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R2*-relaxometry of the pancreas in patients with human hemochromatosis protein associated hereditary hemochromatosis

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ABSTRACT

Purpose: To evaluate pancreatic iron in patients with human hemochromatosis protein associated hereditary hemochromatosis (HHC) using R2* relaxometry.
Materials and methods: 81 patients (58 male, 23 female; median age 49.5, range 10–81 years) with HHC were retrospectively studied. All underwent 1.5 T magnetic resonance imaging (MRI) of the abdomen. A fat-saturated multi-gradient echo sequence with 12 echoes (TR = 200 ms; TE-initial 0.99 ms; Delta-TE 1.41 ms; 12 echoes; flip-angle: 20°) was used for the R2* quantification of the liver and the pancreas. Parameter maps were analyzed using regions of interest (3 in the liver and 2 in the pancreas) and R2* values were correlated.
Results: 59/81 patients had a liver R2* ≥ 70 1/s of which 10/59 patients had a pancreas R2* ≥ 50 1/s. No patient presented with a liver R2* < 70 1/s and pancreas R2* ≥ 50 1/s. All patients with pancreas R2* values ≥ 50 1/s had liver R2* values ≥ 70 1/s. ROC analysis resulted in a threshold of 209.4 1/s for liver R2* values to identify HFE positive patients with pancreas R2* values ≥ 50 1/s with a median specificity of 78.87% and a median sensitivity of 90%.
Conclusion: In patients with HHC R2* relaxometry of the pancreas should be performed when liver iron overload is present and can be omitted in cases with no sign of hepatic iron.

1. Introduction

In recent years magnetic resonance imaging (MRI) has emerged as a powerful non-invasive tool of choice for the evaluation of iron overload mainly in the liver and the heart. MRI has outstanding benefits over biopsy with its obvious disadvantages and is also considered as the new standard of liver iron determination for regulatory purposes [1]. Nowadays various MRI-methods and sequences are available and have become part of the daily clinical routine [2–4]. MRI shows good sensitivity when compared with liver iron concentration (LIC) of liver biopsies and cardiac T2* measurements also correlate well with cardiac iron concentration [2,5]. There is only limited data on the potential of MRI to quantify and evaluate iron in organs other than the liver and the heart.

The role of the pancreas in iron overload is not fully understood and standard MRI techniques for the quantification have not been established yet. Iron leads to impairment of the endocrine and exocrine functions of the pancreas due to tissue atrophy and fibrosis [6]. Several studies already focused on pancreatic iron overload in patients with thalassemia and secondary iron overload [7–10]. It is known that patients can suffer from endocrine damage such as diabetes mellitus due to pancreatic hemosiderosis [11]. This major endocrinopathy is found in 20–30% of adult patients with thalassemia major worldwide [12].

In hereditary hemochromatosis (HHC), increased intestinal absorption of iron leads to iron deposition in liver but also in the pancreas [13]. Although this is an important aspect in managing patients with HHC, literature on pancreatic iron overload is rare.

Our purpose was to evaluate patients with human hemochromatosis protein (HFE)-associated hereditary hemochromatosis with regard to pancreatic iron overload using R2* relaxometry. Secondary the correlation between R2* of the liver and the pancreas was assessed in order to find a possible predictive marker.

Abbreviations: MRI, magnetic resonance imaging; LIC, liver iron concentration; HHC, hereditary hemochromatosis; HFE, human hemochromatosis protein; ROI, region of interest; NTBI, non-transferrin-bound iron.

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2. Materials and methods

This retrospective study was approved by the institutional ethics committee of the Medical University of Innsbruck.

2.1. Patients

The records of all patients that were assigned to the Department of Radiology of the Medical University of Innsbruck for MRI evaluation of hepatic iron between November 2011 and April 2015 were retrieved. Patients were included in the study depending on the following inclusion criteria: (a) positive genetic test for the human hemochromatosis protein (HFE) gene, (b) MRI of the abdomen including liver and pancreas accomplished with the sequence listed below, (c) no history of blood transfusion, (d) increased serum ferritin (>300 μg/L in male patients and >200 μg/L in female patients) or transferrin saturation (>45% in male patients and >50% in female patients). For the genetic testing, the DNA was isolated from whole blood samples using the Qiagen DNA extraction kit. All samples were genotyped at the Hepatology laboratory, Medical University of Innsbruck. DNA was analyzed for rs1799945 (NM_000410.3:c.187C>G,NP_000401.1:p.His63Asp) and rs1800562 (NM 000410.3:c.845G>A; NP 000401.1:p.Cys282Tyr) single nucleotide polymorphisms in HFE using a Taqman allelic discrimination assay (Applied Biosystems, Vienna, Austria). Serum ferritin and transferrin saturation were analyzed at University Hospital's Central Institute for Medical and Chemical Laboratory Diagnostics (ZIMCL) on a Roche COBAS 8000 platform using the Ferritin Elecsys assay. Transferrin saturation was calculated from serum iron and total iron binding capacity (TIBC) also measured on the COBAS platform using Roche's IRON and TIBC assay (Roche, Mannheim, Germany).

A total of 81 patients (58 male, 23 female; median age 49.5, range 10–81 years) met these inclusion criteria.

2.2. MRI protocol and post-processing

MRI was performed using a 1.5 T MR imaging unit (Magnetom Avanto, Siemens Healthcare Sector, Erlangen, Germany). Patients were examined in supine position using a standard anterior 6-element body matrix coil and 6–9 elements of the integrated spine matrix coil. R2* was assessed using a fat-saturated multi-gradient echo sequence with 12 echoes (TR = 200 ms; TE-initial 0.99 ms; Delta-TE 1.41 ms; 12 echoes; flip-angle: 20°). During one breath-hold a single slice with a slice thickness of 10-mm was acquired in transverse orientation and the acquisition was repeated for five different slice positions. The matrix was held constant at 128 × 128 pixels with a field of view of 380 × 380 mm.

In addition a T2 weighted Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) sequence (TR = 1000 ms; TE = 73 ms; SL 5 mm) and a T1 weighted standard in- and opposed phase gradient-echo sequence (TR = 103 ms; TE 2.37/5.05 ms; SL 5 mm) were obtained to get an anatomic overview and to depict the boundaries of the pancreas.

Image analysis was performed independently by a radiologist (identification and evaluation of the pancreas with ROI placement) and a physicist (calculation of R2* maps). Offline post-processing included quantitative image analysis using ImageJ (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA). Regions of interest (ROIs) were placed in the liver and the pancreas. Three ROIs were placed in the liver parenchyma of one transverse section (two in the right lobe and one in the left lobe). For the pancreas in a different transverse section one ROI was placed in the body and another one in the tail of the pancreas, both with clear distance from its boundaries. All ROIs were carefully drawn in order to avoid vascular structures, large ducts, and motion or pulsation artifacts.

Table 1
Detailed patient information and data for the 10 patients with pancreatic R2* ≥ 50 1/s.

No.	Age	Sex	Liver R2* (1/s)	Pancreas R2*	Diabetes mellitus or exocrine dysfunction
1	67	m	513.67	118.70	No
2	60	m	663.53	61.10	No
3	63	f	299.87	121.10	No
4	57	f	402.60	67.80	No
5	48	f	211.50	58.40	No
6	58	m	76.47	60.70	No
7	64	m	627.33	153.05	No
8	10	m	323.43	90.90	No
9	32	m	927.57	231.95	No
10	54	m	311.43	108.60	No

R2* maps were calculated from the magnitude images by pixel-wise fitting with a truncation model using a custom-written ImageJ plugin [14]. All the above measurements were recorded and the mean R2* for each organ was used for statistical analysis. For the liver we used the widely accepted R2* threshold of ≥70 1/s to determine iron overload and for the pancreas R2* below 50 1/s was considered as normal [7,11,15]. For patients with pancreas R2* ≥ 50 1/s clinical follow-up was done for a minimum of one year in order to find or exclude impairment of the endocrine and exocrine functions of the pancreas.

2.3. Statistical analysis

All statistical calculations were performed using R Project for Statistical Computing (R Development Core Team (2006), Vienna, Austria. URL: http//:www.R-project.org, version 2.13.1). Patients were subdivided into two groups: group 1 with pancreas R2* values < 50 1/s and group 2 with pancreas R2* values ≥ 50 1/s. Results were tested for normality using a Kolmogorow–Smirnow normality test. As no normal distribution was found an unpaired Wilcoxon-Test was used to test for a significant difference between groups. For linear regression analysis a linear model was fitted to the data. Results were considered significant for p values less than 0.05. For ROC analysis the pROC package for R was used [16].

3. Results

The mean R2* of the liver for all patients ranged from 27.33 1/s to 927.6 1/s and the mean was 190.2 1/s. For the pancreas the R2* ranged from 17.1 1/s to 232.0 1/s with a mean R2* of 40.35 1/s.

71/81 patients had pancreas R2* values < 50 1/s (range: 17.1 1/s–47.0 1/s). In 10 patients R2* in the pancreas was found ≥ 50 1/s (range: 58.4 1/s–232.0 1/s). All patients with pancreas R2* values ≥ 50 1/s also had liver R2* values ≥ 70 1/s (range: 76.47 1/s–927.6 1/s).

Of all included patients 59/81 had a liver R2* ≥ 70 1/s (range: 70.17 1/s–927.6 1/s) of which 10/59 patients had a pancreas R2* ≥ 50 1/s. No patient presented with a liver R2* < 70 1/s and pancreas R2* ≥ 50 1/s.

A moderate to strong correlation between pancreas and liver R2* values was found (r = 0.622; p < 0.001) as shown in Fig. 1a. The correlation improved if only the 10 patients with pancreas R2* ≥ 50 1/s were included (r = 0.731; p = 0.0164) but strongly decreased for patients without any sign of pancreatic iron overload (r = 0.17; p = 0.156) (Fig. 1b).

Boxplots of pancreas R2* and liver R2* for the used groups are shown in Figs. 2 and 3. Details for the 10 patients with liver R2* ≥ 70 1/s and pancreas R2* ≥ 50 1/s are provided in Table 1.

Patients were divided into 2 groups: group 1 with a pancreatic R2* < 50 1/s (71 patients, 51 male and 20 female) and group 2 with