The Relation between Oxidative Stress and Serum Ferritin in Patients with β-thalassemia Major Treated by Iron Chelating Agents

Maes MK. Alkhyatt, MSc* Kassim SA. Al Neaimy, Ph.D** Madyan MF. Algrer, Specialist in Pediatric***

ABSTRACT

Background: The increased iron level aids the formation of many of oxygen-reactive compounds via Haber-Weiss and Fenton reactions. These compounds participate in the metal regulation of the redox reaction and can affect many organs, erythrocytes and endocrine glands causing disturbances in the function of these organs. Iron chelating therapy is required to detoxify iron's toxic effects to avoid oxidative injury.

Objective: This research aims to determine the relationship between oxidative status and serum ferritin in major β- thalassemic patients treated by iron chelating agents (deferasirox and deferoxamine).

Methods: It is a cross-sectional study, 55 known cases of β-thalassemic patients receiving chelating agents therapy under follow-up participated in the study, their ages ranged between 3-20 years, divided into two groups, group one consisted of 30 patients, 14 male and 16 female, received oral agent deferasirox, Group two consisted of 25 patients, 11 male and 14 female, on Deferoxamine therapy. Total antioxidant capacity (TAOC), serum Malondialdehyde (MDA), haemoglobin and serum ferritin were measured in the studied groups.

Results: the TAOC in the patients group on Deferoxamine, is significantly higher than in the Defrasirox group (34.5±13.2; 29.8±11.8 u/ml) respectively, while MDA is higher in Defrasirox than in patients in the deferoxamine group (8.6±5.4; 5.8 ±4.4 nmol/ml) respectively. A non-significant variation in serum ferritin levels and haemoglobin between the 2 groups was found. A considerable affirmative correlation, between TAOC and serum ferritin, and a non–considerable affirmative correlation between MDA and serum ferritin.

Conclusion: A considerable affirmative correlation, between TAOC and serum ferritin, and anon – considerable affirmative correlation between MDA and serum ferritin when comparing the results of all patients as one group, were found.

Keywords: Thalassemia, Oxidative Stress, Serum ferritin, Deferasirox, Deferoxamine

INTRODUCTION

β-thalassemia is the utmost prevalent major public health problem worldwide. β-thalassemias are a family of genetic haematological diseases depicted by decreased or lack of formation of β-globin string symbolizing one of the farthest widespread autosomal perverted genetic diseases over the world(1-3). As a result of the decreased or lack of β-globin string synthesis, there is a surplus in α-globin strings which are unsteady and deposit in erythrocyte cell precursors leading to unusual cell growth and devastation in the bone marrow, resulting in severe anaemia due to hemolysis and abnormal erythropoiesis (4, 5).

β-thalassemia major patients require repeated blood transfusions to treat the anaemia, in addition, the breakdown products of haemoglobin, and iron absorption are increased from the stomach and intestine causing secondary accumulation (6-8). Iron will be precipitated as hemosiderin in many tissues, and provoke the reduction/oxidation reactions, and formation of reactive oxygen species metabolites, for example, superoxide, hydrogen peroxide, and hydroxyl radical, mainly via Fenton and Haber- Weiss reactions, that are accountable for the progression of oxidative stress in patients with thalassemia, causing damage in lipids, proteins, DNA (9-11).

Although iron excess may be reversed by chelation treatment, the principal issue is organ damage attributed to oxidation (12). Therefore, therapy with chelating agents example deferoxamine, and deferasirox, accompanied by blood transition is the cornerstone for treating anaemia and prevention of iron overload-induced complications (13). Therefore the purpose of the present work is to evaluate the relation between iron overload levels and oxidative stress in the hope of preventing organ damage caused by iron-mediated oxidation in these patients by chelating agents therapy.

PATIENTS AND METHODS

A cross-sectional study was done after obtaining approval from the ethical committee of research in the College of Medicine, University of Nineveh. Au courant paternal endorsement was acquired from all entrants before recruited in the project and carried out on 55 known cases of β-thalassemic patients receiving chelating agents therapy under follow-up, their ages ranged between 3-20 years, divided into two groups, group one consisted of 30 patients, 14 male and 16 female, received oral agent deferasirox tablet at dose 20-40mg/kg. Group two

* College of Pharmacy, Ninevah University, Mosul, Iraq.
** College of Medicine, Ninevah University, Mosul, Iraq.
Email: abdullah.kassim@uoninevah.edu.iq
*** Thalassemia Centre, Ibn-Alatheer Teaching Hospital, Mosul, Iraq.

consisted of 25 patients, 11 male and 14 female, on intravenous therapy with deferoxamine at dose 20-50mg/kg. Biochemical analysis of Total antioxidant capacity (TAOC), serum Malondialdehyde (MDA), and serum ferritin levels were measured in both groups using Colorimetric Assay Kit Elabscience® (USA).

RESULTS

Table (1) shows the statistical characteristics of the enrolled individuals. Both patient groups were similar regarding age and gender. No statistically considerable variation in the age of deferasirox and deferoxamine groups (12.93±4.77; 12.60±4.62), respectively. The number of patients and male-to-female numbers were matched since the ratio was similar. No significant difference in BMI (17.7± 2.5; 18 ± 2.6) respectively.

Table 1. The statistical characteristics of the studied groups

Character	Deferasirox (N=30)	Deferoxamine (N=25)	p-value	Test analysis
Age (years)	12.93±4.77	12.60± 4.62	0.7	t-test
Gendre M F	14 (46.7%) 16 (53.3%)	11 (44.0%) 14 (56.0%)	0.3	Chi-square
BMI (kg/m^2)	17.7±2.5	18±2.6	0.3	t-test

Table 2 shows the TAOC, and MDA, of the studied groups. The TAOC in the patients group on Deferoxamine, is significantly higher than Defrasirox (34.5±13.2; 29.8±11.8 * u/ml), respectively, while MDA is higher in Defrasirox than in patients in the defroxamine group (8.6±5.4 ; 5.8 ±4.4 nmol/ml), respectively.

Table 2. The TAOC, and MDA of both groups

Parameters	Deferasirox N=30	Deferoxamine N=25	p-value
T-AOC (u/ml)	29.8±11.8	34.5±13.2*	0.04
MDA (nmol/ml)	8.6±5.4*	5.8 ± 4.4	0.04
*significantly higher at p<0.05 using t-test			

Table (3): shows the serum levels of serum ferritin and haemoglobine in the studied groups. There is a non –significant difference in haemoglobin levels between the two groups. Serum ferritin concentration is non-significantly higher in the deferoxamine group than in the deferasirox group patients (2597±1016; 2343±852 ng/ml) respectively.

Table 3. The serum levels of serum ferritin and haemoglobin.

Parameters Mean ± SD	Deferasirox (N=30)	Deferoxamine (N=25)	p-value
Hb% (g/L)	6.42±0.81	6.20±1.07	0.3
S. Ferritin (ng/ml)	2343±852	2597±1016	0.3

Figure (1) A positive considerable correlation exists between TAOC and serum ferritin , and non-considerable positve correlation between MDA and serum ferritin in the derasirox group, while deferoxamine shows a positive non considerable correlation exists between TAOC and serum ferritin , and non conisiderable negative correlation between MDA and serum ferritin. There is a considerable affirmative connection between TAOC and serum ferritin and a non-considerable positive connection between MDA and serum ferritin when comparing the results of all patients as one group.

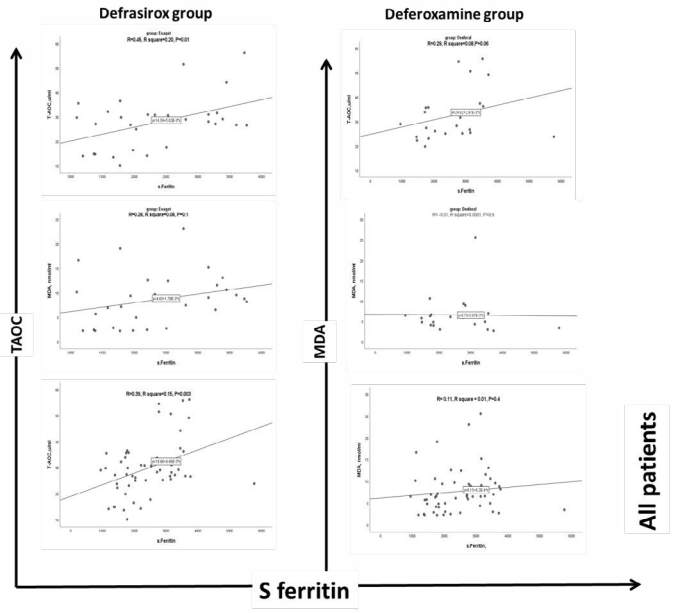

Figure 1. Correlation between oxidative stress parameters and serum ferritin in deferoxamine, deferasirox, and all patient groups.

DISCUSSION

Most consequences in β-thalassemia are accompanied by iron oxidative injury in vital organs mediated by iron excess. In the iron accumulative state, iron participates in the form of low molecular weight, these forms are accountable for helping reactive species reactions and cause oxidative injury to all cells (1-3,6-8). for this reason, confinement of active iron is a goal for using drugs that remove iron, to decrease oxidative stress.

In the present study, the patients had iron excess, manifested by high levels of serum ferritin, decreased TAOC, and enhanced oxidative stress by increased MDA. Serum ferritin concentration is non-significantly higher in the defroxamine group than in deferasirox group patients (2597.32± 1016 ; 2343.07±852 ng/ml) respectively. The increase of ferritin concentration in serum patients had been found in many previous studies, the outcomes gained in this research are that obtained by Abed Mahdy (14) and Zeidan et al., (15), who reported an increase in ferritin levels in patients with beta-thalassemia, abnormally high ferritin levels could indicate iron overload, Al-Kuraishy and Al-Gareeb, (16), found that patients treated with deferoxamine, the serum ferritin levels were high compared with patients treated with deferasirox. The results obtained by Vichinsky et al.,(17) showed that deferasirox is more efficacious in comparison with deferoxamine in the decreasing of iron excess, due to more effectiveness and submission of deferasirox (18).

This study shows that the TAOC in the patients group on Deferoxamine, is significantly higher (34.5±13.2; 29.8±11.8), than Defrasirox, while MDA is higher in Defrasirox than in patients on the deferoxamine group (8.6±5.4 ; 5.8 ±4.4) respectively.

Regarding antioxidants status, an affirmative interconnection between TAOC and serum ferritin. Several studies evaluated the individual's antioxidants enzyme in beta-thalassemia and reported that superoxide dismutase enzyme (SOD) and glutathione peroxidase enzymes

(GPX) were significantly lower in thalassemic patients, because of iron overload (19). Dhawan et al., (20) reported that SOD enzyme activity was low in 209 thalassemia major patients, similar results were obtained in Patne et al., (21), Del Bo et al., (22), who reported that SOD and GPX were significantly reduced in thalassemic patients. Iron can enhance the transformation of oxygen molecules into oxygen free radicals, via the Fenton reaction. Intracellular antioxidant enzymes are responsible for oxidant–antioxidant cellular disequilibrium. Their function is to aid the transformation of free radicals, mainly O2− to H2O. In patients with thalassemia, a huge amount of free radicals build up because of the condition of iron accumulation resulting from blood transfusions, and deficit in erythropoiesis. Decreased levels of these antioxidants lead to an increase in oxidative stress (23).

The results obtained by a study done by Zeidan et al., (15), reported a considerable raising in serum ferritin levels and, a decrease in the levels of glutathione reductase enzyme (GR). El-Gendy et al., (24), found a positive correlation between serum peroxiredoxin 2, an antioxidant system and serum level of ferritin in thalassemia major. while Maskoen et al., (25) found that the correlations between(SOD and GPx)levels and serum ferritin, were not significant.

In contrary Qari et al., (26), and Del Bo et al.,(22), found a presumed increment in the level of antioxidant enzyme SOD in β-TM patients. Simsek et al.,(27), reported no difference in its level of activity. Regarding oxidative stress commonly assessed by measurement of MDA as an indicator of oxidative stress, in this research, no significant linkage between total MDA and serum ferritin level was found. Bhagat et al., (28), reported a worthy enhancement of iron levels in β-thalassemia major associated with increased serum MDA level. Research done by Atmakusuma et al., (29), found no variation in serum MDA value pre and post-blood transition, in spite that blood transition raises the iron cargo. Meantime, no linkage between indexes of iron excess and MDA value, in pre and post-transition.

Gunarsih et al., (30), reported, no connection between MDA and serum ferritin concentration. Cighetti et al.,(31), gained a affirmative linkage between total MDA and non-transferrin-bound iron (NTBI). The contrary and discrepancy in results of many studies may be explained by that, the subjects on the treatment by iron chelating agents and antioxidant complements. Various works have been carried out to assess the impact of iron chelation therapy and antioxidants on alteration in MDA value. MDA amount could be lowered in the patients reaching the normal values as in normal subjects when taking iron chelation therapy for six months up to one year (32).

CONCLUSION

This study provided evidence that β-TM patients have increased serum ferritin levels, decreased antioxidant capacity and increased oxidative stress levels manifested by increased MDA, because of iron overload. Deferasirox is more efficacious than deferoxamine concerning the chelation of iron excess, while not upon the oxidants/ antioxidant status. There is a considerable positive connection between TAOC and serum ferritin in the deferasirox patients group, and a non–considerable positive connection between MDA and serum ferritin, while a non-considerable positive connection between TAOC and serum ferritin in deferoxamine patients group, and a non- considerable negative connection between MDA and serum ferritin were detected, indeed there is a considerable affirmative connection between TAOC and serum ferritin and a non-considerable positive connection between MDA and serum ferritin when comparing the results of all patients as one group.

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