

# Determination of the relationship between transverse relaxation T2\* calculated in cardiovascular MRI using Ferritin Laboratory test in patients with Beta Thalassemia Major

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## ABSTRACT

**Background:** Thalassemia is an autosomal genetic disease in which hemoglobin has lost its natural structure and an ineffective hemoglobin in the body is produced. Blood transfusion to these patients is one of the most important causes of iron deposition in the organs of the body, including the heart. Sediment causes organ dysfunction. One of the best ways of monitoring these patients to examine sediment, using MRI and measurement of T2 \* index in their heart and liver. In this study, the relationship between heart T2 \* and serum ferritin levels in patients with thalassemia major has been evaluated. **Materials and Methods:** Seventeen patients were assigned randomly among the patients referring to the Shahid Rajaee Cardiology Center. Cardiovascular MRI was performed with the relevant protocols for measuring T2 \*, and the values of R2 \* and T2 \* were extracted and then, using Student-t correlation between values with experimental results of serum ferritin was compared and finally the Pearson coefficient was calculated between the results of the above study and the severity of the relationship Between values set. **Results:** In this study, the correlation between the amount of ferritin and T2 \* heart was computed to be 0.36, indicating that high ferritin concentration only accounts for 36% of iron deposition determination role in myocardium and there are other factors contribute to the deposition of 64% of the remainder.

**Keywords:** T2 relaxation time, Cardiac Magnetic Resonance imaging, Ferritin.

## Introduction

Thalassemia is an autosomal disease wherein hemoglobin loses its natural structure as a result of which ineffective hemoglobin is produced in the body. Consequently, the defective hemoglobin is not capable of optimal transporting of oxygen to the body organs. So, in fact, there is no such a thing as overall shortage of hemoglobin in this disease rather abnormal hemoglobin is increased in number.

Hemoglobin is the oxygen-transport part of the red blood cells. Hemoglobin is constructed of two different proteins named alpha and beta. Blood cells do not form in their perfect form in case of the body's inability of producing sufficient amount of

each type of these proteins following which the body organs are not provided with the amount of oxygen they need hence a sort of anemia comes about that is usually rooted in childhood era and lasts till the end of life. Although thalassemia is not a singular disorder but a group of disorders inflict the body through similar ways in thalassemia. It is important to reach an understanding of the various types of thalassemia.

Thalassemia includes two types, called alpha and beta thalassemia. The individuals with shortfalls in alpha protein productions become inflicted with alpha thalassemia. Alpha thalassemia is more prevalent in Africa, Middle-East, India, Southern Asia, Southern China and Mediterranean regions. The individuals with shortage of beta protein production become inflicted with beta thalassemia. Beta thalassemia is more prevalent in the people from Mediterranean regions like Greece and Italy, Arabia Peninsula, Africa, southern Asia and southern China [1].

Unfortunately, numerous dangerous symptoms may occur following the infliction with the disease. The individuals with thalassemia usually have higher than normal iron concentration for such a reason as the repetitive transfusions following which the extra iron in the blood stream of these individuals deposit in

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some organs of their bodies such as in heart, liver and endocrinal glands and this causes such malfunctions in the abovementioned body organs as congestive heart failure, cardiac arrhythmia, hypogonadism, hypothyroidism, diabetes, hypoparathyroidism, thrombophilia, osteoporosis and pseudoxanthoma elasticum [2] in such a manner that the mortality rates are very high amongst these patients; according to the statistics, about 25000 individuals lost their lives as a result of the disease only in 2013 [3].

According to the fact that the transfusion of healthy individuals' blood to these patients is one of the most important factors contributing to iron deposition in their body organs, including heart, the clinical monitoring of these patients in terms of iron deposition as well as the performance of the engaged body organs is of a great importance. To do so, laboratory tests and medical imaging are most widely applied to these individuals as vital monitoring measures in such a way that one of the best methods of monitoring the aforesaid patients for iron deposition is the use of magnetic resonance imaging (MRI) and T2\* index measurement in their livers and hearts as well as serum ferritin measurement in laboratories [4].

In the entire Islamic Iran, cardiovascular MRI and iron deposition monitoring are unfortunately only offered in two medical imaging centers, including Shahid Raja'ei heart and coronary hospital; however, serum ferritin laboratory test and blood iron concentration measurement are generally offered in all of the country's laboratories in a high accuracy. Thus, according to the fact that the international standards indicate blood iron deposition measurement in myocardial tissue and recommend performing cardiac MRI and measurement of transverse relaxation  $T2^*$  time in the cardiac muscle, the present study seeks to assess the relationship between serum ferritin laboratory test of the inflicted patients with the calculated  $T2^*$  times so that the iron deposition could be indirectly determined in the cardiac muscles through only laboratory tests.

## Study Method:

MRI or magnetic resonance imaging is a novel method of medical diagnosis imaging that has become very pervasive during the recent decades and works based on magnetic resonance of hydrogen atoms' nuclei. The waves used in MRI are of radio and magnetic type hence harmless to the human body. MRI makes use of this physical reality that the protons in the atoms' nuclei spin like earth about their axis in a very high speed and form a peripheral magnetic field. In MRI, the patient is exposed to a very strong magnetic field that causes the spinning axis of the protons of the atoms' nuclei (especially protons of the hydrogen atom nucleus extant in water molecules) to be aligned with the MRI magnetic field in the entire body tissues. Then, special radio waves are radiated towards the patient body. These waves that are emitted in pulse form make the protons' axis of spinning change a little. Upon the termination of radio pulse emittance, the protons' spinning axes becomes again aligned with the magnetic field lines. This realignment causes the creation of a new radio

(electromagnetic) wave. Next, the secondary signals emitted from the protons are recorded by the MRI receiver device and sent to a computer. MRI computer is very powerful and features a high calculation power. The signal received by the computer is analyzed rapidly following which images are constructed based on the analyses. MRI images show clear or dark parts of the body resulting from their magnetic properties. Having examined the images on monitor, the radiologist and cardiologist expert offers his or her final and decisive findings.

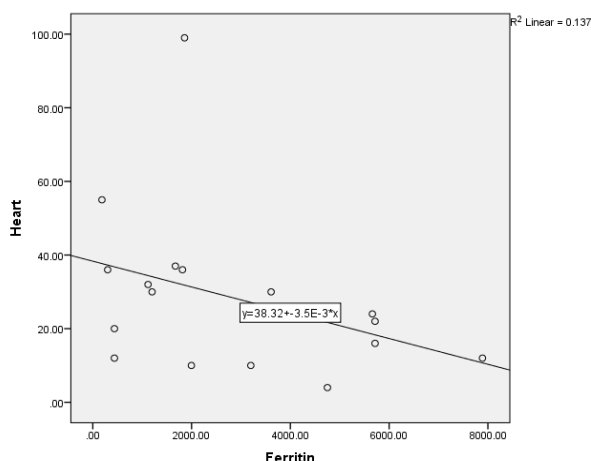
Nowadays, there are numerous methods for the investigation of the nature of the tissues forming an organ using MRI amongst which T2 mapping, T2\* mapping, T1 mapping, LGE imaging, perfusion and diffusion imaging can be pointed out. Despite the existence of many advanced laboratory methods, a great number of the cardiovascular patients' referrals by physicians are to cardiac MRI; because, besides tissue nature of the corresponding organ, the aforementioned modality can investigate the performance, the quantitative indices of the heart ventricles and the existence or nonexistence of edematous tissue. Thus, nowadays, cardiovascular MRI has been turned into the modality of interest by the cardiologists for the tissue examinations, tissue nature determination, iron deposition, myocarditis, ischemia and myocardial infarction.

According to the high prevalence of thalassemia major in Iran and the shortages of cardiovascular MRI centers therein, the present study intends investigating the relationship between common laboratory test of serum ferritin (that is frequently seen in various country's regions even in the underdeveloped parts) and iron deposition in the hearts of the patients inflicted with the disease so that the relationship, if any, can be determined of its rate in such a manner that only common laboratory tests can be applied to reach an estimation of the iron deposition in the hearts of the patients. The work stages are as below:

- 1) Selection of 17 patients based on the physician's discretion in an irregular randomized manner from among the patients who had referred to Shahid Raja'ei's heart and coronary center
- 2) Explanation of the risks and the method of study accomplishment to the entire selected individuals
- 3) Acquiring consent letter and disclaimer letters from the patients in written form and orally
- 4) Performing cardiovascular MRI on the patients as described below:
  - 3 Plane 2D True-Fisp Localizer
  - 2Chamber, 3 Chamber, 4 Chamber, Short-Axis, RVOT Retrospective Cine 2D True-Fisp MR Imaging
  - 4 Chamber, 2 Chamber, Short-Axis 8-Echo-GRE ( $T2^*$  Mapping) MR Imaging
- 5) Performing serum ferritin laboratory test on the inflicted individuals
- 6) Performing statistical analysis

## Findings:

The following diagram displays the relationship between serum ferritin and T2\* of the heart. As it can be seen, there is a linear and inverse relationship holding between the two.



**Figure 1: relationship between serum ferritin and T2\* of the heart.**

**Table 1: Pearson coefficients of correlation between serum ferritin values and t2\* times**

Correlations		Heart	Ferritin
Heart	Pearson correlation	1.000000000	-0.364574058
	Sig. (2-tailed)		0.1502192009
	N	17.00000000	17.00000000
Ferritin	Pearson correlation	-0.364574058	1.000000000
	Sig. (2-tailed)	0.1502192009	
	N	17.00000000	17.00000000

In the above table, Pearson coefficients of correlation between serum ferritin values and t2\* times have been presented. The calculated coefficient is equal to -0.36.

**Table 2: nonparametric correlation test**

		Heart	Ferritin
Heart	Correlation coefficient	1.000	0.000*
	Sig. (1-tailed)	0	0.036
	N	17	17
Spearman's rho	Correlation coefficient	0.000*	1.000
	Sig. (1-tailed)	0.036	0
	N	17	17

\* Correlation is significant at 0.05 level (1-tailed)

Based on Spearman test that is considered as nonparametric correlation test and is applied to determine the correlation between two variables in a small sample volume, the correlation between the two studied variables is equal to 0.36 hence statistically significant (P<0.05).

**Discussion and Conclusion:**

There are several methods of iron level measurement in various organs. In some organs like liver, biopsy is the gold standard of iron level measurement but it is an invasive measure and it

cannot be used for iron level measurement of the heart. Echocardiography is another method that is reliable only for advanced cases of iron deposition in heart.

Anderson et al has recently demonstrated that T2\* is very sensitive in the iron deposition determination in heart and that T2 value is found essentially reduced in patients with intermediate to severe iron deposition in heart from normal state (20ms and higher) to below 20ms [5].

In the present study, the relationship between cardiac T2\* time and ferritin level was investigated. According to the obtained results, blood ferritin level is inversely associated with the cardiac T2\* time for which a Pearson correlation coefficient equal to 0.36 was computed meaning that the high ferritin concentration only accounts for 36% of the iron deposition determination in myocardium and there are other factors playing a role in the determination of the remaining 64%. The test's error rate was 15 per every 100 individuals and it is larger than the standard 5 individuals per 100. So, it can be stated that ferritin is not the major and preliminary cause of iron deposition in myocardium and there are other factor(s) playing a part, as well.

One disadvantage of the present study was the low study sample volume that could have influenced the results.

Based on Spearman test that is recounted as a nonparametric correlation test and is applied for the investigation of the correlation between two variables in low sample volumes, the correlation between serum ferritin and T2\* was found statistically significant and equal to 0.36 (P<0.05).

Based on the study, the final result is that the serum ferritin possesses a weak to intermediate potency in estimating the iron deposition in myocardium so it cannot be reliably applied for the investigation of iron deposition in myocardium and there is a need for further research on a larger study sample volume as well as consideration of the other variables.

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