

The Oxidant and Antioxidant Status in β -Thalassemia Major Patients

ALIAA A.F. IBRAHIM, M.Sc.*; TAMER A. EL-BEDEWY, M.D.*; EBAA H. EL-SHEIKH, M.D.* and AMAL HELMY ABD EL-HAMEED, M.D.**

The Departments of Internal Medicine* and Clinical Pathology**, Faculty of Medicine, Tanta University

Abstract

Background: Thalassemia is associated with anemia and lifelong blood transfusion that lead to oxidant-antioxidant disturbance due to massive iron deposits with generation of labile iron in the red blood cells, which promotes the formation of Reactive Oxygen Species (ROS) with cumulative cell damage.

Aim of the Work: Evaluation of Ischemia Modified Albumin (IMA) as a marker of oxidative stress and Superoxide Dismutase (SOD) as a marker of antioxidant status in patients with β -Thalassemia Major (β -TM).

Subjects and Methods: Forty patients with β -TM were divided into 2 groups well chelated (group 1) and poorly chelated (group 2). Twenty healthy participants of matched age and sex were taken as controls (group 3). All patients and controls were subjected to complete history taking, clinical examination. Serum ferritin, IMA and SOD were measured.

Results: There were significant higher levels of IMA in thalassemia patients than controls (p -value $<0.001^*$). IMA correlated significantly positive with serum ferritin ($r=0.339$, p -value 0.032^*). There were significant lower levels of SOD in thalassemia patients than controls (p -value $<0.001^*$). SOD correlated significantly negative with serum ferritin ($r=-0.718$, p -value $<0.001^*$).

Conclusion: IMA as a new marker of oxidative stress increased in β -TM patients and SOD as a marker of antioxidant status decreased in β -TM patients.

Key Words: β -thalassemia major – Oxidant – Antioxidant – Ischemia Modified Albumin (IMA) – Superoxide Dismutase (SOD).

Introduction

β -THALASSEMIA syndromes are the most common inherited hemoglobinopathies in the world caused by an autosomal recessive genetic deficiency in the β -globin chain synthesis leading to accumulation of unpaired β -globin chains [1].

β -Thalassemia Major (β -TM) is the most severe form and is typically diagnosed with profound anemia during infancy, requiring long-term transfusion and iron chelation therapy for survival [2]. Patient with thalassemia develops several complications including cardiac, endocrinal, and hepatic dysfunctions. Several factors are responsible for these abnormalities including hemolysis and excess iron deposition [3].

The status of iron overload and iron-induced oxidative stress has been repeatedly investigated in patients with β -thalassemia major [4]. Many studies reported increased serum ferritin levels, blood levels of the redox active fractions of Non-Transferrin Bound Iron (NTBI) and Labile Plasma Iron (LPI) in patients with β -thalassemia [5]. It has also been demonstrated that such patients experience decreased antioxidant capacity [6].

Reactive Oxygen Species (ROS) resulting from conditions such as ischemia, hypoxia and free iron can decrease the ability of the N-terminus of serum albumin to bind with transition metals such as cobalt, copper and nickel [7]. Human serum albumin with a decreased binding capacity as a result of ischemic events and oxidative stress is referred to as Ischemia Modified Albumin (IMA) [8].

IMA is currently used as an early marker for myocardial ischemia [9]. However, recent studies have reported increased levels of IMA in conditions other than ischemic heart diseases including diabetes mellitus and hyperlipidemia [10].

Endogenous antioxidants, like Superoxide Dismutase (SOD) is the first barriers to the change of the internal environment influenced by the increase of free radicals and abundant stress, creating superactive oxygen. However, much of the data from thalassemic patients state that SOD level can vary

Correspondence to: Dr. Aliaa A.F. Ibrahim,
The Department of Internal Medicine, Faculty of Medicine,
Tanta University

from a low level, no different from healthy individuals, up to a high level [11].

Subjects and Methods

This cross-sectional study was carried out on 40 patients with beta thalassemia major (β -TM); they were randomly selected from in and out-patients of the Hematology Unit, Internal Medicine Department, Faculty of Medicine, Tanta University in the period from July 2016 to December 2016. Twenty healthy participants of matched age and sex were taken as controls. All participant provided informed written consent and the study was approved by Tanta Faculty of Medicine Ethical Committee.

The subjects were divided into 3 groups:

Group 1: 20 well chelated β -TM patients (with mean serum ferritin <2500ng/ml).

Group 2: 20 poorly chelated β -TM patients (with mean serum ferritin >2500ng/ml).

Group 3: 20 age-matched and sex-matched healthy participants were included in the study as controls.

Exclusion criteria:

Patients with other hemoglobinopathies, other hemolytic anemia, liver cell failure, hypothyroidism, hyperthyroidism, diabetes mellitus, acute inflammation, cardiac diseases.

All patients and controls will be subjected to full history taking including age, sex, disease duration, first time of blood transfusion, number of blood transfusions/year, history of splenectomy, postsplenectomy duration, and type and duration of chelation therapy. Complete clinical examination including weight, height. Laboratory investigations including Complete Blood Count (CBC), serum ferritin level, serum Ischemia Modified Albumin (IMA), serum Superoxide Dismutase level (SOD).

All samples were taken under complete aseptic measures, withdrawal of 5ml venous blood sample was done from both patients and controls, 1ml of which was placed on EDTA-vacationer for complete blood count, 3.5ml was centrifuged at room temperature 10-20 minutes at speed of 2000-3000 r.p.m for serum separation and was stored at -20 degrees for assay of serum ferritin and serum ischemia modified albumin. The remaining 0.5ml of blood was placed on EDTA for measurement of superoxide dismutase level. The sample was cen-

trifuged for 10 minutes at 4000r.p.m, the plasma was aspirated off, erythrocytes were washed 4 times with 3ml of 0.9 NaCl solution, then were centrifuged for 10 minutes at 4000r.p.m after each wash, then 2ml of cold redistilled water was added to the washed centrifuged erythrocytes and immediately was stored at -70 degrees. All samples were taken before transfusion.

Statistical analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests by SPSS (V17). Chi-square the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Linear correlation coefficient was used for detection of correlation between two quantitative variables in one group. ANOVA test was used for comparison among different times in the same group in quantitative data. A *p*-value of less than 0.05 was considered statistically significant.

Results

Our study included 40 adult patients with β -TM (well chelated and poorly chelated) (group 1,2). Twenty healthy participants of matched age and sex were taken as controls (group 3). There were insignificant difference between all the studied groups as regard sex and age respectively (*p*-value= 0.419, 0.909) (Tables 1,2).

Our results showed significantly lower levels of Hemoglobin (Hb) in β -TM patients in comparison with controls (Table 3).

Our results showed significantly higher levels of serum ferritin in β -TM patients in comparison with controls and higher level of serum ferritin in poorly chelated in comparison with well chelated patients. Table (4) and Fig. (1).

There were significantly higher levels of IMA in poorly chelated in comparison with well chelated patients. And, significantly higher levels of IMA in TM patients especially poorly chelated in comparison with controls. Table (5) and Fig. (2).

There were significantly lower levels of SOD in TM patients in comparison with controls. And, significantly higher levels of SOD in well chelated when compared with poorly chelated patients. Table (6) and Fig. (3).

Table (7) and Fig. (4A,B): There were significantly negative correlation between IMA and SOD levels ($r=-0.342$, p -value=0.031 *).

There were significantly positive correlation between IMA and serum ferritin levels ($r=0.339$, p -value=0.032*).

There were insignificant correlation between IMA and (age, Hb) in thalassemia patients (p -value =0.367, 0.916) respectively.

Table (8) and Fig. (5): There were significantly negative correlation between SOD and serum ferritin levels ($r=-0.718$, p -value <0.001 *).

There were insignificant correlation between SOD and (age, Hb) (p -value=0.808, 0.882) respectively.

Table (1): Comparison between all the studied groups as regard sex.

Sex	Groups						Chi-square test	χ^2	p -value
	Thalassemia well chelated (group 1)		Thalassemia poorly chelated (group 2)		Controls (group 3)				
	N	%	N	%	N	%			
Male	10	50.0	9	45.0	13	65.00	1.741	0.419	
Female	10	50.0	11	55.0	7	35.00			
Total	20	100.00	20	100.00	20	100.00			

Table (2): Comparison between all the studied groups as regard age.

Groups	Age (years)		ANOVA test	
	Range	Mean \pm SD	F	p -value
• Thalassemia well chelated (group 1)	18-36	24.900 \pm 5.036	0.096	0.909
• Thalassemia poorly chelated (group 2)	18-38	24.350 \pm 4.902		
• Controls (group 3)	19-35	24.950 \pm 4.489		

Table (3): Comparison between all the studied groups as regard Hemoglobin (Hb) level.

Groups	Hb (gm/dl)		ANOVA test	
	Range	Mean \pm SD	F	p -value
• Thalassemia well chelated (group 1)	6.5-9	7.830 \pm 0.712	238.800	<0.001*
• Thalassemia poorly chelated (group 2)	6.4-9.5	7.700 \pm 0.974		
• Controls (group 3)	11.4-12.8	12.17 \pm 0.408		
TUKEY'S test				
Group 1 & 2	0.842			
Group 1 & 3		<0.001*		
Group 2 & 3			<0.001*	

Table (4): Comparison between all the studied groups as regard serum ferritin level.

Groups	S. ferritin (ng/ml)		ANOVA test	
	Range	Mean \pm SD	F	p -value
• Thalassemia well chelated (group 1)	145-2217	1247.900 \pm 608.709	224.008	<0.001*
• Thalassemia poorly chelated (group 2)	2500-4000	3031.850 \pm 452.926		
• Controls (group 3)	30-280	115.600 \pm 57.348		
TUKEY'S test				
Group 1 & 2	<0.001*			
Group 1 & 3		<0.001*		
Group 2 & 3			<0.001*	

*: Significant.

Table (5): Comparison between all the studied groups as regard Ischemia Modified Albumin (IMA) level.

Groups	IMA (ng/ml)		ANOVA test	
	Range	Mean \pm SD	F	p -value
• Thalassemia well chelated (group 1)	35-111	68.600 \pm 23.473	11.341	<0.001*
• Thalassemia poorly chelated (group 2)	46-368	141.250 \pm 98.766		
• Controls (group 3)	57-68	61.450 \pm 2.819		
TUKEY'S test				
Group 1 & 2	<0.001*			
Group 1 & 3		0.921		
Group 2 & 3			<0.001*	

Table (6): Comparison between all the studied groups as regard Superoxide Dismutase (SOD) level.

Groups	SOD (U/ml)		ANOVA test	
	Range	Mean \pm SD	F	p -value
• Thalassemia well chelated (group 1)	86-153	108.200 \pm 20.320	227.259	<0.001*
• Thalassemia poorly chelated (group 2)	35-70	51.950 \pm 11.537		
• Controls (group 3)	164-260	201.400 \pm 30.956		
TUKEY'S test				
Group 1 & 2	<0.001*			
Group 1 & 3		<0.001*		
Group 2 & 3			<0.001*	

Table (7): Correlation between IMA and (SOD, age, Hb and serum ferritin) in thalassemia patients.

Thalassemia	Correlations	
	r	p -value
SOD (U/ml)	-0.342	0.031*
Age (years)	0.147	0.367
Hb (gm/dl)	-0.017	0.916
S. ferritin (ng/ml)	0.339	0.032*

Table (8): Correlation between SOD and (age, Hb and serum ferritin) in thalassemia patients.

Thalassemia	Correlations	
	<i>r</i>	<i>p</i> -value
Age (years)	0.040	0.808
Hb (gm/dl)	-0.024	0.882
S.ferritin (ng/ml)	-0.718	<0.001*

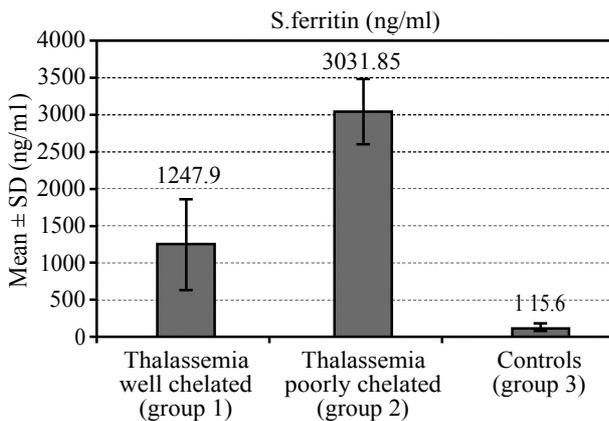


Fig. (1): Comparison between all the studied groups as regard serum ferritin level.

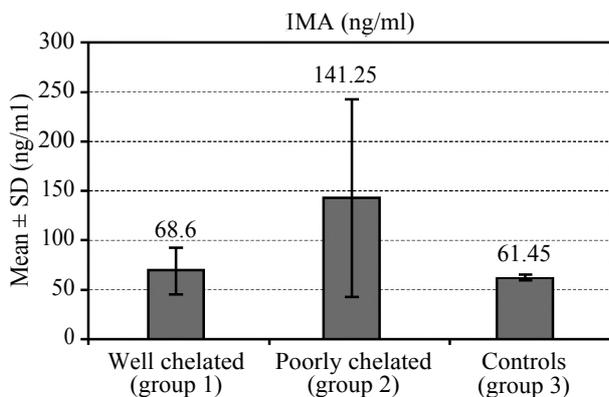


Fig. (2): Comparison between all the studied groups as regard ischemia modified albumin (IMA) level.

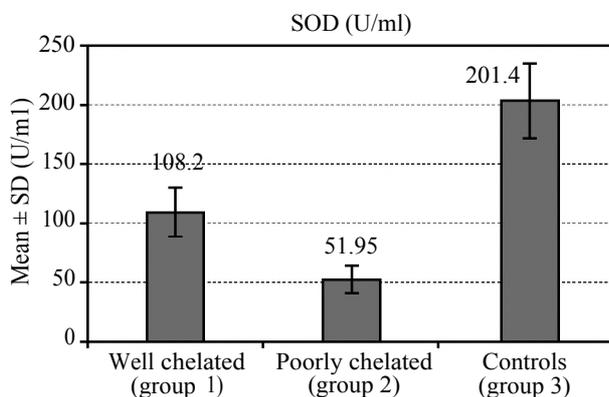
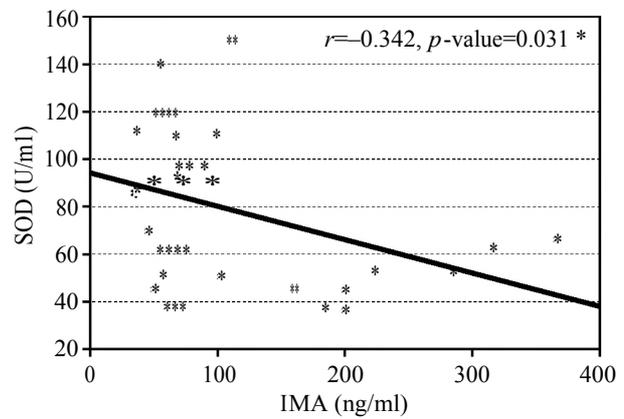


Fig. (3): Comparison between all the studied groups as regard SOD level.



Fi. (4A): Correlation between IMA level and SOD level in thalassemia patients.

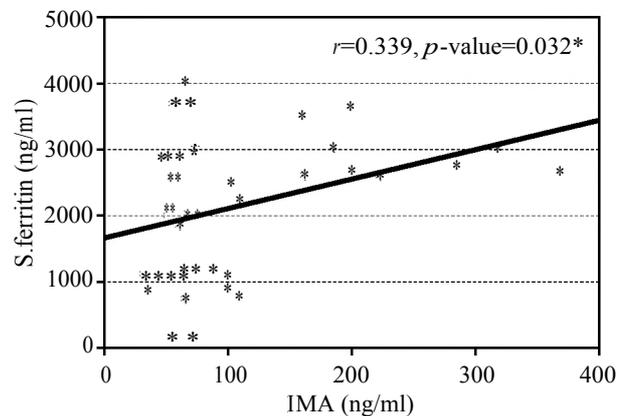


Fig. (4B): Correlation between IMA level and serum ferritin level in thalassemia patients.

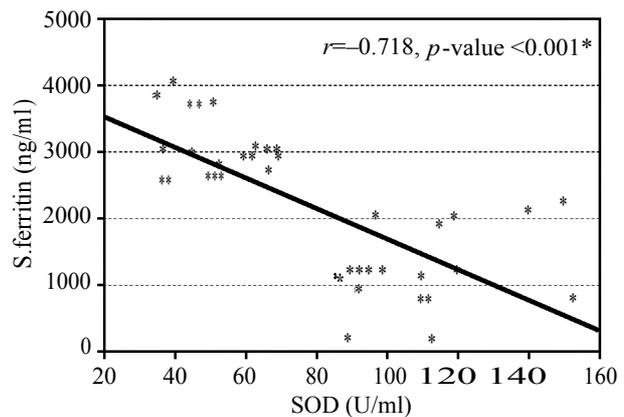


Fig. (5): Correlation between SOD level and serum ferritin level in thalassemia patients.

Discussion

Patients with thalassemia major are transfusion-dependent. Iron overload causes most of the mortality and morbidity and excess iron is deposited in major organs resulting in organ damage [12]. Effective and convenient iron chelation therapy remains one of the main targets of clinical management of thalassemia major [13].

High serum ferritin is a predictable consequence of continuous blood transfusion in thalassemia patients, it remains the most common indicator of iron overload in thalassemia patients [14]. In agreement with these observations, high levels of serum ferritin noted in our patients are strongly suggestive of a state of iron overload. As a result of iron overload, redox active fractions such as Non-Transferrin-Bound Iron (NTBI) and Labile Plasma Iron (LPI) are expected to increase in circulation [5,12]. These fractions can catalyze the production of ROS contributing to significant tissue injury. Under such conditions, it is very possible that such redox active forms of iron could contribute to the formation of IMA in thalassemia patient; a finding that has been noted by this study.

In our study, IMA was significantly higher in thalassemia patients compared with the control ($p < 0.001^*$). In agreement with our results, Awadallah et al., [15]. They attributed their finding to the increased level of IMA in thalassemia patients that are likely to be a result of iron-induced oxidative stress and hence its potential significance as a new marker of oxidative stress in such patients. In addition, Sbarouni et al., [16] postulated that overproduction of Reactive Oxygen Species (ROS) resulting from conditions related to ischemia, hypoxia, acidosis, free radicals, and free iron plays a major role in the formation of IMA. Generation of ROS can transiently modify the N-terminal region of albumin and produce an increase in IMA levels [17].

In our study, we noticed a significant positive correlation between serum ferritin and IMA levels ($r=0.339$, p -value= 0.032^*). This is in accordance with the study by Awadallah et al., [15]. When iron overload exceeds the storage capacity of the cell, free iron start to deposit in the organs and that in turn leads to overproduction of ROS that plays a major role in the formation of IMA [16,18].

Our study proved that IMA level was significantly higher in poorly chelated thalassemia patients with serum ferritin ≥ 2500 ng/ml when compared with well chelated thalassemia patients with serum ferritin < 2500 ng/ml (141.250 ± 98.766 vs 68.600 ± 23.473 , p -value $< 0.001^*$). Similar to our results, Akrawinthewong et al., [19] stated that Deferiprone (DFP) therapy alone improved iron overload and oxidative stress [19]. This can be attributed to the fact that DFP chelates the excess of iron, reducing the circulating and intracellular free iron that lead to decreased formation of ROS [20].

SOD is an intracellular enzyme that is responsible for changes in the oxidant-antioxidant balance

in cells. Enzyme function is to catalyze modifying ion free radicals, especially O_2^- into H_2O [21]. In subjects with thalassemia, enormous free radicals built up due to the state of iron overload (resulting from transfusions and ineffective erythropoiesis). Iron (Fe) is able to accelerate the change of molecular oxygen into reactive oxygen radicals, superoxide, and hydroxyl groups through the Fenton reaction [22,23].

Our study proved that SOD level was significantly lower in thalassemia patients when compared with control (p -value $< 0.001^*$).

Similar to our results, Patne et al., [24] also present data showing that the levels of erythrocyte antioxidant enzymes, especially SOD activity, decreased significantly in patients who were transfusion-dependent.

However, different results were shown by other research centers. Simsek et al., [25] found that the level of SOD in thalassemia patients were higher than the healthy control. Other publications mention that SOD did not show significant differences between healthy controls and thalassemia subjects [26].

Increased levels of antioxidants, including SOD, occur in various circumstances: Including an acute inflammatory phase, a state of trauma, and upon exposure to increased levels of pro-oxidants. The increase was associated with a compensatory mechanism to break down free radicals had been caused by oxidative stress and lipid peroxidation [27,28]. This is supported by other publications, which state that chronic stress in diabetes mellitus, metabolic syndrome, chronic liver disease, SLE, and rheumatoid arthritis affect the decrease in antioxidant enzyme capacity [29-31].

In our study, there was significant negative correlation between SOD and serum ferritin. SOD decreased in poorly chelated patients with s.ferritin ≥ 2500 ng/ml when compared with well chelated with s.ferritin < 2500 ng/ml ($r=-0.718$, p -value $< 0.001^*$).

Research in Jakarta said that the decrease of antioxidant enzymes in patients related to non-chelating subjects, while administration of chelation therapy on a regular basis, could increase the capacity of the enzymes SOD [31-33].

In many cases with impaired oxidant-antioxidant mechanisms, administering an iron chelator will improve the prognosis of various disorders,

including neurodegenerative disease, cardiovascular impairment and iron overload [34-37].

Conclusion:

From this study, we concluded that Ischemia Modified Albumin (IMA) as a new marker of oxidative stress increased in patients with β -thalassemia major especially poorly chelated. Superoxide Dismutase (SOD) is a marker of antioxidant status which decreased in β -thalassemia major patients especially poorly chelated.

Recommendations:

Further studies to investigate oxidant and antioxidant status in thalassemia on large scale of patients for long duration and with more advanced methods, to determine the benefit of administering the selective antioxidant therapy, a well-balanced diet on oxidative injury in thalassemia patients and use of chelating agents to reduce high ferritin level.

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Conflict of interest:

None declared.

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حالة الأكسدة ومضادات الأكسدة فى مرضى الثلاسيميا العظمى-بيتا

يعتبر مرض بيتا ثلاسيميا العظمى من متلازمات البيتة ثلاثيميا وهو الشكل الأكثر حده وعادة ما يتم تشخيص المصابين به عن طريق فقر الدم الحاد أثناء مرحلة الطفولة والذي يتطلب نقل الدم بشكل دائم وعلاج محدد لإزالة الزيادة الكبيرة فى نسبة الحديد بالدم والتي تعرض المريض لأمراض القلب والغدد الصماء والكبد نتيجة تكسير الدم وترسب الحديد الزائد. ويعتبر نقص التروية للزلال المعدل هو نوع متغير للزلال بالدم فى ظل ظروف الأكسدة والتي تحدث لدى مرضى الثلاسيميا العظمى. وجد أن قدرة البيومين المصل البشرى على الارتباط بالعناصر الفلزية الإنتقالية مثل الكوبالت تقل فى حالة نقص التروية ووزيادة الأكسدة وزيادة الحديد ويسمى فى هذه الحالة (الزلال المعدل). والعلاقة بين (نقص التروية للزلال المعدل) ومرض البيتة ثلاسيميا العظمى كعلامة لحالة الأكسدة مازالت تحت البحث بالإضافة للعلاقة بينه وبين زيادة الفريتين. وتعتبر مضادات الأكسدة الذاتية مثل السوبر أكسيد ديسميوتاز هى الحاجز الأول للتغيرات بالبيئة الداخلية والتي تتأثر بزيادة العناصر الحرة وخلق الأكسجين السوبر النشط ومع ذلك فإن الكثير من البيانات عن مرضى الثلاسيميا أظهرت أن مستوى السوبر أكسيد ديسميوتاز يمكن أن يختلف من مستوى منخفض (لا يختلف عن الأصحاء) ويصل إلى مستوى عالى وهذا بإختلاف العلاج.

الهدف من البحث: تهدف الدراسة إلى تقييم مستوى نقص التروية للزلال المعدل كمؤشر للأكسدة ومستوى سوبر أكسيد ديسميوتاز كمضاد للأكسدة فى مرضى الثلاسيميا العظمى-بيتا.

البحث: أجريت الدراسة على أربعين مريضا يعانون من الثلاثيميا-بيتا مقسمين إلى عشرين مريضا مع نسبة فيريتين أقل من ٢٥٠٠ وعشرين مع نسبة فيريتين أكبر من أو يساوى ٢٥٠٠. وأيضا عشرين من المتطوعين الأصحاء ظاهريا فى نفس المتوسط العمرى والجنس (كمجموعة ضابطة). وقد تم إجراء الفحوص التالية: التاريخ المرضى ويشمل (السن، الجنس، تاريخ المرض، نقل الدم، إستئصال الطحال....)، الفحوصات الإكلينيكية (الطول، الوزن،) الفحوصات المعملية وتشمل: صورة دم كاملة، نسبة الفريتين بمصل الدم، نسبة (نقص التروية للزلال المعدل) بمصل الدم، نسبة (سوبر أكسيد ديسميوتاز) بمصل الدم.

النتائج: إرتفاع مستوى الزلال المعدل بالدم ومستوى الفريتين لمرضى الثلاسيميا العظمى مقارنة بالأصحاء. يتناسب مستوى الفريتين بالدم تناسباً طردياً مع مستوى الزلال المعدل بالدم فى مرضى الثلاسيميا العظمى. مستوى الزلال المعدل بالدم أعلى فى مرضى الثلاسيميا الغير منتظمين على تناول مستقبات الحديد (نسبة الفريتين أكبر من أو يساوى ٢٥٠٠) عن المرضى المنتظمين فى تناول مستقبات الحديد (نسبة الفريتين أقل من ٢٥٠٠). إنخفاض مستوى السوبر أكسيد ديسميوتاز فى مرضى الثلاسيميا العظمى مقارنة بالأصحاء.

يتناسب مستوى الفريتين بالدم تناسباً عكسياً مع مستوى السوبر أكسيد ديسميوتاز فى مرضى الثلاسيميا العظمى.

مستوى السوبر أكسيد ديسميوتاز أقل فى مرضى الثلاسيميا الغير منتظمين على تناول مستقبات الحديد (نسبة الفريتين أكبر من أو يساوى ٢٥٠٠) من المرضى المنتظمين فى تناول مستقبات الحديد (نسبة الفريتين أقل من ٢٥٠٠).

التوصيات: يجب على الدراسات المستقبلية أن تتناول حالات أكبر وفترة زمنية أطول ووسائل متقدمة فى تقييم حالة الأكسدة فى مرضى الثلاسيميا. المزيد من الدراسات لتقييم دور مضادات الأكسدة وتناول الطعام الصحى المتوازن وتأثيره فى حالة الأكسدة فى مرضى الثلاسيميا.