

## Role of Gradient Echo T2 Star in Assessment of Secondary Hemosiderosis in Pediatric Patients with Thalassemia Major

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### Abstract

**Background:** Thalassemia patients have diabetes mellitus subaltern to hemosiderosis.

**Aim of Study:** To assess iron overload in pancreas of pediatric beta-thalassemia major patients by T2\* gradient echo MRI and to correlate results of MRI with serum ferritin level, hepatic hemosiderosis, diabetes and spleen removal.

**Patients and Methods:** 20 patients with thalassemia major (11 males and 9 females) were evaluated with MRI using T2\* gradient echo sequence on 1.5 magnet and signal intensity ratio of the liver and the pancreas were calculated in addition to clinical assessment and laboratory investigation.

**Results:** Striking reduction in hepatic and pancreatic signal intensity ratio was appeared in the twenty patients contrasted with controls. Patients with anomalous glucose tolerance demonstrating a more level of secondary hemosiderosis in the form of low signal intensity of pancreas and hepatic tissue contrasted with patients with typical glucose tolerance or controls. Surgical removal of the spleen had essentially bring down SIR of pancreas contrasted with intact spleen patients ( $p < 0.047$ ).

**Conclusions:** T2\* GRE MRI assume a vital part in detection of iron over-burden. After spleen removed, iron deposition might be more out of control in the pancreas.

**Key Words:** Pancreatic iron overload – MRI gradient echo imaging – Thalassemia.

### Introduction

**REPEATED** transfusion as a treatment for thalassemia major cause iron over-burden which leads to cell demise and organ weakness [1]. These patients should be under regular follow-up to detect early complication of blood transfusion and this is the aim of this study to assess iron overload in pediatric B thalassemia major patients and to

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correlate the results with serum ferritin level, diabetes and spleen removal.

Principle locales of iron collection are liver, spleen, heart and endocrine organ chiefly pancreas and pituitary organ. Chelation treatment has been utilized to dispose of it [2,3]. Serum ferritin is the principle test done to assess press store [4].

In cases of primary hemochromatosis or secondary hemosiderosis, the liver is the site where iron accumulates mainly [5]. Usually, evaluation is done by needle biopsy, which is invasive way carry a many of complication [6,7].

There is increased risk of diabetes in this kind of patients which is likely to caused by expanded fringe protection from insulin and direct poisonous impact of overabundance press in the pancreatic cells [8-10].

Gradient Echo T2 star imaging is an excellent method to assess iron deposition in the liver which shows decent connection with biopsy results, however biopsy is invasive with considerable complication [11,12].

Gradient Echo T2 star imaging evaluates iron deposition in the liver and pancreas which shows great benefits in confirming the finding, characterizing the seriousness and watching treatment [13].

### Patients and Methods

Twenty Egyptian patients with thalassemia major including eleven males and nine females underwent MRI scan on 1.5 magnet in time from September 2016 to November 2017. Ages of patients ranged between 6-18 years ( $11.700 \pm 3.701$ ). All thalassemic patients suffer from pallor and hepatomegaly. All patients were regular transfused

each 2 to 4 weeks to save hemoglobin level at 9-11gm/dl. Patients were advised to take chelation therapy with subcutaneous deferoxaminemesylate (Desferal,) (thirty to forty milligram/kilogram body weight per day) or oral desferasirox (twenty to forty milligram/kelogram/day). Patients diseased with acute infection were briefly prohibited from the investigation to avoid the impact of disease on ferritin. Ferritin level ranged between (101-11000 ng/dl) (Table 1). Spleen surgically removed in 14/20 patients (70%).

Fasting and post prandial glucose test (FG, PPG) have been performed which shows the number of Normal Glucose Tolerance (NGT) to the Impaired Tolerance (IGT) patients represents 30 to 10 respectively.

Ten healthy children, 6 males and 4 females; introduced as control group, in the same range of age of our patients, with normal CBC, serum ferritin and FBG and PPG.

#### Gradient echo T2 star imaging technique:

Gradient echo T2 star has been performed with GE medical, sigma explorer 1.5 Tesla scanner. The axial scan cuts must start just above the hepatic dome and extend downwards involving all pancreatic tissue including head, body and tail. Examination has been performed in supine position. TR= 13.9ms, flip angle 35°; with 8 echo times, first echo time in 1ms and interval was 1.3ms.

#### Image interpretation:

In this study (S. AX. Cardiac R2\* BH) is used for measuring the signal intensity of organs. The intensity of the signals (SI) of the liver and pancreas were measured by 2 circles of interest (ROIs) each measured 1cm<sup>2</sup>, down away from vessels, ducts and organ edges and the average is calculated. The (S.AX.Cardiac R2\*BH) introduce mean of signal intensity of different (ROIs) in form of T2\*=(N) and R2\*=(N) (N=number), T2\* is indirectly proportional with iron overload, and R2\* is directly proportional with iron overload. So, the hemosiderosis level in pancreas classified into (mild when R2\*=30-100Hz, moderate when R2\*=100-400Hz and sever when R2\* >400Hz).

#### Statistical analysis:

Test of data was done by SPSS [17]. This study compared between thalassemic and controls, thalassemic non diabetic and diabetic patients by using students *t*-test & mann-Whitney U-test for non parametric measures. Controls, thalassemic non diabetic and thalassemic diabetic groups have been

compared by using kruskal-wallis test. Pearson correlation coefficient was also used.

## Results

Iron overload confirmed when R2\* value of pancreas more than 30Hz and classified as mild, moderate and sever. Mild hemosiderosis is considered when the value is ranging from thirty to one hundred 30-100Hz, moderate hemosiderosis is considered when the value is ranging from one hundred to four hundred 100-400Hz and sever hemosiderosis is considered when the value is more than four hundred 400Hz. Pancreatic hemosiderosis is evident in 17/20 (85%) of patients.

Signal intensity of pancreas was correlated with liver ( $p<0.003$ ) and with age of diagnosis ( $p<0.002$ ). pancreatic SIR in our cases decreased when serum ferritin increased in most of cases denoting a negative correlation ( $p<0.004$ ) as shown in (Table 1).

Table (1): Correlation of ferretin level with pancreatic T2\*.

Cases	Serum ferritin	T2* of pancreas
1	216	42.5ms (normal)
2	2900	4.8ms (moderate iron overload)
3	3990	9.1ms (moderate iron overload)
4	6000	1.9ms (sever iron overload)
5	1000	39.5 (normal)
6	1000	19.2ms (mild iron overload)
7	3400	2.6ms (moderate iron overload)
8	1100	25.2ms (mild iron overload)
9	4144	6.6ms (moderate iron overload)
10	101	37ms (normal iron overload)
11	1900	14.5ms (mild iron overload)
12	1600	7.5ms (moderate iron overload)
13	2800	2ms (sever iron overload)
14	3500	10.1ms (mild iron overload)
15	5000	3.5ms (moderate iron overload)
16	11000	9.2ms (moderate iron overload)
17	5000	7.1ms (moderate iron overload)
18	3400	2ms (sever iron overload)
19	10000	2ms (sever iron overload)
20	7850	2.2ms (sever iron overload)

Correlation between serum ferritin and T2\* of pancreas.

$r=-0.610$ .

$p$ -value=0.004.

Moderate negative significant correlation.

There is positive correlation between reduction of pancreatic signal intensity and affection of the patient with diabetes. Control group and non diabetic thalassemic patients show higher pancreatic T2\* value as compared to diabetic patients (Table 2).

Pancreatic signal intensity was correlated with hepatic signal intensity ( $p<0.003$ ) and with age of diagnosis ( $p<0.002$ ). Pancreatic SIR in this study

decreased when serum ferritin increased in most of cases denoting a negative correlation ( $p < 0.004$ ). Table (3) shows values of serum ferritin.

Table (2): Correlation between thalassemic patients (diabetic and non diabetic) and controls in pancreatic signal intensity.

Diabetic/ non diabetic	T2* pancreas			Kruskal-Wallis Test	
	Range	Median	*IQR	$\chi^2$	p-value
Non diabetic	2.6-42.5	9.2	18.6	16.764	<0.001*
Diabetic	1.9-2.5	2	0.3		
Controls	38-45	41.5	4.25		
Mann-Whitney Test					
	N & D	N & C	D% C		
	0.001*	0.005*	0.008*		

\*IQR: The interquartile range.

Table (3): Ferritin level of thalassemic of patients.

	Range	Median	IQR
Ferritin level (ng/dl)	101-11000	3400	3775
HbF	3-88	29.5	29.5

Thalassemic patients with surgically removed spleen (12 cases) showed clear reduction in intensity of signal of the pancreas compared to intact spleen patients (6 cases) ( $p < 0.047$ ).

Correlation of pancreatic signal intensity with age, sex, family history and consanguinity history is not significant. Correlation with hemoglobin level and platelet count and HbF also is not significant. Hepatic hemosiderosis is severe in 80%, moderate in 5% and mild in 15% of the cases. Pancreatic hemosiderosis is severe in 25%, moderate in 40% and mild in 20% of cases while 15% show normal pancreatic signal intensity.

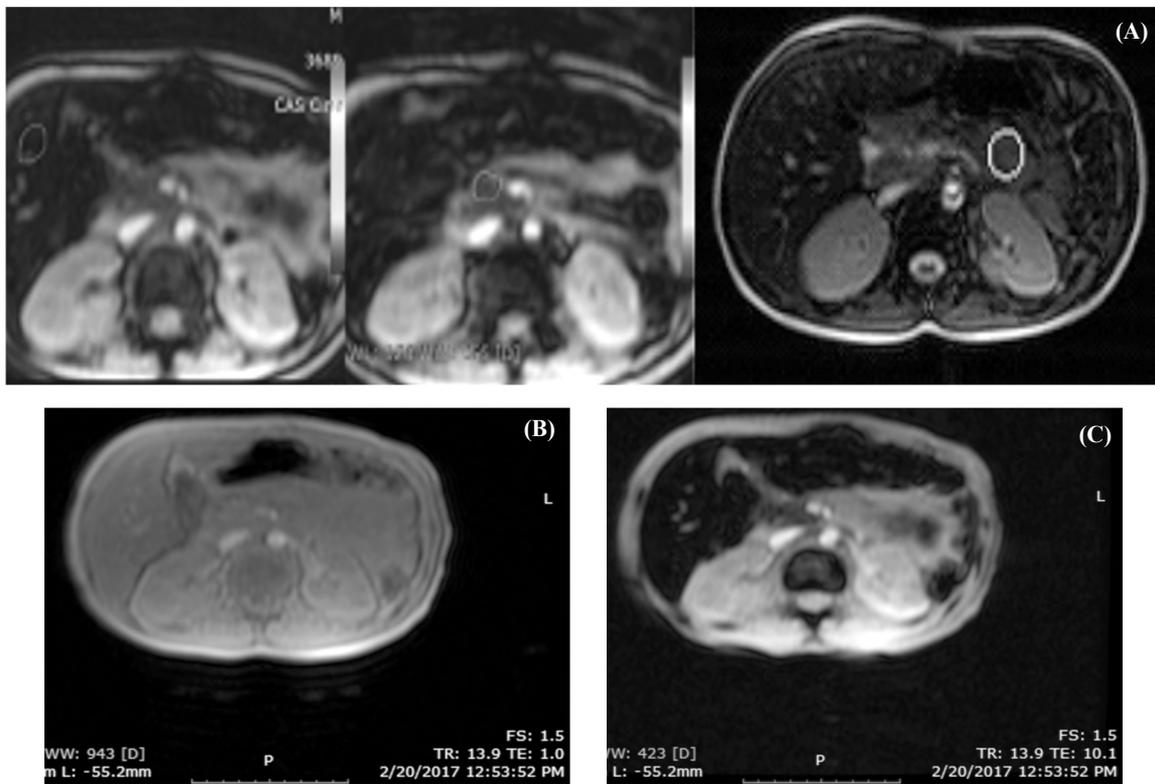


Fig. (1): (A) Axial images showing manually drawn ROI of liver and head and body of pancreas. (B,C) MRI T2\* multi-echo sequence of upper abdominal cut of male patient aged 9 years old, diagnosed as B-thalassemia major at 2 years with Hb F=25% (N up to=1%), Hb=6g/dl, platelet count=506000/cmm and blood transfusion every 6 weeks... Serum ferritin level=3990ng/ml and splenectomy is done (TR 13.9ms, flip angle 35, TE first=1ms, TE interval=1.3ms, 8 echoes, acquisition time: 14.5s) showing loss of signal intensity of liver and pancreas from the first echoes... Denoting iron overload.

T2\* of pancreas=9.1ms. T2\* of liver=2.9ms.

Diagnosis: Moderate hemosiderosis of pancreas and liver.

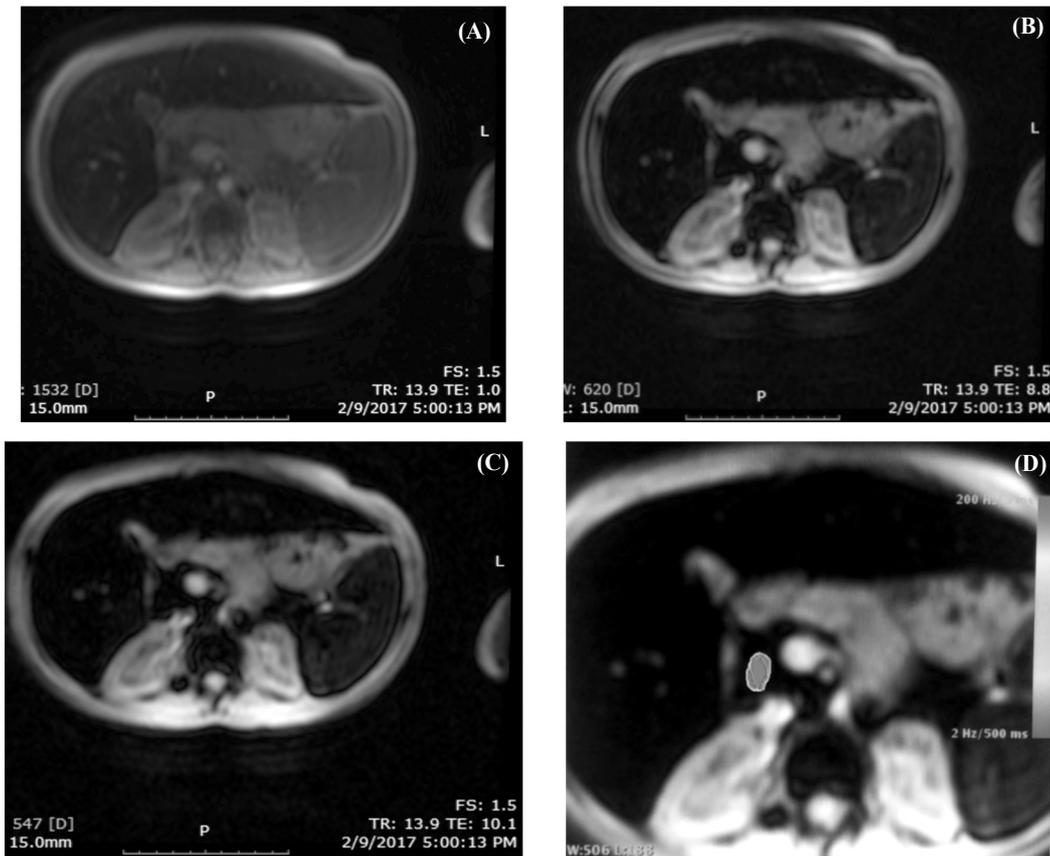


Fig. (2): (A,B,C) MRI T2\* multi-echo sequence of upper abdominal cut of female patient aged 10 years, diagnosed as thalassemic at 1 month with Hb F=14% (N up to=1%), Hb=7mg/dl, platelet count=506000mg/dl, blood transfusion every 15 day. Serum ferritin level=6000ng/ml and not splenectomized. The patient is diabetic also. (TR 13.9ms, flip angle 35, TE first=1ms, TE interval=1.3ms, 8 echoes, acquisition time: 14.5s) showing loss of signal intensity of liver and pancreas from the first echoes. Denoting iron overload.

T2\* of pancreas=1.9ms. T2\* of liver=1.4ms.

(D) Axial image showing manually drawn ROI of liver and head and body of pancreas.

*Diagnosis:* Severe pancreatic hemosiderosis leading to diabetes.. Severe hemosiderosis of liver.

## Discussion

Gradient echo T2 star imaging is a widely accepted method to evaluate iron deposition in the liver. The treatment of the main disease with repeated need for blood leads to iron accumulation which cause cell damage so the patients suffering increased with risk of diabetes which is likely to caused by expanded fringe protection from insulin and direct poisonous impact of overabundance press in the pancreatic cells. Biopsy may be replaced by gradient echo T2 star imaging in assessment of the iron level in its stores as both techniques have near similar results, however biopsy has complications and may be refused by the patient [1].

This study use the single breath T2\* gradient echo sequence because of its short filtering time which is more advantageous in youngsters.

The percent of diabetes in thalassemia major patients is 25% and this come in concurrence with different examinations changed from 8% up to 27% [18-20].

There is hepatic and pancreatic lower signal intensity ratio of patients with thalassemia contrasted with controls (Table 1). The conclusion of hepatic siderosis was shown up in 20/20 patients (100%) (15% mild, 5% moderate and 80% severe) and analysis of pancreatic siderosis was in 17/20 patients (85%) (20% mild, 40% moderate and 25% severe). Midiri et al., Papakonstantinou et al., Au et al., and Noetzli et al., said that pancreatic secondary hemosiderosis lead to abnormal dark pancreatic signal due to press over-burden up to 75-100% of the patients [22-25].

There is additionally recognized lower hepatic & pancreatic signal in the patients with IGT in

connection with patients with NGT (Table 1), in concurrence with Matter et al., Doaa Mohammad Youssef et al., and Papakonstantinou et al., [23,35,36].

Au et al., concluded that there was decrease in iron overload in pancreas with age, so T2\* increase in this case. In other hand, Christoforidis said that there was a decrease of T2\* of liver with increasing of age [24,26]. In this study there is positive significant relation between iron overburden and the age at the time of diagnosis.

There is additionally negative noteworthy connection between the signal of the pancreas and s. ferritin, like Midiri et al., [22] yet not concurrence with others [23,27].

Argyropoulou et al., stated that there was no relationship between pancreatic iron deposition/siderosis and serum ferretin. Argyropoulou et al., said the way that T2 relaxation time relies upon not only siderosis but also fatty invasion of the pancreas [27].

Likewise, negative relationship between serum ferritin and signal of liver was distinguished in concurrence with numerous examinations [27-30] while no comparative connection was noted in different investigations [26,31].

There is strong relation of pancreatic T2\* and hepatic T2\*. This result was like Brewer et al., [32], but no similar correlation in Papakonstantinou et al., Au et al., and Noetzli et al., [23-25,33]. This conflict may be due to their patients are adult and pancreatic parenchyma is replaced by fat which is affect values of MRI.

In this study there is huge decrease in pancreatic signal in surgically removed spleen of thalassemic patients contrasted with those with in place spleen in concurrence with Doaa Mohammad Youssef et al., [36]. This due to lack of other store for iron as spleen in our case [32,34,35].

The inclusion of children B thalassemic patients who not affected yet by fatty infiltration and many other disease is the main advantage of this study, and all of them are examined in one MRI machine and same doctors. The main study limitation is that the patients are very young, so they afraid from MRI machine and need every time psychological sedation. MRI is useful in follow-up risky thalassemic patients who exposed to diabetes to prevent further complication.

#### Conclusion:

T2\* gradient weighted MRI assume a vital part in detection of iron over-burden in B thalassemic

patients. Serious chelation system is prescribed in this study and it is much more important for patients with IGT. Regular follow-up by susceptibility weighted sequences of magnetic resonance imaging to survey change of secondary hemosiderosis of pancreatic tissue is recommended.

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## دور الرنين المغناطيسى فى قياس مستوى ترسب الحديد فى أعضاء مرضى أنيميا البحر الأبيض المتوسط

مرض أنيميا البحر المتوسط من أكثر الأمراض الجينية الوراثية شيوعا، يتميز بمعالجته بنقل دم متكرر. العرض الجانبى المشهور لهذا الدم المتكرر هو زيادة نسبة الحديد فى دم المرضى. وبالتالي ترسب الحديد فى الأعضاء الحيوية مما يؤدي إلى أذى خلاياها وبالتالي فقدان وظائفها.

هناك طرق لقياس مستوى الحديد فى الدم فى المعامل لكنها غير دقيقة لقياس ترسب هذا الحديد فى الأعضاء خصوصا فى حالات الإلتهابات الكبدية التى تعطى نتائج مزيفة لزيادة معدل الحديد فى الدم.

يقاس كمية الحديد فى الكبد بدقة عن طريق أخذ عينة الكبد وتحليلها. هذه الطريقة تحمل مضاعفات كآى عملية جراحية أخرى من النزيف إلى التلوث تصل إلى (٥٪) إضافة إلى أن المرضى لا يفضلونها.

تلف الوظائف الإفرازية للبنكرياس من أهم المضاعفات التى تحدث لمرضى أنيميا البحر الأبيض المتوسط من ترسب الحديد فيه، لذلك عادة ما يصاب هؤلاء المرضى بمرض السكر نتيجة لتلف الوظائف البنكرياسية فى إفراز الأنسولين.

الرنين المغناطيسى من أفضل الطرق لقياس نسبة ترسب الحديد فى الكبد والبنكرياس بطريقة غير جراحية وغير مؤذية.

ويعد دراسة قيمة هذا الموضوع تبيين أن: إنخفاض شديد فى درجة الإشارة فى رنين كبد وبنكرياس مرضى أنيميا البحر الأبيض المتوسط مقارنة بغير المرضى.

إنخفاض أكبر فى كبد وبنكرياس مرضى أنيميا البحر الأبيض المتوسط المصابين بمرض السكر مقارنة بمرضى أنيميا البحر الأبيض المتوسط الغير مصابين به.

مرضى أنيميا البحر الأبيض المتوسط المستأصل طحالهم تنخفض إشارة الكبد والبنكرياس فى الرنين المغناطيسى مقارنة بالغير مستأصل طحالهم.

وأخيرا... نرى أنه يجب متابعة قوية لمرضى أنيميا البحر الأبيض المتوسط بعلاج ترسب الحديد وتقييم تأثير العلاج بالرنين المغناطيسى للكبد والبنكرياس والقلب لمعرفة كمية الترسب ووضع المضاعفات فى الحسبان.