholic fatty pancreatic disease, imaging diagnosis

***Acknowledgments*:** Thanks the editage for polishing the language of the manuscript.

***Abbreviations*:** MRI, magnetic resonance imaging; CT, computed tomography; PS, Pancreatic steatosis; NAFPD, non-alcoholic fatty pancreas disease; BMI, body mass index; TE, transient elastography; PDFF, proton density fat fraction; T2DM, type 2 diabetes mellitus; NASP, non-alcoholic steatopancreatitis; MASH, metabolic-associated steatohepatitis; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; US, ultrasonography; MRS, magnetic resonance spectroscopy; CAP, controlled attenuation parameter; ARFI, acoustic radiation force impulse; ROI, region of interest; HU, Hounsfield units; HOMA-IR, homeostatic model assessment-insulin resistance; CSI, Chemical shift imaging; CAP, controlled attenuation parameter; MRE, Magnetic resonance elastography;

***Authors' Contributions*:** Zhao-Chun Chi proposed the idea of the paper and wrote the manuscript.

***Competing interests*:** The authors declare that they have no conflict of interest.

***Citation*:** Chi ZC. Research progress in the imaging diagnosis of non-alcoholic fatty pancreas disease. *Gastroenterol Hepatol Res*. 2021;3(1):4. doi: 10.12032/ghr2021-03-030.

***Executive Editor*:** Shao-Hui Geng.

***Submitted*:** 27 October 2020, ***Accepted*:** 10 December 2020, ***Online*:** 09 March 2021

TMR
doi: 10.53388/ghr2021-03-030

1. Introduction

Pancreatic steatosis (PS), also referred to as non-alcoholic fatty pancreas disease (NAFPD), is characterized by fat accumulation in the pancreas associated with obesity or metabolic syndrome. In 1933, Oligvie was the first to describe PS using the term lipomatosis to describe excessive storage of fat in pancreatic tissue and observing that obese individuals had a higher incidence of fatty pancreas (17% vs. 9%) than lean individuals [1].

The etiology of PS is similar to that of non-alcoholic fatty liver disease (NAFLD), with advanced age, obesity, metabolic syndrome, and insulin resistance being common risk factors. PS is significantly associated with high body mass index (BMI) [2]. Other causes may include some congenital syndromes, toxic substances, or viral diseases. Imaging modalities are the first choice for the diagnosis of NAFPD, consisting of three categories: ultrasonographic diagnosis, magnetic resonance imaging (MRI) diagnosis, and computed tomography (CT) diagnosis. Imaging has been widely accepted by patients owing to its non-invasiveness. Among the many imaging-based clinical examination methods, B-scan ultrasonography, transient elastography (TE), and MRI-proton density fat fraction (PDFF) are the most widely used, with a high diagnostic value [3]. Clinical practices have confirmed that NAFPD is closely associated with type 2 diabetes mellitus (T2DM), NAFLD, cardiovascular diseases, and tumors. NAFPD may also increase the burden of acute pancreatitis, which is associated with pancreatic cancer.

Clinical diagnosis of NAFPD is often based on physical examination. Baseline data include sociodemographic variables such as age and sex; basic variables such as height, weight, BMI, systolic blood pressure, and diastolic blood pressure; medical history variables such as DM, stroke, kidney disease, and anemia; laboratory test results such as aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, amylase, total cholesterol, triacylglycerol, high-density lipoprotein, low-density lipoprotein, fasting blood sugar, and hemoglobin A1c; antihypertensive agents, oral hypoglycemic agents, and lipid-lowering drugs; and lifestyle factors such as alcohol consumption, the Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking), weight gain, exercise, physical activity, walking speed, eating before sleep, eating after dinner, breakfast skipping, and enough sleep [4]. However, none of the above diagnostic criteria has as high a diagnostic value as the imaging diagnostic methods.

PS is a generic term for pancreatic fat accumulation, specifically referring to fatty replacement, fat infiltration, lipoma-like hypertrophy, NAFPD, and non-alcoholic steatopancreatitis (NASP). NAFPD refers to obesity-related fat accumulation without heavy alcohol consumption. Due to the lack of standardized screening tests, limited data are available on the prevalence of NAFPD [5]. At present, the reported prevalence varies greatly among studies due to their use of different diagnostic methods and standards, which remain to be unified to improve the diagnosis.

Histologically, NAFPD is a heterogeneous process characterized by the accumulation of intracellular lipids and the infiltration of adipocytes in pancreatic tissue. Pancreatic islet cells are considered resistant to fatty infiltration, but it has been suggested that the whole process is similar to that of the liver, i.e., metabolic-associated fatty liver disease progressing to metabolic-associated steatohepatitis (MASH) versus NAFPD progressing to NASP. Under oxidative stress, adipose-derived cytokines are released, which cause local inflammation and organ dysfunction. In addition, adipose tissue has endocrine functions and produces adipocytokines, including leptin, adiponectin, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). Macrophages sequentially produce IL-1β and myeloperoxidase, which further aggravate the inflammatory process [6]. This led to the hypothesis that NAFPD increases pancreatitis (and worsen its severity), pancreatic cancer [7], β-cell dysfunction, and T2DM [8].

2. Current status of imaging diagnosis of NAFPD

The deep retroperitoneal location of the pancreas means that it is challenging to study it non-invasively. This, combined with its variable shape, poorly defined borders, uneven fat distribution, and epigastric location (susceptible to motion artifacts) [9], makes it a challenge for all imaging modalities to quantitatively assess the pancreatic volume and fat content. Histological and biochemical measurements are the most direct and effective methods to assess PS. In contrast to the accumulation of triacylglycerol in the liver, PS is histologically characterized by adipocyte infiltration and intracellular fat deposition in the glandular acini and pancreatic islet cells. However, because of the difficulties of obtaining adequate pancreatic specimens and rapid autolysis encountered in the autopsy, no dichotomous histopathological cutoff has been proposed to define “fatty pancreas.” Recently, several imaging techniques have been used to detect PS, including ultrasonography (US), CT, MRI, and magnetic resonance spectroscopy (MRS). MRS has already been in use for the detection of PS. However, there is no consensus on a “gold standard” for the in vivo quantification of pancreatic fat content and on how to diagnose pancreatic fat. The optimal method should be able to determine both the presence

of fat and its amount in the gland in a non-invasive manner. Imaging methods play the most important role in diagnostics [10].

2.1 Abdominal ultrasound examination

Ultrasound diagnosis is a non-invasive, less-expensive method for the diagnosis of NAFPD. In most studies, the diagnostic criteria for NAFPD using abdominal ultrasonography have been an increase in the echogenicity of the pancreatic body over that of the kidney, which is metabolically more stable than the liver. The main feature of PS is the increase in the number of adipose cells in the pancreas, as the production of adipose cells may be easier than the infiltration of triacylglycerol into hepatocytes. The size of adipose cells is well suitable for scattering ultrasound beams to form ultrasound images of the parenchymal organs. This may account for differences in the ultrasound examination results of the liver versus those of the pancreas. Since the pancreas cannot be directly compared with the kidneys within the same acoustic window, the examiner needs to compare echo differences between the liver and the kidneys as well as between the liver and the pancreas so as to achieve an indirect, yet objective, comparison of pancreatic versus renal echoes. However, overlying intestinal gas or obesity can obscure the pancreas because the pancreas is located in the retroperitoneal space. Therefore, abdominal ultrasound evaluation of the pancreas is highly dependent on the skill of the operator and quality of the instrument [11].

Both transabdominal and endoscopic ultrasonography can be used to observe the pancreas [12-14]. The fatty pancreas appears hyperechoic (hyperechoic pancreas, HP) relative to the liver or relative to the spleen or kidneys if the liver is also hyperechoic. As the kidney and pancreas are usually not visible in the same acoustic window, an indirect comparison may be performed between the kidneys and liver and then between the liver and pancreas.

The pancreas can be examined by transabdominal or endoscopic ultrasonography. Due to gas coverage of the stomach/small intestine, transabdominal ultrasonography usually only partially reveals the pancreas. In contrast, endoscopic ultrasonography allows the sensor to be placed very close to the pancreas and thus is likely to provide more detailed images of the entire organ, but this method is mainly subject to the disadvantage of invasiveness. Studies comparing the echotexture of the pancreas with that of the kidneys, liver, or spleen have revealed a higher pancreatic echogenicity, which is indicative of fatty infiltration. Transabdominal ultrasonography is a relatively rapid, relatively affordable, and well-tolerated imaging method for the pancreas that does not involve ionizing radiation. However, it is operator-dependent (the mean interobserver agreement for ultrasonographic diagnosis of fatty pancreas is as low as 72%) [12], and the pancreas is not always visualizable (14.5% of all cases), especially in obese patients [15]. Most importantly, the liver or kidneys to be compared with the pancreas may have abnormal echotexture, making it impossible to obtain reliable quantitative information from ultrasound echoes or their intensity ratios.

At present, the major advancement in ultrasound technology for steatosis quantification is the controlled attenuation parameter (CAP). Ultrasound will be significantly attenuated when propagating in fatty liver parenchyma, and the more severe the steatosis, the more significant the attenuation. Therefore, the degree of liver steatosis can be calculated based on the attenuation of ultrasound according to the principles of physics, which is the basic principle for CAP. Due to differences in study populations, the diagnostic cutoff values for CAP are not identical from cohort to cohort, and there is no universally accepted diagnostic cutoff value recommended in the guidelines. No large cohort study has been conducted on CAP detection and analysis for NAFPD. It is necessary to strengthen research in this regard and establish uniform diagnostic standards as soon as possible.

Some researchers have even graded the severity of pancreatic fatty infiltration based on ultrasound echoes alone or based on the angle of the pancreatic duct and the presence of parenchymal “salt and pepper” dots [16-17]. Transabdominal ultrasonography is affordable, rapid, and non-invasive, but the pancreas is not always visualizable, especially in obese patients. Another limitation of transabdominal ultrasonography and endoscopic ultrasonography is that they are operator-dependent. More importantly, HP may not be a specific indicator of pancreatic fatty infiltration, as the fibrotic pancreas is also hyperechoic [18].

2.2 EUS diagnosis

EUS is superior to CT and MRI in diagnosing PS. Its disadvantages are its surgical invasiveness, the risk of complications, and the need for sedation. EUS remains the most sensitive method for pancreatic screening; however, pancreatic biopsy is by far the best method to measure pancreatic fat content.

EUS can provide detailed images of the entire pancreas while comparing the echoes of the pancreas and adjacent organs in real-time. With EUS, the echo of the pancreas can also be compared with that of retroperitoneal fat. In addition, EUS may also be combined with fine-needle aspiration for cytology [19].

Several grading systems for classifying NAFPD intensity based on EUS-detected echoes from the pancreatic parenchyma and pancreatic duct margins have been reported. Although abdominal ultrasonography and EUS are cost-effective methods to screen for NAFPD, they fail to accurately quantify the extent of PS. Cosmas et al.[20] analyzed the data of

TMR
doi: 10.53388/ghr2021-03-030

162 patients (75 women and 87 men) and found that 43 patients (26.5%) had pancreatic malignancy and 53 (32.7%) had fatty pancreas, which is common in patients with pancreatic cancer. Logistic regression analysis showed that age, sex, DM, and chronic pancreatitis were not significant risk factors for pancreatic malignancy, with fatty pancreas being the only significant risk factor for pancreatic cancer. It was concluded that the prevalence of NAFPD was high in patients with pancreatic cancer. More studies are needed to confirm whether EUS can be used as an early screening tool for pancreatic malignancy in NAFPD patients. Moreover, prospective cohort studies are required to elucidate the causal relationship between fatty pancreas and pancreatic cancer.

2.3 Ultrasound elastography

Elastography measures the response of biomechanical tissues to physical stress applied. The deep location of the pancreas in the abdominal cavity excludes the application of TE, but acoustic radiation force impulse (ARFI) can be used to deliver localized stress under the guidance of standard B-scan ultrasonography. Fat deposition softens the liver and thus decreases liver stiffness with the progression of hepatic steatosis. Its application to the pancreas is limited to a higher extent [21], and studies are often based on the assumption that progressive PS leads to a reduction in stiffness, but results have been conflicting. One study observed reduced pancreatic stiffness in patients with pancreatic insufficiency in cystic fibrosis [22], whereas another revealed no difference between the normal pancreatic tissue and NAFPD tissue [21]. Nevertheless, this is an ever-developing field, and larger-sample studies are needed to identify the potentially useful applications of ARFI for NAFPD, although such applications may be limited by the small size of the region of interest (ROI) of ARFI and difficulties with pancreas visualization [23].

2.4 CT diagnosis

The amount of PS can be assessed in Hounsfield units (HU). Compared with the spleen, the CT attenuation of the fatty pancreas is somewhat lower. However, the clinical value of CT in the diagnosis of NAFPD remains controversial. Some studies have shown that CT is a less valuable technique in judging PS compared with other imaging. Lee et al. conducted a study to compare the echogenicity on sonography with objective HU on CT and found no significant difference in clinical and biochemical parameters between NAFPD and non-NAFPD individuals. Inconsistent findings of abdominal ultrasonography versus abdominal CT may be due to the uneven distribution of pancreatic adipose tissue infiltration, which resulted in large variation of HU among CT-scan modalities. On the contrary, Kim et al. observed that pancreatic attenuation on CT was well negatively correlated with the histologic pancreatic fat fraction and, thus, proposed that CT is a reliable method to quantify pancreatic fat content.

CT has been widely applied to all abdominal organs. Compared with the spleen, the fatty pancreas has a lower HU density [24, 25]. In severe fatty replacement, CT attenuation of the fatty pancreas is comparable to that of adjacent retroperitoneal fat. When the disease is severe, steatosis can be distinguished from pancreatic hypoplasia by evaluating the ductal system, as the ductal system will be involved in fat replacement but not in pancreatic hypoplasia. Plain CT is preferred because the normal pancreatic parenchyma between fatty areas can lead to CT contrast enhancement, allowing CT signals arising from focal fatty replacement to resemble those from a real mass.

When validating CT diagnosis of PS, the fat/parenchyma ratio calculated from CT is analogous to histological evaluation. Moreover, Kim et al. found that pancreatic fat fraction in the histological evaluation was significantly correlated with the difference between pancreatic and splenic attenuation on CT ($P < 0.01$) and the pancreas-to-spleen attenuation ratio ($P < 0.01$). CT is well suited to image the pancreas due to its short acquisition time, high availability, and wide range of clinical applications. However, ionizing radiation and the use of intravenous contrast agents compromise its use in research, especially in serial studies. Contraindications to intravenous imaging include renal damage (associated with diabetic nephropathy), which is a major challenge in the evaluation of diabetic patients [26].

Pancreatic fatty infiltration can be seen on CT when interlobular fat is increased, but there are no standardized criteria for CT diagnosis of PS. Various techniques have been applied, including the calculation of pancreatic attenuation on unenhanced CT images using three ROIs on the head, body, and tail of the pancreas. Using this method to determine the average pancreatic attenuation, the threshold for diagnosing PS is <36 HU [24]. Other studies have used the ratio of pancreatic to splenic attenuation on unenhanced and post-contrast arterial and portal venous phase CT to demonstrate significant correlations with histological fat fractions. More complex segmentation methods have been proposed, including the use of semi-automatic techniques to determine pancreatic margins, with subsequent histogram analysis with local thresholding [24, 25]. Pancreatic ectopic fat is unevenly distributed throughout the organ, and certain fat infiltration patterns may have specific clinical relevance. CT cannot distinguish between fat in adipocytes and intracellular fat in parenchymal cells, so a given ROI may not accurately represent total organ fat. Pancreatic margins are not clearly displayed on CT, especially in case of atrophy, which will complicate the location of the ROI and may lead to partial volume effects [26].

2.5 MRI diagnosis

MRI is a sensitive, non-invasive, and safe examination method. For these reasons, it is currently the most commonly used method to evaluate pancreatic fat content, especially in prospective studies. Single-voxel MRS is considered almost equivalent to histological and biochemical measurements, so it is currently the standard measurement method for pancreatic lipomatosis [27, 28].

To determine the severity of PS, the area of steatosis as a percentage of total pancreatic volume is measured using the T1W and T2W sequences and divided into grades 1-3, which have steatosis scores of 0-33%, 34-66%, and 67-100% for the whole pancreatic tissue, respectively [29].

Currently, there is strong evidence that MRI and MRS can be used to detect and quantify PS. Similar to CT, MRI and MRS are non-invasive and reproducible techniques to measure the fat content of the entire pancreas. MRI is based on signal differences between fat and water, whereas MRS is based on differences in proton resonance frequency. Pancreatic fat content determined by MRS has a good correlation with the biochemically determined triacylglycerol content of the pancreatic islets, suggesting that MRS-determined fat content of the entire pancreas is a useful surrogate marker for the fat content of the pancreatic islets. However, MRI and MRS still have some limitations, such as high cost, long scanning duration, and susceptibility to MR chemical shift artifact as a result of the surrounding visceral fat [30, 31].

2.5.1 MRI

MRI is the best imaging technique to assess PS. The technique can measure pancreatic fat in several manner, with the three most common methods being the in-phase/opposed-phase technique, Dixon method, and spectral-spatial excitation techniques. Wong et al. [32] found that the prevalence of steatosis in Chinese volunteers in Hong Kong was approximately 16% using fat-water MRI and proton MRS and observed that central obesity, hypertriglyceridemia, and hyperferritinemia were related to fatty pancreas. The study also pointed out that individuals with fatty pancreas have greater insulin resistance but no obvious β-cell dysfunction. The PDFF includes two major types: MRS-determined (MRS-PDFF) and MRI-determined (MRI-PDFF). Research has shown that MRI-PDFF is better than CAP in detecting steatosis.

Dual-echo imaging at 3.0-T MR is a routine clinical MRI technique based on a dual-echo sequence, and its application to fat quantification is affected by T1 and T2* relaxation. There is no detailed report on the separate influence of T1 and T2* relaxation on pancreatic fat quantification using dual-echo imaging at 3.0-T MR. Yuan et al. [33] verified the influence of T1 and T2* relaxation on pancreatic fat quantification by dual-echo imaging at 3.0-T MR and explored simplified correction strategies for clinical application.

Wong et al. [32] performed fat-water MRI and proton MRS on 685 healthy volunteers from the general population. Among subjects without significant alcohol consumption or any component of metabolic syndrome, 90% had pancreatic fat between 1.8% and 10.4%. Based on the upper limit of normal of 10.4%, 110 (16.1%; 95% confidence interval 13.3%–18.8%) subjects had fatty pancreas. Multivariable analysis indicated that high serum ferritin levels, central obesity, and hypertriglyceridemia were independent factors associated with fatty pancreas. Subjects with both fatty pancreas and fatty liver had higher homeostatic model assessment-insulin resistance (HOMA-IR) than those with either condition alone. Fatty pancreas was not associated with HOMA-β after adjusting for liver fat and BMI.

MR signals of biological tissues mainly come from protons in water and fat molecules. The protons in the two molecules exist in slightly different chemical environments and thereby have slightly different resonance frequencies, which can be used for quantification [30]. MR methods that have been applied to pancreatic fat quantification include MRS and MRI. Early research focused on chemical shift imaging, which evolved into a spectral-spatial fat-selective method, multipoint Dixon technique, and finally the PDFF method. PDFF can be measured by MRI to quantitatively assess the steatosis of ROIs. Although PDFF is usually used for liver steatosis quantification, pancreatic PDFF varies greatly depending on the location of the ROI due to heterogeneity of pancreatic fat accumulation [33].

Fat-water MRI is a useful non-invasive tool for quantitative fat analysis. PDFF calculation is a chemical shift-based water and fat separation technique. Based on T1 relaxation and chemical shift properties, it can separate fat (F) and water (W) components and differentiate fat from lean tissues. When ROIs are set in the organ of interest, the software computes fat percentage in the ROIs on a voxel-by-voxel basis. This fat percentage, also known as PDFF, is calculated by the following formula: $PDFF=F/(F+W) \times 100\%$ [34].

Chemical shift imaging (CSI) refers to the acquisition of imaging signals at two or more echo time intervals to match the chemical shift between the main peaks of fat and water. Next, the generated "in-phase" and "out-of-phase" images (where fat and water have constructive and destructive interference, respectively) can be subtracted to estimate the fat content. Qualitative assessment of fat content is feasible, but quantification of tissue fat content is susceptible to inhomogeneity of the background magnetic field (B_0) and difficulty in the quantitative measurement of very-high/low-fat fractions [30, 35].

TMR
doi: 10.53388/ghr2021-03-030

This is a major challenge in a small organ such as the pancreas, where small volume islands of pancreatic parenchymal tissue, surrounded by infiltrating extralobular fat, are prone to quantification errors arising from high extralobular fat content, low pancreatic parenchymal fat, and partial volume (where both extralobular fat and parenchymal fat co-exist within a voxel) (Figure 1). Studies using CSI have reported correlations between pancreatic and visceral fat but no association with insulin resistance, BMI, subcutaneous adiposity, or other metabolic syndrome features once data were adjusted for the effects of age, sex, and visceral adipose tissue [36-38].

Several methods to overcome the limitations of CSI have been proposed. Spectral-spatial fat-selective imaging overcomes the challenge of B_0 inhomogeneity, errors arising from noise when quantifying small fat fractions, and imaging artifacts that arise at fat-water interfaces (seen at pancreatic tissue boundaries). Using high-quality local shimming, spectral-spatial fat-selective imaging applies spectral- and spatial-selective excitations within a multislice imaging scheme to generate fat fraction maps. No correlation between spectral-spatial fat-selective pancreatic and liver fat has been reported. However, a negative correlation has been reported between pancreatic fat and insulin secretion in patients with impaired glucose tolerance.

The multipoint Dixon method is developed to overcome the challenges of B0 inhomogeneity and ambiguity due to fat content being >50%. Standard CSI relies on signal amplitudes obtained from at least two echo times; by imaging at three or more echo times, complex data (including amplitude and phase images) can be used to map B_0 and correct for inhomogeneities and estimate fat fractions exceeding 50%. This is important as while pancreatic intralobular fat fractions are low, infiltrating (extra and interlobular) fat is likely to have fat fractions >50%. Multipoint Dixon methods have been applied to the pancreas with varying additional modifications for improvement of measurement accuracy.

2.5.2 MRS

MRS is generally regarded the gold standard for non-invasive pancreatic fat quantification. This technology requires the user to manually position a voxel usually in dimensions of 2.0 × 1.0 × 1.0 cm or a volume of 2.0 cm^3 to include as much pancreatic tissue as possible (while avoiding blood vessels and the main pancreatic duct) to derive a resonance frequency histogram (spectrum) of the constituent proton signals (Figure 2). Measured raw spectra are then fitted to the expected spectra, and the relative area under spectral peaks of interest (water peaks and detectable peaks for chemical environments of protons within fat) is used to estimate voxel fat fraction.

Deriving spectra from such a small voxel requires high-quality local shimming and multiple averaging, thereby extending acquisition time. Therefore, susceptibility to respiratory motion and cardiac motion artifacts (from adjacent pulsating arteries) is a major challenge. Voxel contamination and extra-pancreatic tissue (usually visceral or peritoneal fat) impair shim quality and can cause significant changes in measured spectra. Early studies reported that significant increase in lipid signals in some measured spectra may be caused by the subject's deep breathing. It has been shown that respiratory and cardiac gating can reduce this challenge, which, however, extends the acquisition time (as much as 30 min per voxel). Even with respiratory gating, it is reported that the data exclusion rate due to motion artifacts is as high as 8%. As the imaging protocol may require multi-voxel measurement and additional sequences, prolonged acquisition times will in turn cause discomfort to the subject, thereby exacerbating the patient's motion [39]. Operator expertise in the placement of the MRS voxel is also required. Spatial mismatch arising from the time between anatomical imaging used to plan the MRS study and MRS acquisition has also been reported as a source of error. A common problem with MRS and other imaging-based methods of MR fat quantification is fitting raw spectra for quantification [40]. The fitting process involves prior knowledge of where the spectral peaks may appear, which depends on the chemical environment of the intracellular fat and varies from tissue to tissue. A single broad 1.3 ppm (methylene group) peak has been proposed for the pancreas, but the same peak also appears in extracellular fat, making it difficult to determine whether a measured pancreatic spectrum is the result of voxel contamination or arises from intralobular pancreatic tissue itself (Figure 2). However, fitting to incorrect spectra has significant effects on quantification [37]. Finally, intralobular pancreatic fat content is very low and prone to noise-related errors. Even MRS-determined pancreatic fat content may increase in DM patients, which is likely to represent increased fatty infiltration (i.e., extralobular fat within the MRS voxel) and age-related loss of β-cell mass (and parenchymal volume) rather than an impaired β-cell function arising from a true increase in intralobular fat [37].

Due to these technical challenges, the repeatability and reproducibility of the reported pancreatic MRS measurements have been poor and consistently lower than the liver measurements. In addition, reported associations between MRS-based measurements of pancreatic fat and metabolic factors have been conflicting. MRS studies have confirmed that pancreatic fat increases in case of DM, obesity, and impaired glucose tolerance [40]. No association with visceral fat has been reported, and data on the association with β-cell function has been inconsistent [39].

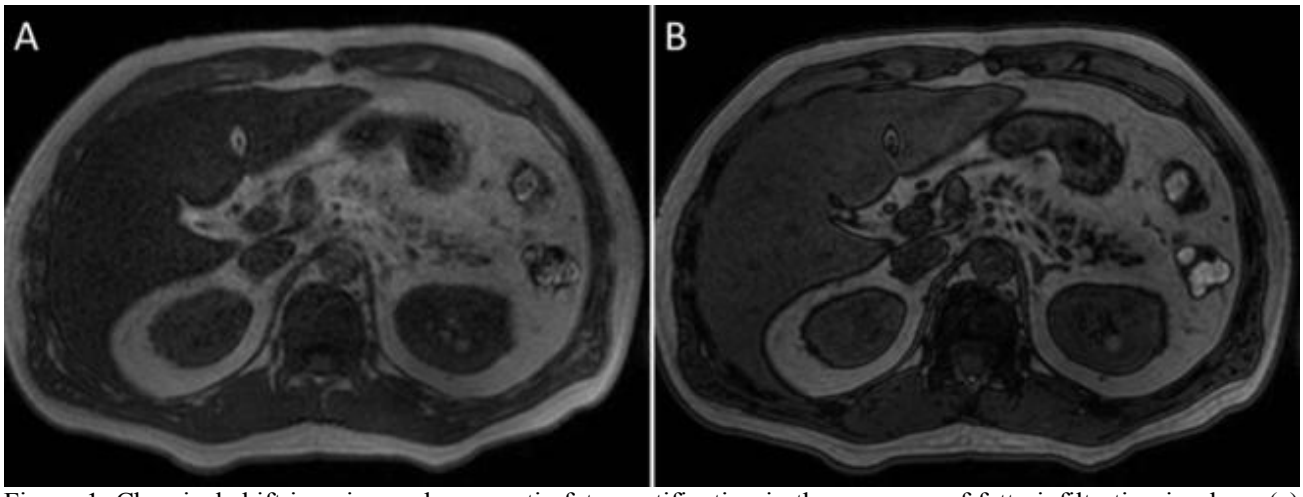

Figure 1. Chemical shift imaging and pancreatic fat quantification in the presence of fatty infiltration in-phase (a) and out-of-phase (b) CSI with significant pancreatic fatty infiltration.
Note the "India-ink" artifact at fat-water interfaces on out-of-phase images (b), which, when combined with in-phase imaging, makes quantification in small islands of the tissue prone to partial volume errors.

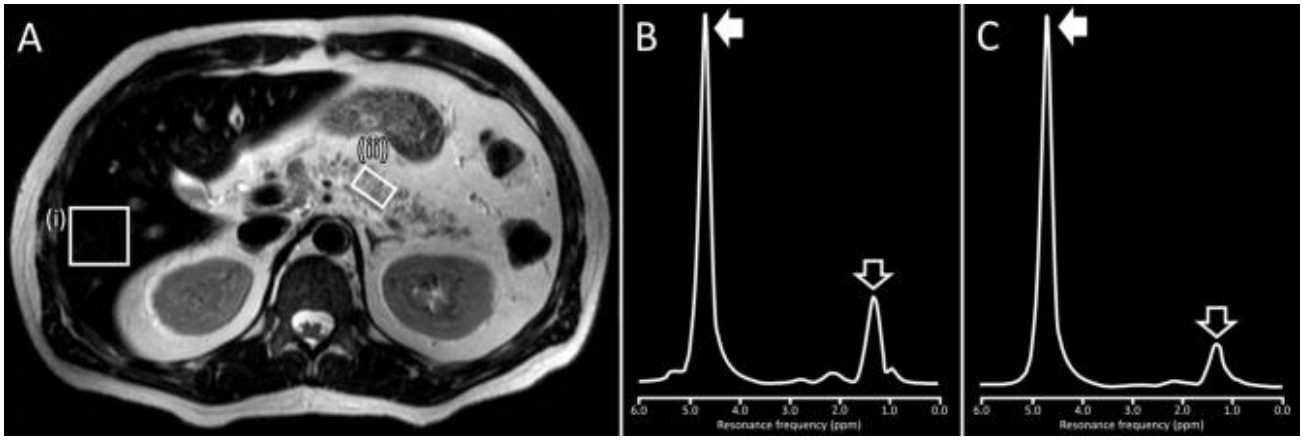

Figure 2. MRS and the different spectral complexity of pancreatic fat MRS study planning (a) of the liver (i) and pancreas (ii), with corresponding spectra arising from the liver (b) and pancreatic (c) voxel.
Note different voxel sizes and the challenge of ensuring the inclusion of purely pancreatic tissue within the MRS voxel (a, ii). The water peak is shown in both spectra (b, c) at 4.7 ppm (solid white arrow). Liver fat spectra (b) demonstrate six peaks (at 5.3, 4.2, 2.75, 2.1, 1.3, and 0.9 ppm), while pancreatic fat spectra (c) are dominated by a single 1.3-ppm methylene peak (clear white arrow). It is not known if this reflects genuine pancreatic fat content or contamination from extra lobular fat.

2.5.3 PDFF mapping

PDFF imaging addresses the limitations of multipoint Dixon quantification, many of which are particularly relevant to pancreatic imaging (Figure 3). In chronic pancreatic inflammation, T1 weighting is altered and can amplify the relative fat signal [41]. By ensuring that the acquisition flip angle is as small as possible, errors caused by T1 signal deviation can be reduced. T2 and T2* can both be altered by pancreatic pathology (inflammation and pancreatic iron deposition, respectively). In addition, the decay of T2 and T2* in the process of fat signal collection will also affect fat quantification, and PDFF mapping accounts for such spectral complexity of fat by modeling fat signal using multipeak fat models, rather than a simple single peak model [35]. Finally, low-fat fractions, as observed in measurements of intralobular pancreatic fat, are subject to noise bias. Complex data containing positive and negative signals tend to underestimate, while magnitude-based methods tend to overestimate true fat fraction [37]. Phase-constrained/magnitude discrimination methods have been applied to minimize these errors.

Pancreatic PDFF validation data with MRS are limited, partly because of some of the limitations of pancreatic MRS [40] and non-uniform distribution of fat in the pancreas, as measured with PDFF [42]. The association of pancreatic PDFF with DM is controversial, and large-sample studies report increased levels of pancreatic fat [43, 44]. Association with insulin resistance has also been reported, as has modest associations with visceral and subcutaneous adiposity.

doi: 10.53388/ghr2021-03-030

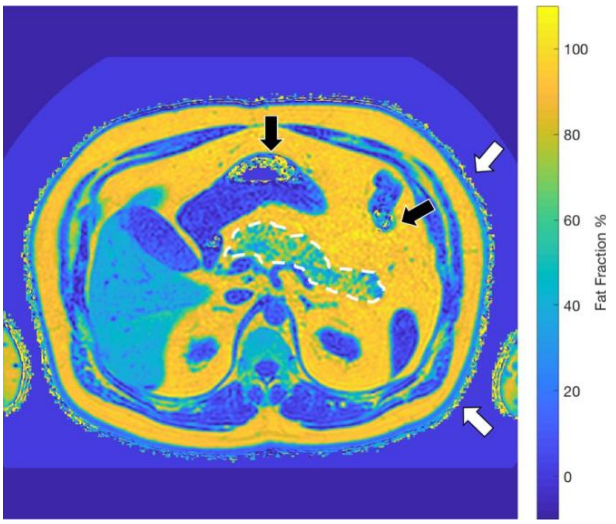

Figure 3. Water-only and fat-only PDFF images are used to generate a parametric fat fraction map across an axial slice.
Note low pancreatic intralobular fat fractions (despite fatty infiltration, white-dashed outline). Errors arising from intraluminal (solid black arrows) and peripheral gas (solid white arrows) result in incoherent pixilation.

3. Prospect

MRI-PDFF is currently the most advanced MR fat quantification method, but it also has its limitations. The design of PDFF sequences is tailored toward the measurement of hepatic (not pancreatic) fat. Therefore, there is room for optimization, which may lead to more robust quantification. The spectral complexity of pancreatic fat has been fully studied, and it is currently presumed that the *in vivo* spectrum is prone to contamination from extralobular fat. Surgical specimens may be a potential approach but are also likely to include significant extralobular fat (especially in the presence of fatty infiltration). Closely linked to this challenge is the lack of reliable reference standard data for validation. Histological sampling is invasive and tends to be derived from surgical specimens (different from liver biopsy, which is more routine and requires only minimally invasive image guidance). The measured pancreatic fat fraction is usually lower than that in the liver, making it more susceptible to noise. Although the PDFF approach includes methods to minimize noise, a more robust method is needed to deal with the high level of noise that affects pancreatic fat measurements [37].

At present, the major advancement in ultrasound technology for steatosis quantification is the controlled attenuation parameter (CAP). Ultrasound will be significantly attenuated when propagating in fatty liver parenchyma, and the more severe the steatosis, the more significant the attenuation. Therefore, the degree of liver steatosis can be calculated based on the attenuation of ultrasound according to the principles of physics, which is the basic principle for CAP. Due to differences in study populations, the diagnostic cutoff values for CAP are not identical from cohort to cohort, and there is no universally accepted diagnostic cutoff value recommended in the guidelines. There is no large cohort study on CAP detection and analysis for NAFPD. It is necessary to strengthen research in this regard and establish uniform diagnostic standards as soon as possible.

The best imaging technique to assess PS is MRI. MRI-PDFF for hepatic fat quantification is second in accuracy only to pathology as the gold standard. It is necessary for this technique to generate more examination data.

Magnetic resonance elastography (MRE) is an emerging non-invasive technique for the diagnosis of fibrosis. It is operator-independent, not limited by obesity, ascites, or hepatodiaphragmatic interposition of the bowel loops, and allows for the observation of the entire liver, pancreas, and other abdominal organs. Because MRE also measures pancreatic stiffness, it is also affected by pancreatic inflammation. Studies have shown a significant correlation between MRE values and inflammatory activity. To date, diagnosis based on MRE-PDFF has not yet been universally established; thus, more tests and experience are required.

References

1. Khoury T, Asombang AW, Berzin TM, et al. The clinical implications of fatty pancreas: a concise review. Dig Dis Sci. 2017;62:2658-2667.
2. Paul J, Shihaz AVH. Pancreatic steatosis: a new diagnosis and therapeutic challenge in gastroenterology. 2020;57:216-220.
3. Sakai NS, Taylor SA, Chouhan MD. Obesity, metabolic disease and the pancreas-Quantitative imaging of pancreatic fat. Br J Radiol. 2018;91:20180267.
4. Lee JS, Kim SH, Jun DW, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroentero. 2009;15:1869-1875.
5. Romana BS，Chela H, Dailey FE, et al. Non-alcoholic fatty pancreas disease (NAFPD): a silent spectator or the fifth component of metabolic syndrome? a literature review. Endocr Metab Immune Disord Drug Targets. 2018;18:547-554.
6. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15:6184-6223.
7. Smits MM, Van Geenen EJ. The clinical

significance of pancreatic steatosis. Nat Rev Gastroenterol Hepatol. 2011;8:169-177.
8. Mathur A, Marine M, Lu D, et al. Nonalcoholic fatty pancreas disease. HPB. 2007;9:312-318.
9. Matsumoto S, Mori H, Miyake H, et al. Uneven fatty replacement of the pancreas: evaluation with CT. Radiology. 1995;194:453-458.
10. Dite P, Blaho M, Bojkova M, et al. Nonalcoholic fatty pancreas disease: clinical consequences. Dig Dis. 2020;38:193-149.
11. Shilin LI, Liyang SU, Guorong LV, et al. Transabdominal ultrasonography of the pancreas is superior to that of the liver for detection of ectopic fat deposits resulting from metabolic syndrome. Medicine (Baltimore). 2017;96(37):e8060.
12. Wang CY, Ou HY, Chen MF, et al. Enigmatic ectopic fat: prevalence of nonalcoholic fatty pancreas disease and its associated factors in a Chinese population. J Am Heart Assoc. 2014;3:e000297.
13. Uygun A, Kadayifci A, Demirci H, et al. The effect of fatty pancreas on serum glucose parameters in patients with nonalcoholic steatohepatitis. Eur J Intern Med. 2015;26:37-41.
14. Jeong HT, Lee MS, Kim MJ. Quantitative analysis of pancreatic echogenicity on transabdominal sonography: correlations with metabolic syndrome. J Clin Ultrasound. 2015;43:98-10.
15. Lesmana CR, Pakasi LS, Inggriani S, et al. Prevalence of non-alcoholic fatty pancreas disease (NAFPD) and its risk factors among adult medical check-up patients in a private hospital: a large cross sectional study. BMC Gastroenterol. 2015;15:174.
16. Lee JS, Kim SH, Jun DW, et al. Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. World J Gastroenterol. 2009;15:1869-1875.
17. Sepe PS, Ohri A, Sanaka S, et al. A prospective evaluation of fatty pancreas by using EUS. Gastrointest Endosc. 2011;73:987-993.
18. Ustundag Y, Ceylan G, Hekimoglu K. Pancreatic hyperechogenicity on endoscopic ultrasound examination. World J Gastroenterol. 2011,17:2061-2062.
19. Khan NA, Amin MS, Islam MZ. Pancreatic lipomatosis with massive steatorrhea. Mymensingh Med J. 2011;20:712-714.
20. Lesmana CRA, Gani RA, Lesmana LA. Non-alcoholic fatty pancreas disease as a risk factor for pancreatic cancer based on endoscopic ultrasound examination among pancreatic cancer patients: a single-center experience. JGH Open. 2017;1862(10PtB):1260-1272.
21. Yashima Y, Sasahira N, Isayama H, et al. Acoustic radiation force impulse elastography for noninvasive assessment of chronic pancreatitis. J Gastroenterol. 2012;47:427-32.
22. Goertz RS, Schuderer J, Strobel D, et al. Acoustic radiation force impulse shear wave elastography (ARFI) of acute and chronic pancreatitis and pancreatic tumor. Eur J Radiol. 2016;85:2211-2216.
23. Friedrich-Rust M, Schlueter N, Smaczny C, et al. Non-invasive measurement of liver and pancreas fibrosis in patients with cystic fibrosis. J Cyst Fibros. 2013;12:431-439.
24. Lim S, Bae JH, Chun EJ, et al. Differences in pancreatic volume, fat content, and fat density measured by multidetector-row computed tomography according to the duration of diabetes. Acta Diabetol. 2014;51:739-748
25. Sakai N, Taylor SA, Chouhan MD. Obesity, metabolic disease and the pancreas-Quantitative imaging of pancreatic fat. Br J Radiol. 2018;91:20180267.
26. Kim SY, Kim H, Cho JY, et al. Quantitative assessment of pancreatic fat by using unenhanced CT: pathologic correlation and clinical implications. Radiology. 2014;271:104-112.
27. Gaborit B, Abdesselam I, Kober F, et al. Ectopic fat storage in the pancreas using 1H-MRS: importance of diabetic status and modulation with bariatric surgery-induced weight loss. Int J Obes. 2015;39:480-487.
28. Begovatz P, Koliaki C, Weber K, et al. Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans. Diabetologia. 2015;58:1646-1655.
29. Yuan F, Song B, Huang Z, et al. Quantification of pancreatic fat with dual-echo imaging at 3.0-T MR in clinical application: how do the corrections for T1 and T2* relaxation effect work and simplified correction strategy. Acta Radi. 2018; 59:1021-1028.
30. Bray TJ, Chouhan MD, Punwani S, et al. Fat fraction mapping using magnetic resonance imaging: insight into pathophysiology. Br J Radiol. 2018;91:20170344.
31. Kato S, Iwasaki A, Kurita Y, et al. Three-dimensional analysis of pancreatic fat by fat-water magnetic resonance imaging provides detailed characterization of pancreatic steatosis with improved reproducibility. PLoS One. 2019;14:e0224921.
32. Wong VWS, Wong GLH, Yeung DKW, et al. Fatty pancreas, insulin resistance, and β-cell function: a population study using fat-water magnetic resonance imaging. Am J Gastroenterol. 2014;109:589-597.
33. Pezzilli R, Calculli L. Pancreatic steatosis: Is it related to either obesity or diabetes mellitus?

doi: 10.53388/ghr2021-03-030

World J Diabetes. 2014;5:415-419.
34. Hu HH, Kim HW, Nayak KS, et al. Comparison of fat-water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. Obesity. 2010;18:841-847.
35. Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging. 2011;34:729-749.
36. Sijens PE, Edens MA, Bakker SJ, Stolk RP. MRI-determined fat content of human liver, pancreas and kidney. World J Gastroenterol. 2010;16:16.
37. Begovatz P, Koliaki C, Weber K, et al. Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans. Diabetologia. 2015;58:1646-1655.
38. Targher G, Rossi AP, Zamboni GA, et al. Pancreatic fat accumulation and its relationship with liver fat content and other fat depots in obese individuals. J Endocrinol Invest. 2012;35:748-753.
39. Szczepaniak LS, Victor RG, Mathur R, et al. Pancreatic steatosis and its relationship to β-cell dysfunction in humans: racial and ethnic variations. Diabetes Care 2012;35:2377-2383.
40. van der Zijl NJ, Goossens GH, Moors CC. Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on β-cell function in individuals with impaired glucose metabolism. J Clin Endocrinol Metab. 2011;96:459-467.
41. Tirkes T, Lin C, Fogel EL, et al. T1 mapping for diagnosis of mild chronic pancreatitis. J Magn Reson Imaging. 2017;45:1171-1176.
42. Kühn JP, Berthold F, Mayerle J, et al. Pancreatic steatosis demonstrated at MR imaging in the general population: clinical relevance. Radiology. 2015;276:129-136.
43. Heber SD, Hetterich H, Lorbeer R, et al. Pancreatic fat content by magnetic resonance imaging in subjects with prediabetes, diabetes, and controls from a general population without cardiovascular disease. PLoS One. 2017;12:e0177154.
44. Idilman IS, Tuzun A, Savas B, et al. Quantification of liver, pancreas, kidney, and vertebral body MRI-PDFF in non-alcoholic fatty liver disease. Abdom Imaging. 2015;40:1512-1519.