



# T1 and T2-mapping in pancreatic MRI: Current evidence and future perspectives

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## ABSTRACT

Conventional T1- and T2-weighted magnetic resonance imaging (MRI) of the pancreas can vary significantly due to factors such as scanner differences and pulse sequence variations. This review explores T1 and T2 mapping techniques, modern MRI methods providing quantitative information about tissue relaxation times. Various T1 and T2 mapping pulse sequences are currently under investigation. Clinical and research applications of T1 and T2 mapping in the pancreas include their correlation with fibrosis, inflammation, and neoplasms. In chronic pancreatitis, T1 mapping and extracellular volume (ECV) quantification demonstrate potential as biomarkers, aiding in early diagnosis and classification. T1 mapping also shows promise in evaluating pancreatic exocrine function and detecting glucose metabolism disorders. T2\* mapping is valuable in quantifying pancreatic iron, offering insights into conditions like thalassemia major. However, challenges persist, such as the lack of consensus on optimal sequences and normal values for healthy pancreas relaxometry. Large-scale studies are needed for validation, and improvements in mapping sequences are essential for widespread clinical integration. The future holds potential for mixed qualitative and quantitative models, extending the applications of relaxometry techniques to various pancreatic lesions and enhancing routine MRI protocols for pancreatic pathology diagnosis and prognosis.

## 1. Introduction

The pancreatic signal intensity in conventional T1- and T2-weighted magnetic resonance imaging (MRI), predominantly based on qualitative criteria, is different depending on the different scanner, the magnetic field and the pulse sequences used. Different signal quantification methodologies in MRI have been studied in the past. Signal intensity ratios, which normalize the signal intensity of the pancreas relative to another organ, such as liver, spleen, or paraspinal muscle, are semi-quantitative estimations and do not measure the absolute tissue relaxation time, thus being limited by image contrast and scanner variation, as well as the fact that the organ chosen for signal normalization differs from patient to patient [1,2]. T1 and T2 mapping, also known as T1 and T2 relaxometry, are modern MRI techniques that allow for non-invasive characterization of body tissues. These techniques are based on the measurement of real longitudinal (T1) and transverse (T2) relaxation

times of hydrogen atoms in tissues, which are influenced by the composition and structure of the tissue itself. T1 and T2 mapping could provide quantitative information about the physiology and pathology of the pancreas, such as fibrosis, inflammation, and neoplasms [3]. This paper aims to review the main current clinical and research applications of T1 and T2 mapping in the pancreas, highlighting the advantages and actual limitations of these techniques.

## 2. T1 and T2 relaxation times

T1 mapping generates a parametric map from a series of images acquired at various longitudinal recovery times, from which the T1 for each voxel can be calculated. T1 reflects the time required for longitudinal magnetization to return to equilibrium after an inversion or saturation pulse. T1 depends on the magnetic field, phase contrast, temperature, and water concentration in the tissue. T1 is shorter in

*Abbreviations:* AIP, Autoimmune Pancreatitis; AP, Acute Pancreatitis; CP, Chronic Pancreatitis; ECV, Extracellular Volume; MRI, Magnetic Resonance Imaging; VFA, Variable Flip Angle.

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tissues with a high protein concentration and rough endoplasmic reticulum, which is rich in protein, such as the pancreas, compared to other surrounding tissues [4–7]. T1 is also influenced by the presence of gadolinium-based contrast agents, which distribute in the interstitial and intravascular space, reducing tissue T1. T1 mapping can be performed with or without gadolinium administration. Native T1 mapping can provide information about tissue composition, such as water, collagen, protein, lipid, and even iron content, considering that iron causes T1, T2, and T2\* to shorten. Pre- and post-contrast T1 mapping can provide information on extracellular volume (ECV), an index of fibrosis and edema [3]. ECV is calculated as the ratio of the contrast distribution fraction in the tissue to that in the plasma. Post-contrast T1 mapping and hematocrit are needed to calculate ECV fraction.

T2 mapping generates a parametric map from a series of images acquired at various transverse decay times, from which the T2 for each voxel can be calculated. T2 reflects the time required for the loss of phase coherence of transverse magnetization after an excitation pulse. T2 depends on the presence of spin-spin interactions, which are more frequent in tissues with a high-water concentration, such as the pancreas. T2 is also influenced by the presence of superparamagnetic substances, such as iron and deoxyhemoglobin, which generate local field heterogeneity thus reducing tissue T2 and especially T2\*. T2 mapping can be performed with a spin-echo sequence, measuring true T2, or with a gradient-echo sequence, measuring T2\*, a combination of T2 and field heterogeneity. T2 mapping is useful for studying fluid-rich areas or pathology such as edema or inflammation, as these often have longer T2 relaxation times. T2\* mapping can be useful to study magnetic susceptibility effects in hemorrhage or iron deposition.

T1 and T2 mapping can also be acquired simultaneously in a multiparametric mapping acquisition; many of these multiparametric MRI techniques (e.g. MR Fingerprinting), have been used also in pancreatic imaging [8] acquiring T1 and T2 relaxation times of the pancreatic tissues both with a 1.5 T and 3 T equipment, considering that the relaxation times are dependent on magnetic field intensity [9].

T1 and T2 mapping in the pancreas have various clinical and research applications, which will be illustrated in the following paragraphs.

### 3. Current relaxometry sequences and protocols

Several abdominal T1 mapping pulse sequences are currently available on systems of various manufacturers (Fig. 1), but there is no consensus in literature on the ideal sequence for abdominal imaging. In the past, the application of T1 mapping in abdominal imaging was restricted due to long scan times of spin-echo sequences. However, more recent 3D Variable Flip-Angle (VFA) gradient echo and parallel imaging techniques can now generate T1 maps in a single breath-hold [3].

The most studied abdominal T1 mapping pulse sequences are VFA, modified look-locker inversion recovery (MOLLI), inversion recovery snapshot (IR-SNAPSHOT), and saturation recovery single-shot acquisition (SASHA), originally developed for cardiac imaging. VFA generates a T1 map acquiring voxel signals at steady state using multiple flip angles [10]. IR-SNAPSHOT is based on the quantification of longitudinal relaxation after the application of an inversion radiofrequency pulse after which several quick acquisitions are collected at different delay times and fitted using the relaxation model [11]. MOLLI is another inversion recovery sequence where the acquisitions after the inversion pulse are synchronized with ECG to acquire signal only during the diastolic phase [12]. Even SASHA is based on inversion recovery technique but uses a saturation pulse instead of an inversion pulse. A comparison study of these four MRI sequences on the pancreas and liver T1 mapping concluded that IR-SNAPSHOT, MOLLI, and SASHA provide similar almost perfect precision, slightly higher than VFA which however reaches precision higher than 98% [12]. However, MOLLI and SASHA acquire few slices in one breath-hold, whereas IR-SNAPSHOT can acquire slightly more images, therefore risking that the entire volume of the

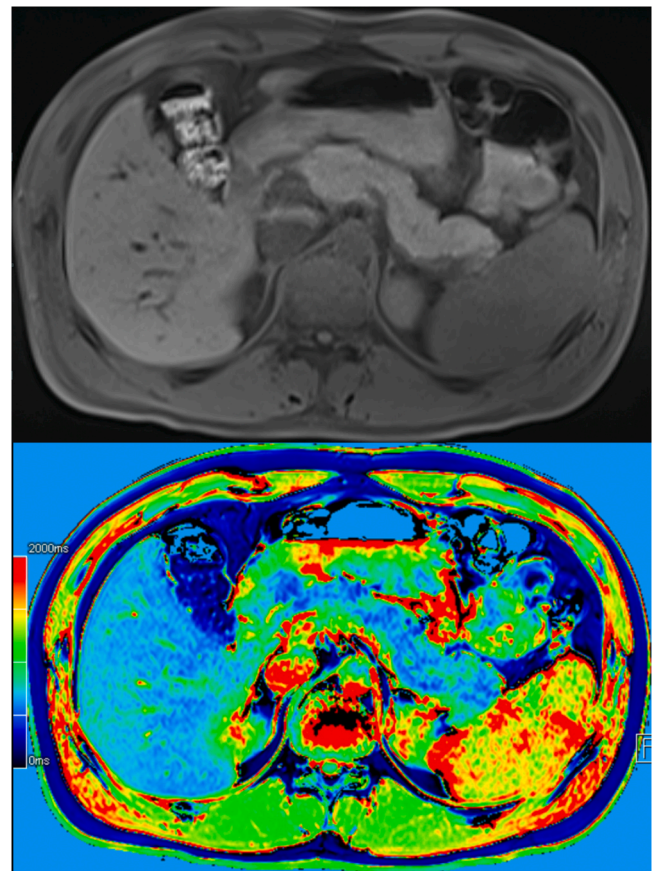


Fig. 1. Healthy pancreas in a 38-year-old patient. Axial T1 VIBE sequence (up) and associated VFA gradient echo sequence providing T1 map of pancreas (down), with mean T1 values of the parenchyma of 580 ms in a 1.5 T scanner.

pancreas is subject to numerous breathing artefacts considering its physiological mobility during the respiratory cycle. Generating a 3D acquisition in a single breath-hold, VFA can overcome this problem, while remaining intrinsically sensitive to pulsatile aortic flow and magnetic field inhomogeneity of the scanner, even if correctable with the application of a B<sub>1</sub> map correction [12,13]. More studies are needed to provide the highest precision in a single breath-hold acquisition with high spatial coverage for abdominal T1 mapping [12,14]. Furthermore, considering that the evaluation of relaxation times is influenced by the presence of fat deposition, fat suppression techniques in T1 mapping are essential for evaluating the relaxation time of pancreatic parenchyma [15].

ECV quantification is a technique which permits to quantify the interstitial space fraction of any tissue, which can be altered by fibrosis and edema [4]. The ECV map is built by performing T1 mapping before and at least 15 minutes after gadolinium administration as an extracellular contrast agent. To generate the ECV map, concentrations of gadolinium is evaluated using both unenhanced and post-contrast equilibrium phases using the T1 relaxation times of the pancreas and the aortic blood. The value is calculated using the formula:

$$ECV = \frac{(1 - \text{hematocrit}) \times \Delta R1p}{\Delta R1b}$$

where  $\Delta R1p$  and  $\Delta R1b$  represent the difference in  $1/T1$  in the pancreas and blood respectively after gadolinium administration which is directly proportional to gadolinium concentration when both tissues are in equilibrium [3]. The hematocrit evaluation is essential because  $(1 - \text{hematocrit})$  should be considered the ECV of blood. Despite the well-known differences in T1 relaxation times between 1.5 T and 3 T,

ECV fractions remain consistent across different magnet strengths [3, 12].

In the past, long acquisition times and motion sensitivity have limited the application of T2 mapping in the abdomen and in the pancreas [2]. Newer pulse sequences with k-space undersampling and respiratory gating can provide pancreatic T2 maps in a few minutes [16]. As with T1 mapping, since T2 mapping is a substantially new technique in the pancreatic field and still the subject of research, there is no consensus on the best MRI sequences for the evaluation of T2 mapping of the pancreas. Half-Fourier acquisition single-shot fast spin-echo (HASTE) and balanced steady-state free precession (bSSFP) readout sequences have been used in the past [17,18]. More recently, respiratory triggered multi-echo spin-echo (MESE) sequences have been successfully used with shorter acquisition time [16]. Moreover, a prototype radial turbo-spin-echo (rTSE) sequence, optimized for multi-slice T2 mapping in the abdomen has been recently used to acquire accurate precise liver T2 maps during one single breath-hold, and the same sequence could be suitable also for fast T2 mapping evaluation of the pancreas in the future [19].

The T2\* mapping is based on focal magnetic field inhomogeneity and is normally performed with gradient echo imaging. Multi-slice multi-echo gradient-echo sequences have been used for the abdomen [20,21]. Those sequences require few breath-hold acquisitions to acquire a T2\* map of the abdomen. Despite the T2\* measurements can be affected by different local magnetic fields of the different scanners, the multi-echo gradient-echo T2\* sequences are proven to be accurate and reproducible for the quantification of pancreatic iron and may be transferred among different MRI scanners [22,23].

#### 4. T1-mapping and ECV quantification

The T1 mapping and ECV quantification appears to correlate with the degree of fibrosis of the pancreatic parenchyma (Fig. 2), therefore current clinical research is mainly oriented towards the study of these techniques in chronic pancreatitis (CP), even if T1 evaluation could be a potential biomarker for several diseases [3]. Reported median T1 of pancreatic parenchyma is around 650 ms at 1.5 T and 720 ms at 3 T, while median ECV values are 0.28 at 1.5 T and 0.25 at 3 T [14,24]. A statistically significant increase in T1 relaxation time was observed in mild chronic pancreatitis compared to healthy pancreatic tissue, thus reflecting the increase in the degree of fibrosis and the reduction of acinar proteins and rough endoplasmic reticulum of the healthy parenchyma [1,5]. The T1 relaxation time cut-off of 900 ms at 3 T is 80% sensitive and 69% specific for mild CP, while ECV greater than 0.27 demonstrated 92% sensitivity and 77% specificity; the combination of T1 and ECV is 85% and 92% sensitive for the diagnosis of mild CP (AUC 0.94) [5]. The current classification of chronic pancreatitis is based only on the modifications of the pancreatic ductal system foreseen by the Cambridge classification, which primarily captures periductal fibrosis and does not directly assess the fibrosis in the rest of the pancreas or the loss of acinar cells, not taking into account the tissue evolutions of the pancreatic parenchyma [25]; T1 mapping and ECV quantification techniques, in addition to diffusion weighted imaging and the morphological changes of the gland visible in conventional MRI, can help in the classification of CP cases, especially in the initial stages such as mild CP, more subject to interindividual evaluation, where still no changes occur in the main pancreatic duct (as in moderate and severe cases) [24,26,27]. Furthermore, a significant difference between the T1 relaxation times and the ECV fraction was demonstrated even between cases of moderate and severe pancreatitis compared to the control groups of healthy patients [25]. More large-scale studies are needed to clarify what the actual T1 relaxation times and ECV values of healthy parenchyma are and what the precise cut-offs are for diagnosing and stratifying the degrees of CP [5].

T1 mapping has been also tested for the exocrine and endocrine evaluation of pancreatic function. A significant negative correlation was

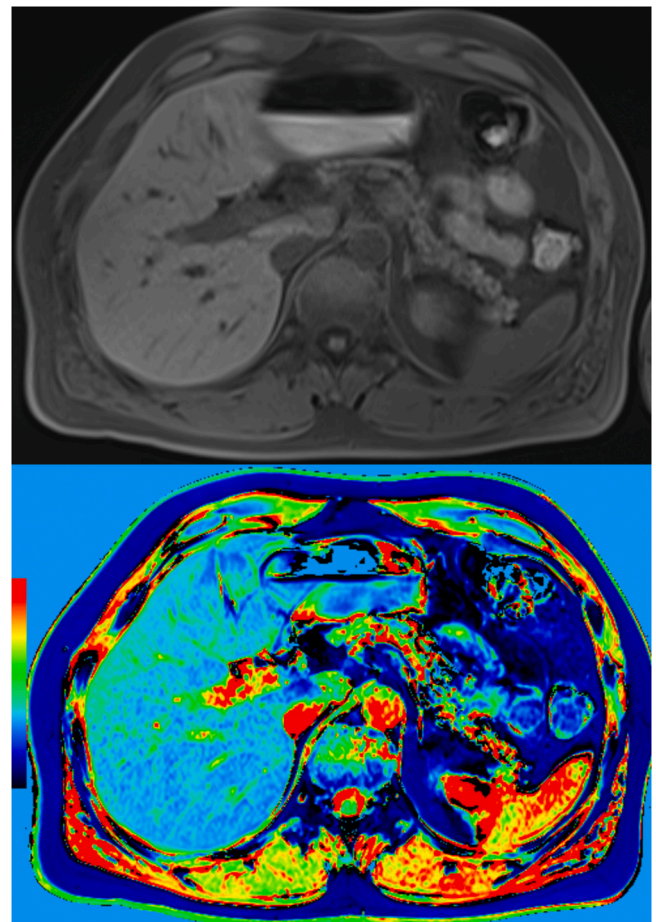


Fig. 2. Chronic pancreatitis in a 67-year-old patient. Axial T1 VIBE sequence (up) and associated VFA gradient echo sequence providing T1 map of pancreas (down), with mean T1 values of the parenchyma of 1124 ms in a 1.5 T scanner.

observed between the parenchymal T1 and pancreatic exocrine function measured by fecal elastase-1 dosage, suggesting the possibility of estimating pancreatic exocrine status by pancreatic T1 mapping [28]. Moreover, pancreatic T1 is reported to be significantly longer in type-2 diabetes mellitus than in no-diabetes and prediabetes subjects, and significantly longer in prediabetes than in no-diabetes subjects [29]. A positive correlation between HbA1c values and both pre-contrast pancreatic T1 and ECV fraction has been observed [30]. Thus, pancreatic T1 can be used for the assessment of impaired glucose tolerance, serving as a potential biomarker for detecting possible glucose metabolism diseases [29,30]. Finally, T1 mapping has been investigated in the quantification of short-term and mid-term response of autoimmune pancreatitis (AIP) to corticosteroid treatment [31,32]. T1 relaxation time of AIP is reported to be significantly longer than normal pancreatic tissue. After 4 weeks of corticosteroid therapy, T1 relaxation time shortened significantly, further shortening towards normalization in 12 weeks. In AIP patients with elevated serum IgG4 at baseline, T1 relaxation time demonstrated a significant positive correlation with serum IgG4 level; in patients with normal serum IgG4, T1 relaxation time shortening preceded or was in accordance with symptom relief, suggesting a promising role of T1 mapping as a treatment outcome measure [31].

#### 5. T2 and T2\* mapping

The study of pancreatic pure T2 relaxation time currently finds few spaces in the literature, which has mainly focused on the study of T2\* mapping especially in the evaluation of pancreatic iron overload. Body

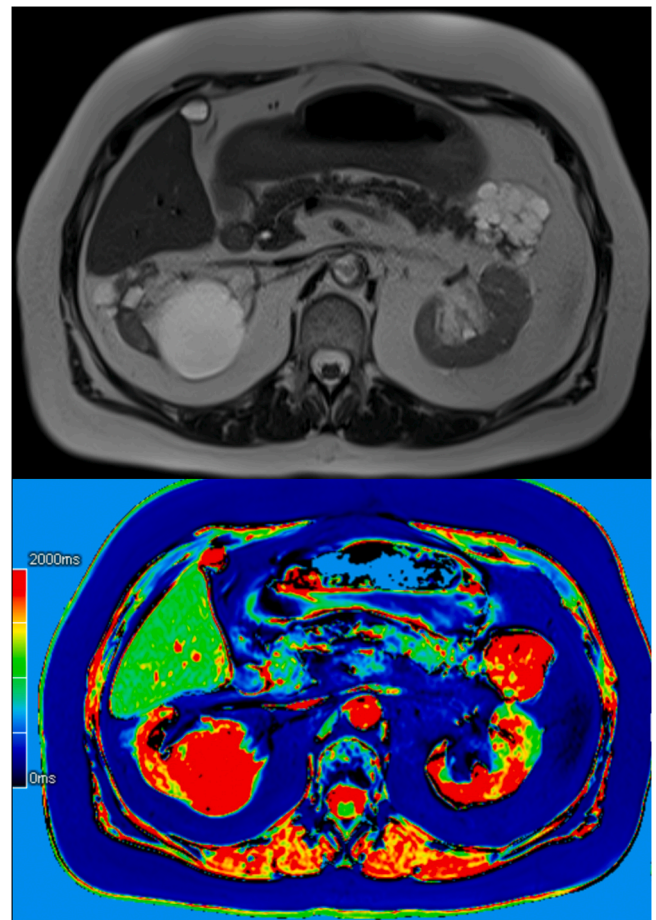


T2\* relaxometry revealed differences in the degree or distribution of iron overload between organs [20]. Quantification of pancreatic iron is clinically important since it might be considered as an early predictor of cardiac siderosis [33]. The reported mean T2\* of healthy pancreas is  $21.06 \pm 2.64$  ms, significantly different between the head and body/tail of the organ [21]. Correlation between T2\* relaxation time as an index of iron overload and beta cell function and glucose metabolism have been studied in thalassemia major patients; in these patients, the T2\* relaxation time is correlated with beta cell reserve and insulin resistance, as well as abnormal glucose metabolism [32,34,35]. The T2\* mapping proved to be an accurate and reproducible technique for the quantification of pancreatic iron and may be transferred among MRI scanners by different vendors [23]. Considering that fatty infiltration can degrade the ability of the MRI to assess iron overload, the application of fat saturation to the T2\* mapping pulse sequence is recommended [22].

Quantification of T2 mapping in acute pancreatitis (AP) is poorly studied but can potentially be a useful biomarker considering the higher T2 of the edema [32]. MRI is not essential for the detection of AP, but is useful in assessing its severity and complications. Conventional contrast enhanced T1-weighted and T2-weighted MRI can assess morphologic changes of pancreatitis, such as pancreatic enlargement, edema, and fluid collections, also differentiating viable from necrotic tissue, thus differentiating between interstitial edematous and necrotizing pancreatitis. T2 mapping could be useful to quantify the degree of pancreatic edema and inflammatory changes, providing a prognostic assessment [2,16]. Moreover, T2\* relaxation time of the pancreas in AP is higher than in healthy pancreas and is significantly different between edematous AP and necrotizing AP, in which local hemorrhage could result in a decreased T2\* and signal loss [21]. T2\* also correlates with the Magnetic Resonance Severity Index (MRSI) of pancreatitis, therefore potentially contributing to assessing AP severity [21].

## 6. Actual limitation and future perspectives

The use of T1 and T2 mapping in clinical practice currently still has limitations. First of all, there is still no consensus between which sequences are most suitable, fast and reproducible on a large scale, providing comparable and precise values between different scanners from different vendors, both on 1.5 T and 3 T. Furthermore, normal values of a healthy pancreas and the precise cut-offs beyond which a disease can be detected have not yet been widely studied, and further large-scale studies will be necessary in this sense. Furthermore, the mapping sequences will need to be perfected to ensure robust and reproducible results even in reasonable times, in order to be able to be integrated into routine MRI abdominal analysis protocols in the future [24]. Once large-scale pancreatic relaxometry MRI techniques will be validated, the integration of these methods into the main guidelines and classifications, creating mixed qualitative and quantitative models, will be a probable future prospect [25]. Moreover, the application of these methods will be extended not only to the evaluation of diffuse and inflammatory pathology of the pancreas, but also to focal lesions, studying what the benefit of such methods could be in the tissue characterization of cystic (Fig. 3) and solid lesions of the pancreas, such as ductal adenocarcinoma [36]. Finally, the development of multiparametric sequences will further expand the possibility of pancreatic tissue characterization in the future. Even if coronal acquisition was found to be more optimal for studying the upper abdomen in order to avoid most of the artefacts encountered with axial imaging, challenges associated with multiparametric sequences are the same for any quantitative MRI technique: motion, spatial resolution, field non-uniformity, magnetization transfer and partial volume [9]. The improvement of these MRI sequences in the near future will therefore expand the use of these techniques, probably allowing them to be introduced into normal clinical routine to support diagnosis and prognosis of pancreatic pathology in a fast, easy, cost-effective and reliable manner.



**Fig. 3.** Pancreatic tail serous cystadenoma in a 52-year-old patient. Axial T2 HASTE sequence (up) and related axial VFA gradient echo sequence (down) providing T1 map of the upper abdomen showing the spatial resolution of the modern mapping sequences.

## 7. Conclusion

T1 and T2 mapping, T2\* and ECV imaging represent promising MRI techniques for the evaluation of pancreatic physiology and pathology in a fast and reproducible manner. These methods will need to be validated in large population studies before being introduced into clinical practice.

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**Giovanni Morana:** Writing – original draft. **Davide Canonico:** Validation. **Alessandro Belei:** Writing – original draft.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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