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Normal T_1 Relaxometry and Extracellular Volume of the Pancreas in Subjects with No Pancreas Disease – Correlation with Age and Gender

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Abstract

OBJECTIVE—Determine normal T_1 and extracellular volume (ECV) of the pancreas in subjects with no pancreas disease and correlate with age and gender

SUBJECTS AND METHODS—We imaged 120 healthy subjects (age range: 20-78 years) who are on annual screening with MRI/MRCP for the possibility of pancreatic cancer. Subjects had a predisposition to develop pancreatic cancer, but no history of pancreas disease or acute symptoms. Equal number (n=60) of subjects were scanned on either 1.5 T or 3 T scanner using dual flip angle spoiled gradient echo technique incorporating fat suppression and correction for B_1 field inhomogeneity. Optimization of imaging parameters were performed using a T_1 phantom. ECV was calculated using pre- and post-contrast T_1 of the pancreas and plasma. Regression analysis and Mann-Whitney tests were used for statistical analysis.

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Disclosures
None

Review Board:
This study was approved by the Institutional Review Board and the requirement for informed consent was waived.

RESULTS—Median T_1 on 1.5 T was 654 ms (IQR: 608-700); median T_1 on 3 T was 717 ms (IQR: 582-850); median ECV on 1.5 T was 0.28 (IQR: 0.21-0.33) and median ECV on 3 T was 0.25 (IQR: 0.19-0.28). Age had a mild positive correlation with T_1 (r= 0.24, p= 0.009), but not with ECV (r= 0.06, p=0.54). T_1 and ECV were similar in both genders (p >0.05).

CONCLUSION—This study measured the median T_1 and ECV of the pancreas in subjects with no pancreas disease. Pancreas shows longer T_1 relaxation times in older population, whereas extracellular fraction remains unchanged. Median T_1 values were different between two magnet strengths; however, no difference was seen between genders and ECV fractions.

Keywords

Pancreas; MRI; Quantitative Imaging; T1 Relaxometry; Extracellular Volume

INTRODUCTION

Quantitative MRI is becoming increasingly common in current radiology research and practice, assisting in the clinical assessment of many patients with a spectrum of diseases [1]. Novel quantitative MR imaging techniques provide in vivo characterization of tissues and has potential to be a non-invasive biomarker to diagnose certain solid organ pathologies. Quantitative imaging metrics can also be used to monitor the course of therapy in clinical trials [2]. T_1 relaxometry measures the specific T_1 relaxation time of a tissue. A number of quantitative MRI studies have been published reporting the alterations of T_1 in a variety of pathologic conditions in the abdomen [3–5]. These studies focused on detecting tissue fibrosis; seen with cirrhosis [6–8], chronic pancreatitis [9] and kidney failure [10]. T_1 measured during pre and post-contrast phase are used to calculate the extracellular volume (ECV). ECV imaging calculates the extracellular fraction of a solid organ, which is known to increase as a result of adverse tissue remodeling leading to tissue fibrosis [4,5]. It has been shown to be useful for evaluation of myocardial fibrosis [11,12], cirrhosis [8,4] and chronic pancreatitis [5]. However, there is insufficient data on normal quantitative metrics of the pancreas and correlation with biometric parameters (e.g., age and sex). More investigations are needed to determine the normal values and reach a consensus on the amount of change that should be considered clinically significant pathology. The purpose of this study was to determine normal T_1 and ECV of the pancreas in subjects with no pancreas disease and correlate these quantitative metrics with age and gender.

SUBJECTS and METHODS

Subjects

This study was compliant with the Health Insurance Portability and Accountability Act and waiver of informed consent was obtained from the Institutional Review Board. We prospectively imaged 120 non-consecutive subjects between June 2016 and December 2018. The subjects were enrolled in the pancreatic cancer screening program and were being screened annually for pancreatic cancer with magnetic resonance cholangiopancreatography (MRCP). The purpose of this screening program is to do surveillance on subjects with a family history of pancreatic cancer or was found to have a genetic predisposition (e.g.,

positive BRCA) to develop pancreatic cancer, but otherwise were healthy individuals. All subjects were screened with serum amylase, lipase, AST, alkaline phosphatase, CEA, CA19-9, and c-peptide levels before enrolling into the program. MRCP images of all the subjects were reviewed by a single radiologist and only those with Cambridge grade 0 (normal) [13] were included in the study. Subjects who did not receive intravenous contrast (n=17), diagnosed with cystic pancreatic neoplasm (n=11) or pancreatic adenocarcinoma (n=1) were also excluded from the study.

T_1 imaging

T_1 maps were acquired at pre-contrast and 6-minute late enhancement phases using a dual flip angle three-dimensional (3D) spoiled gradient echo technique (Figure 1). Subjects were imaged on either 1.5 T (Magnetom Avanto Fit, Siemens Medical Solutions, Malvern, PA) or 3 T scanner (Magnetom Verio, Siemens Medical Solutions, Malvern, PA) using a commercially available T_1 mapping pulse sequence (MapIt, Siemens Medical Solutions, Malvern, PA). Fat suppression was not utilized. Vendor supplied correction for B_1 field inhomogeneity was employed. The imaging parameters were; 48 axial slices of 4 mm thickness, field of view of 360, acquisition matrix of 320 ×168 and parallel imaging factor of 2 (Siemens GRAPPA). The 1.5 T scanner used TR of 7.4 ms, TE of 2.39 ms, flip angles of 3° and 19°, while the 3 T scanner used TR of 3.87 ms, TE of 1.32 ms and flip angles of 2° and 13°. Acquisition time was approximately 20 sec (1 breath hold). T_1 maps were reconstructed on the MR scanner using vendor supplied software. To ensure accurate measurements of the T1, phantom testing was performed using a commercially available unit (System phantom model 130, High Precision Device, Inc.,). This phantom includes an array of elements of which T_1 values were verified by the National Institute of Standards and Technology (NIST). The phantom tests showed excellent precision for both 1.5 T (ρ_c = 0.9962) and 3 T scanners (ρ_c = 0.9974).

ECV imaging

Gadobenate dimeglumine (MultiHance, Bracco Diagnostics Inc., Monroe Township, NJ) was administered in all subjects using the manufacturer recommended dose of 0.1 mmol/kg. T_1 relaxation time was measured by a single radiologist in pre and post-contrast phases, using average of the region of interest values obtained from the head, body, and tail of the pancreas. Attention was given to obtain the signal from the homogenous part of the gland, excluding the duct and vessels. The approximate diameter of the circle region of interest was 15 mm. Blood pool signal was obtained from the aortic lumen to find out the plasma T_1 relaxivity. The aortic lumen signal is prone to inflow artifact and therefore, T_1 was measured from the aortic lumen by taking the average ROI value of 5 consecutive image slices below the level of pancreas. These values were entered into this formula to calculate ECV fraction:

$$ECV = \frac{(1 - \text{hematocrit}) \times \Delta\, \text{R1}\ target}{\Delta\, \text{R1}\ blood}$$

where $\Delta R1_{target}$ and $\Delta R1_{blood}$ are defined as the change of $1/T_1$ relaxation rate in pancreas and blood pool relaxivity before and after contrast administration. T_1 is a time constant describing the longitudinal relaxation rate, and its reciprocal ($1/T_1$) is referred to as R_1. The

change in R_1 (ΔR_1) is defined as: ΔR_1 = (R_1 post-contrast) – (R_1 pre-contrast). ΔR_1 is proportional to Gadolinium (Gd) concentration when both tissues are in equilibrium; ΔR_1 pancreas / ΔR_1 blood = $[Gd]_{pancreas}$ / $[Gd]_{blood}$. Since the gadolinium chelates, such as Gd-BOPTA are extracellular agents, the ratio of contrast agent concentrations between pancreas and blood equals the ratio of extracellular volume between the tissues: $[Gd]_{pancreas}$ / $[Gd]_{blood}$ = $ECV_{pancreas}$ / ECV_{blood}. The ECV of the blood is defined as the fraction of the blood volume which is not composed of blood cells, in other words, the fraction composed of plasma. The plasma volume was easily calculated as: ECV_{blood} = [1 – hematocrit], ECV maps were generated offline, using a prototype software (MR Arithmetics; Siemens Healthcare) (Figure 2). Non-rigid registration was also performed using this software between the pre- and post-contrast T_1 maps to eliminate misregistration due to differences in breath hold.

MRCP imaging

Secretin enhanced MRCP was performed following intravenous administration of 16 μg of secretin (ChiRhoStim, ChiRhoClin Inc., Burtonsville, MD) via slow infusion over one minute. Immediately following injection, the pancreas was imaged using a coronal 2D single-shot turbo spin echo sequence (HASTE, Siemens Medical Solutions, Malvern, PA), which is repeated every 20 seconds up to 8 minutes. No adverse events were encountered.

Statistical analysis

Regression analysis was used to evaluate the correlation of the T_1 and ECV with the age. Correlation coefficients were interpreted as; mild, 0.2; moderate, 0.5; strong, 0.8; and perfect 1.0 [14], Mann-Whitney test was used to determine the median and interquartile range (IQR) at different age groups for the T_1 and ECV, also for assessing the differences between the gender, 1.5 T and 3 T magnet strengths. If the resulting P value is <0.05, a statistically significant difference between the two samples was accepted. The precision of the T_1 imaging technique was evaluated using the concordance correlation coefficient. The concordance correlation coefficient quantifies the agreement between two measures such that when they are plotted against each other, higher concordance correlation coefficient corresponds to a lesser deviation from the 45-degree line. The scale of concordance correlation coefficient (ρ_c) is considered as poor <0.90; moderate 0.90-0.95; substantial 0.95-0.99 and almost perfect >0.99 [15]. Statistical analyses were performed using MedCalc version 18.11.3 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Subjects were between 20-78 years of age (mean: 48). There were 32 males and 88 females. Table 1 shows that there was no difference between two genders in terms of age of subjects scanned at 1.5 T (p=0.77) and 3 T (p=0.84); ECV at 1.5 T (p= 0.09) and 3 T (p=0.55) and T_1 at 1.5 T (p= 0.47) and 3 T (p= 0.09). Therefore, results from both genders were combined in the analysis.

Table 2 lists T_1 measured at 1.5 T and 3 T scanners. Median T_1 at 1.5 T was 654 ms (IQR: 608-700) and was statistically different than Ti of 717 ms (IQR: 582-850) measured at 3 T

(p=0.03). Table 3 lists the median ECV calculated at 1.5 T and 3 T scanners. Median ECV at 1.5 T was 0.28 (IQR: 0.21-0.33) and was similar to ECV of 0.25 (IQR: 0.19-0.28) at 3 T (p=0.06).

T_1 relaxation time had a mild positive correlation with age (r= 0.24 p= 0.009) (Figure 3). ECV did not have a correlation with age (r= 0.06, p=0.54).

DISCUSSION

T_1 relaxometry and ECV may provide useful applications in the abdominal imaging however more investigations are needed to explore the full potential. The primary objective of this study was to determine the normal T_1 and ECV of the pancreas in subjects with no pancreas disease. We expect that this information can be used as a reference in future studies. Secondary objectives were to determine whether T_1 and ECV change with age, gender or MR signal strength. To our knowledge, none of this information was previously reported in the radiology literature.

Our first observation was that the median T_1 of the pancreas were different between 1.5 T and 3 T scanners when all age groups were combined. It is well known that the longitudinal relaxation time (T_1), is longer at higher magnetic field than at lower magnetic field [16,17] therefore different threshold values should be used for different magnet strengths. As the main B_0 field strength increases, the resonance frequency of the excited spins also increases (from approximately 64 MHz at 1.5 T to 128 MHz at 3 T) [18]. The higher frequency of the spins reduces the efficiency of energy transfer, resulting in longer T_1 relaxation times at 3 T [19]. We found that ECV fractions at 1.5 and 3 T to be similar.

Our second significant finding was that age had a mild positive correlation with T_1. Many studies reported correlation of T_1 signal intensity of the pancreas with fibrosis (determined by histopathology), bicarbonate level measured via endoscopic pancreatic function tests, or evidence of chronic pancreatitis determined by Cambridge classification [20–23]. This is the first study showing that pancreas is slowly losing its shorter T_1 relaxation property over the period of decades. On the other hand, ECV remained the same over a wide range of subjects age (20 – 78 years), indicating that extracellular to intracellular ratio is not altered in subjects with no pancreas disease.

Our third finding was that, both genders had similar ECV fraction and T_1. Therefore, we combined both genders in the analysis.

We used a commercially available T_1 mapping pulse sequence which utilizes 3D dual flip angle spoiled gradient echo technique to acquire T_1 maps of the entire upper abdomen in one breath-hold. Currently, there is no consensus about which T_1 mapping pulse sequence is ideal for abdominal imaging. Conventional Look-Locker T_1 mapping sequences require long imaging times [24] and will be challenging for abdominal imaging which large spatial coverage is essential. Efforts have been made to modify the Look-Locker method [25] by combining it with a stack-of-spirals acquisition accelerated using 3D through-time spiral GRAPPA reconstruction; producing 32 images per breath hold. These new methods require more studies for validation and support from vendors. Recently, a novel approach named

MR fingerprinting was introduced [26]. Instead of using a repeated, serial acquisition of data for the characterization of individual parameters of interest, MR fingerprinting uses a pseudorandomized acquisition that causes the signals from different tissues to have a unique signal evolution or 'fingerprint' that is simultaneously a function of the multiple material properties. The processing after acquisition involves a pattern recognition algorithm to match the fingerprints to a predefined dictionary of predicted signal evolutions. A recent MR fingerprinting study on 14 asymptomatic subjects reported T_1 of the liver, kidney, spleen, skeletal muscle and fat [27] but did not report T_1 of the pancreas.

ECV imaging can distinguish intra- and extracellular spaces of the tissues and calculates the fraction of the extracellular volume. ECV imaging is based on the concept that extracellular matrix increases when tissues are subjected to repetitive inflammation leading tissue remodeling and eventually fibrosis. MRI is an ideal modality to calculate ECV since the gadolinium diffuses from the intravascular to the extracellular space of the tissues. ECV is calculated by measuring the T_1 of the plasma and the target tissue before and after contrast injection. We used the aortic lumen to determine the blood plasma relaxivity since it has a larger diameter than other vessels and has been successfully used in prior studies [5,28]. It should be noted that the dual flip angle sequence is susceptible to pulsatile flow in the aorta. Other pulse sequences with cardiac gating produce more stable aortic signal; however the downside is acquisition of only 1-3 images per breath hold.

One of the limitations of this study was that the population of 120 subjects became small when divided by 6 age groups, especially in the age 70-78 group. The subjects were predominantly females however, results showed that gender difference did not effect T_1 and ECV. Our study included subjects with a genetic predisposition for pancreatic cancer, however, had no known pancreatic disease or symptoms at the time of the study. We further screened the subjects with secretin enhanced MRCP and included only those with Cambridge grade 0. Nevertheless, when determining the normal quantitative MR metrics, it would be ideal to image healthy volunteers at multiple institutions by comparing different MR vendors and imaging techniques.

In conclusion, this study measured the median T_1 and ECV of the pancreas in subjects with no pancreas disease. Pancreas shows longer T_1 relaxation times in older population, whereas extracellular fraction remains unchanged. No difference was seen between genders. Separate T_1 values should be used for 1.5 and 3 T scanners.

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ABBREVIATIONS

ECV	Extracellular Volume
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
3D	Three-dimensional

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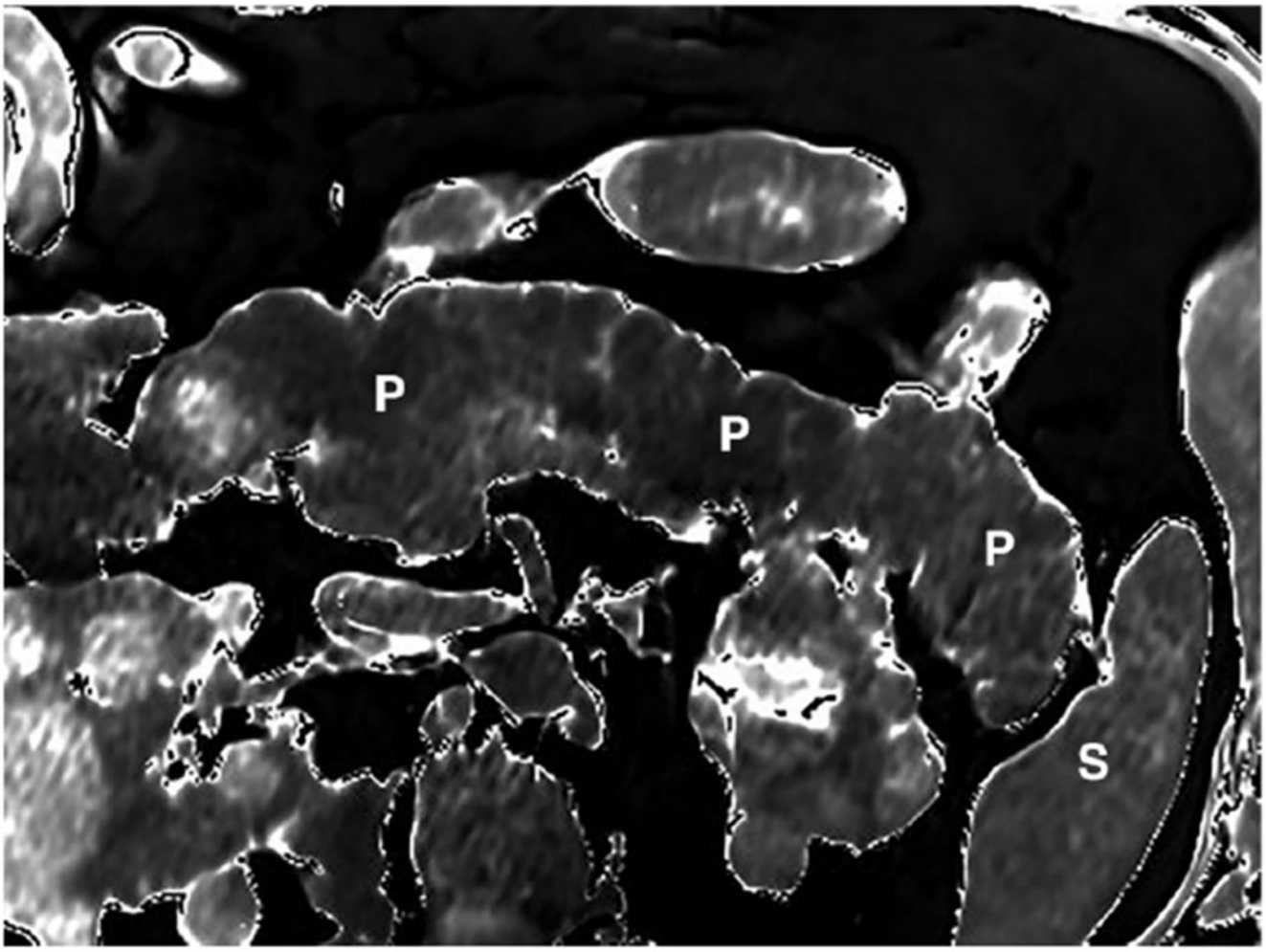

Figure 1.
This is an axial T1 map in a 51-year-old man with family history of pancreatic cancer on surveillance. T1 maps can be depicted either as a grayscale or colormap. Region of interest measurements obtained from the grayscale image reveals the T_1 relaxation time (P: pancreas, S: spleen).

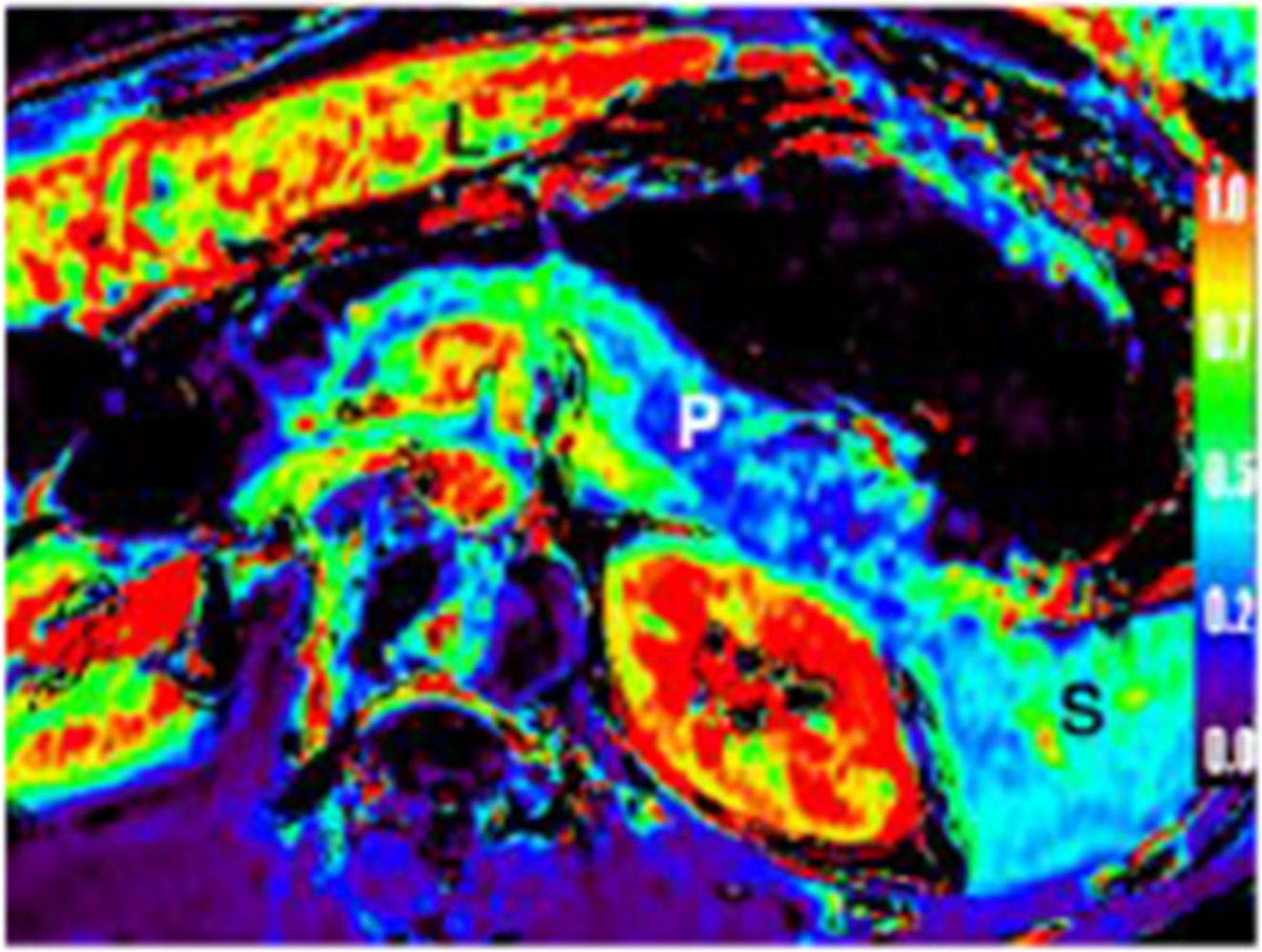

Figure 2.
ECV map of the pancreas. This is a 37-year-old woman with BRCA 2 gene mutation on surveillance for pancreatic cancer. An axial color scale ECV map is shown. (P: pancreas, S: spleen, L: liver)

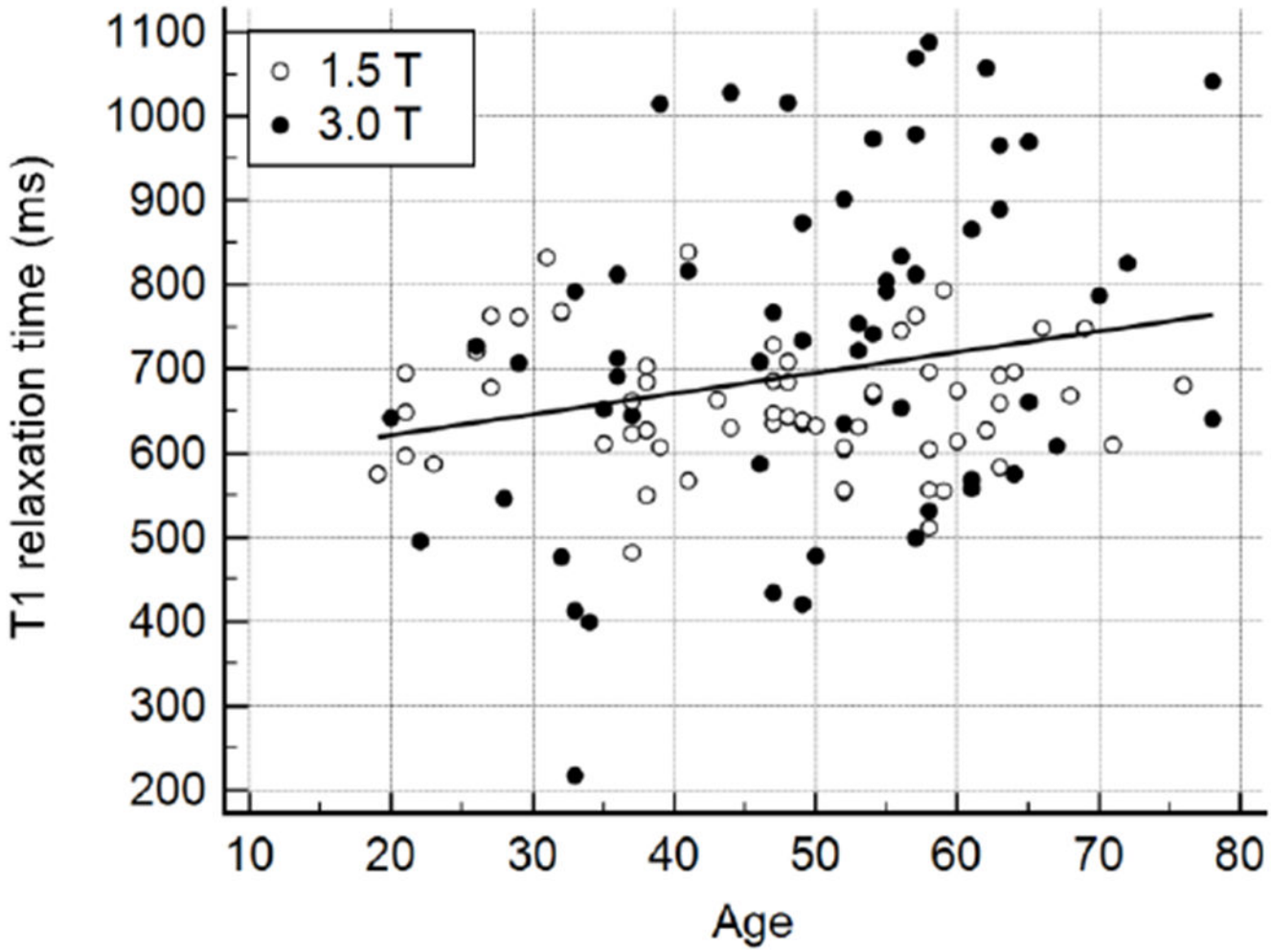

Figure 3.
Effect of age on T_1 properties of the pancreas. There is a mild positive correlation between T_1 relaxation time and age (r= 0.24 p= 0.009).

Table 1.

Effect of gender and MR field strength on T_1 relaxation time (ms) and ECV of the pancreas. There was no statistically significant difference between two genders in terms of T_1, ECV and age.

		Male n=32		Female n=88		
		Median	**IQR**	**Median**	**IQR**	**P value**
T_1 (ms)	1.5 T	659	[571-707]	649	[609-696]	0.47
	3.0 T	636	[551-712]	753	[637-871]	0.09
ECV (fraction)	1.5 T	0.25	[0.17-0.32]	0.29	[0.24-0.34]	0.09
	3.0 T	0.24	[0.20-0.26]	0.25	[0.19-0.29]	0.55
Age (years)	1.5 T	48	[37-59]	48	[37-58]	0.77
	3.0 T	52	[43-58]	52	[43-59]	0.84

ECV: Extracellular volume fraction. IQR=Interquartile range

Table 2.

T_1 relaxation time of the pancreas at 1.5 T and 3 T magnet field strength separated by age groups. There was a significant difference in T_1 between the 1.5 and 3 T when all age groups were combined (p=0.03).

	T_1			
Age Groups	1.5 Tesla	n	3 Tesla	n
All ages	654 ms [608-700]	60	717 ms [582-850]	60
Age 20-29	678 ms [575-763]	9	642 ms [533-712]	5
Age 30-39	645 ms [609-735]	12	653 ms [428-772]	11
Age 40-49	655 ms [637-697]	12	734 ms [600-859]	11
Age 50-59	608 ms [557-690]	15	753 ms [640-885]	19
Age 60-69	671 ms [628-697]	10	762 ms [576-965]	10
Age 70-79	645 ms [610-680]	2	807 ms [714-984]	4

Numbers in bracket indicate interquartile range (IQR).

Table 3.

ECV of the pancreas at 1.5 and 3 T scanners separated by age groups. There was no significant difference in median ECV between the two magnet strengths when all age groups were combined (p=0.06).

	ECV fraction			
Age Groups	1.5 Tesla	n	3 Tesla	n
All Ages	0.28 [0.21-0.33]	60	0.24 [0.19-0.28]	60
Age 20-29	0.34 [0.30-0.39]	9	0.25 [0.22-0.26]	5
Age 30-39	0.25 [0.19-0.29]	12	0.19 [0.14-0.23]	11
Age 40-49	025 [0.20-0.33]	12	0.24 [0.19-0.33]	11
Age 50-59	0.31 [0.22-0.36]	15	0.26 [0.22-0.27]	19
Age 60-69	0.27 [0.22-0.28]	10	0.27 [0.22-0.32]	10
Age 70-79	0.23 [0.23-0.23]	2	0.27 [0.23-0.34]	4

ECV: Extracellular volume fraction. Numbers in bracket indicate interquartile range (IQR).