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T2*-ADC Comparison in Liver Iron Quantification in Thalassemia Patients

Talasemi Hastalarında Karaciğer Demir Ölçümünde T2*-ADC Karşılaştırması

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ABSTRACT

Objective: *Repetitive transfusion is a treatment option in patients with thalassemia, but this causes iron accumulation in various organs, especially the liver. In this study, it is aimed to present our own experience in the correlation of serum ferritin concentrations with liver T2* MR measurements and ADC values in thalassemia patients.*

Materials and methods: *Seventy-four consecutive patients who underwent T2* MR examination of the liver due to beta thalassemia were included in the study. Liver T2* and ADC measurements and ferritin measurements of the patients included in the study were compared. MRI examination was performed with 3T scanner. Multiecho gradient echo was used for T2* MRI examinations. T2* and ADC measurements were made from 4 different regions of the liver, one each from the medial and lateral segments of the left lobe and one each from the anterior and posterior segments of the right lobe. Spaerman correlation analysis was performed to evaluate the correlation between serum ferritin levels and R2* and ADC measurements.*

Results: *Thirty-two patients (43.24%) were female and and forty-two (56.76%) were male. There was moderate correlation between serum ferritin and liver T2* measurements (r= -0.52 p<0.01). The highest T2 value was measured in the left lobe medial segment of the liver as 7.85 ms and the lowest was measured in the right lobe posterior segment of the liver as 6.5 ms. There was weak correlation between serum ferritin and ADC (r= -0.41, p<0.01). The highest ADC value was measured in the left lobe medial segment of the liver as 908.90 mm2/s and the lowest was measured in the right lobe anterior segment of the liver as 766.78. There was a moderate-high correlation between liver T2* measurements and ADC measurements. This correlation was higher than the correlation between serum ferritin and liver T2* measurements.*

Conclusion: *Correlations between the serum ferritin measurements and both ADC and T2* measurements are lower than those found with 1.5T in the literature. The correlation of ADC with serum ferritin is lower than the correlation between serum ferritin and T2*MR, so we do not think ADC is as useful as T2* measurements in assessing liver iron accumulationin in thalassemia patients.*

ÖZET

Amaç: *Talasemi, hastalarında tekrarlayıcı transfüzyon bir tedavi opsiyonudur, fakat bu durum başta karaciğer olmak üzere değişik organlarda demir birikimine neden olmaktadır. Bu çalışmada talasemi hastalarında, serum ferritin konsantrasyonları ile karaciğer T2* MR ölçümleri ve ADC değerlerinin korelasyonu konusundaki kendi deneyimimizin sunulması amaçlanmıştır.*

Gereç ve yöntem: *Beta talasemi nedeni ile karaciğere yönelik T2* MR tetkiki yapılan ardışık 74 olgu çalışmaya dahil edilmiştir. Olguların karaciğer T2* ve ADC ölçümleri ile ferritin ölçümleri karşılaştırıldı. MR incelemesi 3T tarayıcı ile yapıldı. T2* MR incelemelerinde multieko gradyan eko kullanıldı. Karaciğer sol lob medial ve lateral segmentten birer ve sağ lob anterior ve posterior segmentlerden birer adet olmak üzere toplam 4 farklı bölgeden T2* ve ADC ölçümleri yapıldı. Serum ferritin düzeyleri ile R2* ve ADC ölçümleri arasındaki korelasyonu değerlendirmek için Spearman korelasyon analizi yapıldı.*

Bulgular: *Hastaların 32'si (%43,24) kadın, 42'si (%56,76) erkekti. Serum ferritin ile karaciğer T2* ölçümleri arasında orta düzeyde negatif bir korelasyon vardı (r= -0,52 p<0,01). En yüksek T2* değeri 7,85 ms ile karaciğerin sol lob medial segmentinde, en düşük T2* değeri ise 6,5 ms ile karaciğerin sağ lob arka segmentinde ölçüldü. Serum ferritini ile ADC arasında negatif zayıf bir korelasyon vardı (r= -0.41, p<0.01). En yüksek ADC değeri 908,90 mm2/s ile karaciğerin sol lob medial segmentinde, en düşük ADC değeri ise 766,78 ile karaciğerin sağ lob ön segmentinde ölçüldü. Karaciğer T2* ölçümleri ile ADC ölçümleri arasında orta-yüksek korelasyon mevcuttu. Bu korelasyon serum ferritin ile karaciğer T2* ölçümleri arasındaki korelasyondan daha yüksekti.*

Sonuç: *Serum ferritin ölçümleri ile hem ADC hem de T2* ölçümleri arasındaki korelasyonlar literatürde 1,5T ile bulunanlardan daha düşüktür. ADC'nin serum ferritin ile korelasyonu, serum ferritin ve T2*MR arasındaki korelasyondan daha düşük olduğundan, talasemi hastalarında karaciğer demir birikiminin değerlendirilmesinde ADC'nin T2* ölçümleri kadar yararlı olduğunu düşünmüyoruz.*

Keywords:
T2 MRI*
ADC
Iron-loaded liver

Anahtar Kelimeler:
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Demir yüklü karaciğer

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INTRODUCTION

Thalassemia is a heterogeneous group of diseases characterized by anemia caused by damaged synthesis of one or more of the hemoglobin chains (1). According to the severity of anemia, recurrent transfusion is a treatment option in these patients (2). Repetitive transfusions show iron accumulation in several organs in the body (3). Accumulating iron damages tissues and organs (4). Liver are one of the target organs for iron accumulation (5,6). Chelator drugs are used in the treatment of iron accumulation (7). This treatment significantly improved survival in patients with thalassemia (8).

The most reliable method to calculate body iron deposition is histochemical or biochemical assessment of iron in a liver biopsy specimen but that is an invasive procedure (2). Serum ferritin levels are widely used to monitor chelation therapy and to assess iron accumulation (9). However, it should be noted that serum ferritin level may be affected by many inflammatory conditions (10).

In early 1990s it has been reported a very close correlation between T2 relaxation rate and liver iron accumulation on magnetic resonance imaging (MRI) (11). In the early 2000s, T2* MRI techniques were used to evaluate liver iron accumulation (12). Nowadays, the amount of liver iron accumulation can be calculated by measuring liver T2* signals using multiecho gradient echo sequences with MRI. In recent years there have been reports that diffusion-weighted imaging (DWI) is a useful method for evaluating liver changes and iron accumulation (13).

Standards have been established in 1.5T MR scanners used in liver T2* measurements for many years. In 3T scanners, the situation is not as clear as in 1.5T scanners. Due to the increased magnetic field strength, the susceptibility effect of iron has increased significantly. In this case, it makes it difficult to measure T2* reliably in patients with iron accumulation in the liver (14). The aim of this study was to evaluate the correlation between serum ferritin concentrations and liver T2* measurements and apparent diffusion coefficient (ADC) values in thalassemia patients in 3T MR scanners.

MATERIALS AND METHODS

Study Population and characteristics

This retrospective study was approved by Muğla Sıtkı Koçman University Human Research Ethic Committee (Number 85/2019). The study was conducted from January 2018 to November 2018. Seventy-four patients who examined T2* MRI due to beta-thalassemia were included in the study. Beta-thalassemia was diagnosed by complete blood count, hemoglobin electrophoresis test, and clinical evaluation by an experienced hematologist. Only patients with complete MRI examination (including T2* MRI and DWI sequences) were included. All patients were follow-up cases of our center. Four patients with prominent motion artifacts and 2 patients with inconclusive liver T2* (the serum ferritin levels were significantly elevated) were excluded from the study. There were 74 patients in the study population. A total of 38 patients had splenectomy. A total of 67 patients, 27 women and 40 men, were receiving chelation therapy. Patients characteristics are summarized (Table 1).

Liver T2* and ADC measurements and ferritin measurements of the patients included in the study were compared. Serum ferritin levels were measured on the same day with MRI examination. Serum ferritin level was measured by electrochemiluminescence method (Roche Diagnostics). Since ferritin is an acute phase reactant, detailed clinical examination and c-reactive protein (CRP) measurements were performed to rule out possible infectious/ inflammatory processes. Additionally, transaminase results such as alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reviewed to evaluate processes that could affect liver measurements such as hepatitis. There was no infectious/inflammatory process in the study population.

MRI acquisition and measurements

MRI examination was performed with 3T scanner (Siemens Skyra, Erlangen, Germany). Multiecho gradient echo was used for T2* MRI examinations. A breath-hold sequence was used to reduce respiratory artifacts. Liver

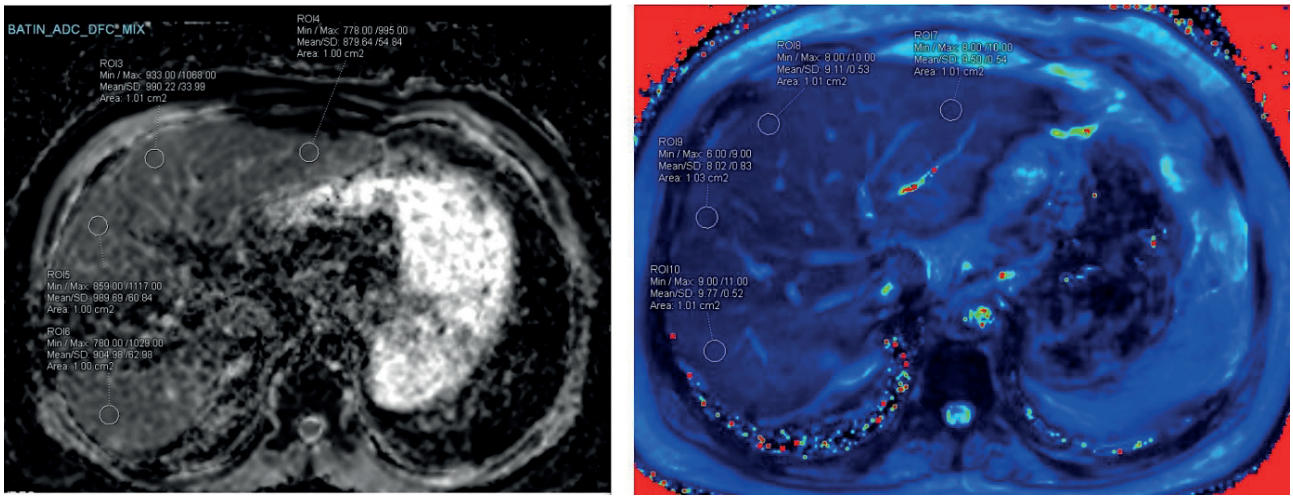

Figure 1: Both ADC and T2 measurements were made from four different regions of the liver. The illustration shows the areas where the measurements are made.

Table 1: Patients characteristics.

Characteristic		
Age (year) median (min-max)		25.30 (9-53)
Gender n (%)	Female	32 (43.24)
	Male	42 (56.76)
Splenic size (mm) median (min-max)		144.75 (101-200)
Ferritin level (ng/ml) median (min-max)		753.45 (127-2540)

examination parameters: Field of view 25x18 cm, TR 177 ms, slice thickness 5 mm, spacing between slices 5.5 mm, matrix 256x192, number of excitation 1, flip angle 60˚. There were 7 different echo times in protocol (TE 2.54-17.22 ms, increasing by increments of 2.45 ms). T2* and ADC measurements were made from 4 different regions of liver left lobe medial and lateral segment and right lobe anterior and posterior segments (figure 1). Each measurement was made using approximately 1 cm2 ROI. All four T2* and ADC measurements were averaged. Data analysis was performed using Syngovia workstation (Siemens, Germany). R2* calculated from measured T2* values (R2*=1/T2*). The equation ((R2* × 0.0254) +0.202) was used in the LIC calculation from R2* (15)

Statistical analysis

All statistical analysis was performed by SPSS version 22. Descriptive analysis of quantitative variables was performed. Spaerman correlation analysis was performed to evaluate the correlation between serum ferritin levels and R2* and ADC measurements. Correlation coefficients were accepted as negligible correlation between 0.00-0.30, weak correlation between 0.30-0.50, moderate correlation between 0.50-0.70, high correlation between 0.70-0.90 and very high correlation above 0.90 (16). Student's t-test was used to compare the mean of the groups. Results were assessed within 95% confidence intervals and $p < 0.05$ was considered as significant.

Table 2: Comparison of measurements by gender.

	Female n=32	Male n=42	p
Ferritin level (ng/ml)	879.41	660.35	0.57
Liver T2* (ms)	7.50	6.75	1.00
Liver iron concentration	6.20	5.76	1.00
Liver ADC (mm2 /s)	784.13	845.1	0.87

RESULTS

Thirty-two patients (43.24%) were female and mean age was 27.18 years old, and forty-two (56.76%) were male and mean age was 23.48 years old. The male to female ratio was 1.3/1. There was no statistically significant difference in serum ferritin, liver T2*, LIC concentration, liver ADC values between women and men (Table 2).

There was moderate correlation between serum ferritin and liver T2* measurements ($r= -0.52$ $p<0.01$). The highest T2 value was measured in the left lobe medial segment of the liver as 7.85 ms and the lowest was measured in the right lobe posterior segment of the liver as 6.5 ms. There was weak correlation between serum ferritin and ADC ($r= -0.41$, $p<0.01$). The highest ADC value was measured in the left lobe medial segment of the liver as 908.90 mm2/s and the lowest was measured in the right lobe anterior segment of the liver as 766.78. There was a moderate-high correlation between liver T2* measurements and ADC measurements. This correlation was higher than the correlation between serum ferritin and liver T2* measurements. All correlations is given in table 3.

DISCUSSION

The correct measurement of liver iron accumulation is important in the treatment of diseases that cause iron accumulation in the body, such as thalassemia. Different methods have strengths and weaknesses in monitoring iron accumulation in the body. Serum ferritin measurements are low-cost and easily accessible, but their accuracy in short-term follow-up is low. MRI is an expensive method and not easily accessible, however, its accuracy is high in short-

Table 3: Relationship between serum ferritin, liver T2 * and liver ADC values. The correlation of each variable with the other can be cross-compared.

		Serum ferritin	Median ADC	Liver T2*	LIC
Serum ferritin	CC	1.000	-0.410	-0.520	0.517
	Sig.		-0.009	0.001	0.001
	N	80	80	80	80
Median ADC	CC	-0.410	1.000	0.598	-0.599
	Sig.	0.009		0.000	0.000
	N	80	80	80	80
Liver T2*	CC	-0.520	0.598	1.000	-1.000
	Sig.	0.001	0.000		0.000
	N	80	80	80	80
LIC	CC	0.517	-0.599	-1.000	1.000
	Sig.	0.001	0.000	0.000	
	N	80	80	80	80

CC: Correlation coefficient, LIC:Liver iron concentration, ADC: Apperent diffusion coefficient

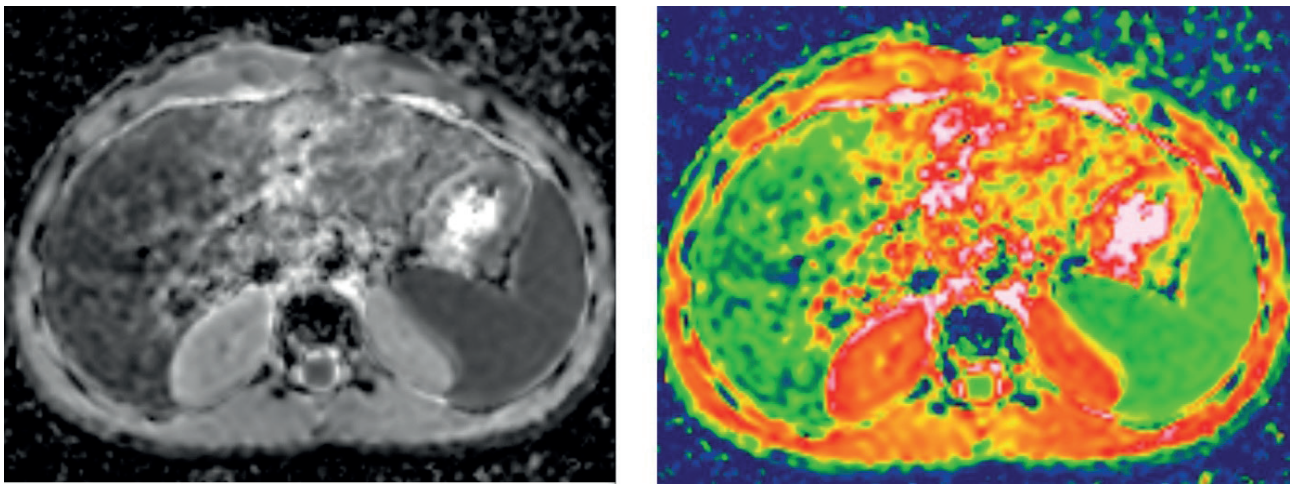

Figure 2: The picture shows heterogeneity in the left lobe in liver ADC measurements. This is evident in the color maps on the left.

term follow-ups and it can measure iron accumulation in each organ individually (17). Therefore, MRI has become the standard imaging method for evaluating iron deposits in the liver and heart of thalassemia patients. A good correlation between serum ferritin levels and liver T2* measurements has been reported in the literature (18). In this study, a moderate correlation was found between serum ferritin level and liver T2* level. In this study, serum ferritin levels were found as 956 ng/mL and 2540 ng/mL in two patients who had a very similar T2* values as 2.07 and 2.16 respectively. T2* values were close to each other in these two cases ferritin values were very different from each other.

The correlation between serum ferritin and liver T2* measurements were -0.58 ($p < 0.001$ in Karakaş et al.' study. Majd et al. found a good correlation between ferritin levels and liver T2* levels ($r = 0.698$, $p < 0.001$) (19). In our study, these rates were found as -0.52 ($p < 0.05$). Although the value we found for the liver is slightly lower, it is just about similar to that of the studies of the Karakaş et al. and lower than found Majd et al. 1.5T scanners were used in the studies of both Karakaş and Majd. In our study, 3T scanner was used. The difference may be related to the magnet power. In their study to compare 1.5T and 3T MRI scanner, Storey et al. suggested that liver T2* values in patients with iron overload could be significantly shortened and this would make precise measurement difficult (20). They suggested that 1.5T imaging should be preferred to 3T because of the increase in magnetic field strength. In order to prevent this, they reported that if there is more tissue iron concentration than 37 mg Fe/g dry weight, sequences using shorter TE durations may be needed for precise measurement of T2* in strong magnetic fields. Patel et al. found the correlation between serum ferritin and liver T2* moderately significant ($r = 0.41$), which is lower than the rate in our study (21).

In this study, the correlation between ADC measurements and serum ferritin levels were found weak. The correlation of ADC with serum ferritin is significant lower than the correlation between serum ferritin and T2* MRI. Akpınar et al. suggested that DWI may be a sensitive method to assess the severity of liver iron accumulation. It may be thought that it could be due to the paramagnetic effect of iron rather than diffusion restriction. However, multiple measurements are required to perform T2* mapping of a tissue. In this way, the exponential decay curve of the tissue can be extracted with multiple samples. ADC measurements do not correlate as highly as T2* measurements (22). ADC measurements appear not to be useful for follow-up in cases of liver iron accumulation in 3T MR scanners.

There are some limitations in this study. Firstly it was retrospective and relatively small size cohort. T2* measurements were higher in the medial segment of the left lobe of the liver than in the other parts of the liver. We think that this is due to the heterogeneity of cardiac and aortic pulsations (motion artifacts) in this region rather than heterogeneous distribution of iron (figure 2).

CONCLUSION

In conclusion, correlations between the serum ferritin measurements and both ADC and T2* measurements are lower than those found with 1.5T in the literature. The correlation of ADC with serum ferritin is lower than the correlation between serum ferritin and T2*MR, so we do not think ADC is as useful as T2* measurements in assessing liver iron burden.

Conflict of Interest: No conflict of interest was declared by the authors.
Ethics: The study was approved by the Muğla Sıtkı Koçman University Ethics Committee (Decision no: 2019/95).
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