

Serum ferritin level in transfusion dependent β -thalassaemia patients in Mosul

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ABSTRACT

Objectives: To establish a correlation between serum ferritin and different clinical, biochemical and haematological parameters and to determine the efficacy of chelation therapy using desferrioxamine measured by serum ferritin.

Patients and Methods: A case-series of one hundred patients with transfusion dependent β -thalassaemia were included in the study during a period of one year (Nov. 2007-Nov.2008). The study included clinical evaluation, routine haematological tests and serum ferritin level.

Results: Mean value of serum ferritin in our patients was 1886.74 ng/ml. It was found that serum ferritin was higher in older patients, those who received higher number of blood transfusions to date and those of higher annual blood consumption. β -thalassaemic patients with serum ferritin level equal or higher than 2500 ng/ml were older, of shorter stature, had higher percentage of splenectomy, higher number of blood transfusions to date and higher annual blood consumption than patients with serum ferritin level less than 2500 ng/ml. It was found that patients with good compliance to chelation therapy with desferrioxamine had lower mean serum ferritin than patients with poor compliance. Thirty seven percent of our patients had growth retardation regarding weight for age and 57% were low in height for their age.

Conclusions: Serum ferritin was higher in older patients, those with higher annual blood consumption and those with poor compliance to desferrioxamine therapy when compared to patients with good compliance. Patients with serum ferritin equal to or more than 2500 ng/ml were older and of shorter stature for their age than patients with serum ferritin less than 2500 ng/ml.

الخلاصة

الاهداف:

- ١- إيجاد قيم حديد المصل في مرضى التلاسيميا نوع بيتا المعتمدين على نقل الدم في الموصل.
 - ٢- تم تطبيق ارتباط بين حديد المصل ومختلف القياسات السريرية والمخبرية (الدموية والكيمائية).
 - ٣- قياس كفاءة دواء الدسفيروكسامين في القدرة على طرح عنصر الحديد من الجسم باستخدام حديد المصل.
- الحالات والطرق:** شملت الدراسة ١٠٠ مريض بالتلاسيميا نوع بيتا المعتمدين على نقل الدم خلال الفترة الممتدة من (تشرين الثاني ٢٠٠٧ - تشرين الثاني ٢٠٠٨). تضمنت الدراسة تقيماً سريرياً وفحص الدم الكامل بالإضافة إلى فحص حديد المصل.

النتائج: معدل حديد المصل لدى مرضانا هو ١٨٨٦,٧ نانوغرام/مللتر. وجد أن حديد المصل كان أعلى عند المرضى الأكبر سناً وأولئك الذين استلموا العدد الأعلى من قناني الدم حتى وقت إجراء الفحص وأولئك الذين يكون استهلاك الدم السنوي لديهم عالياً. وجد أيضاً أن مرضى التلاسيميا نوع بيتا المعتمدين على نقل الدم الذين كان لديهم حديد المصل مناظراً أو أعلى من ٢٥٠٠ نانوغرام/مللتر كانوا أكبر سناً وأقصر قامة ولديهم نسبة أعلى من عمليات رفع الطحال وأستلموا عدداً أكبر من قناني الدم حتى وقت إجراء الفحص واستهلاكهم السنوي للدم كان أعلى من أولئك الذين كان لديهم

حديدين المصل أقل من ٢٥٠٠ نانوغرام/مللتر. وجد أيضاً أن المرضى الذين كان لديهم التزام جيد بعلاج الدسفيريوكسامين فان حديدين المصل عندهم أوطأ من أولئك المرضى الذين لا يلتزمون بالعلاج بصورته الصحيحة. ٣٧% من مرضانا المعتمدين على نقل الدم كان لديهم تأخر في النمو عند قياس وزنهم بالنسبة لعمرهم و٥٧% منهم كانوا قصيري القامة بالنسبة لعمرهم.

الاستنتاجات: حديدين المصل كان أعلى عند المرضى الأكبر سناً والذين يكون استهلاك الدم السنوي لديهم عالياً والمرضى الذين لا يلتزمون جيداً بعلاج الدسفيريوكسامين عند مقارنتهم بالمرضى الملتزمين بالعلاج. كما أن المرضى الذين لديهم حديدين المصل مساوياً أو أعلى من ٢٥٠٠ نانوغرام/مللتر هم أقصر قامة وأكبر سناً من المرضى الذين لديهم حديدين المصل أقل من ٢٥٠٠ نانوغرام/مللتر.

Thalassaemia is the commonest single gene disorder in man, characterized by a lack or decreased synthesis of one or more of the globin subunits of haemoglobin molecule⁽¹⁾. β -thalassaemia is classified into β^0 thalassaemia with complete absence of β globin chain and β^+ thalassaemia in which the production of β globin chain is reduced⁽²⁾. Iron overload causes most of the morbidity and mortality associated with thalassaemia.⁽³⁾

Two factors are responsible for iron overload in β -thalassaemia:

- 1- Increased intestinal absorption of iron due to erythroid hyperplasia despite tissue iron overload.
- 2- Transfusional siderosis with up to 200 mg iron is added per packed RBC unit.⁽⁴⁾

The iron storage protein, ferritin, plays a key role in iron metabolism.

Its ability to sequester the iron gives ferritin the dual function of iron detoxification and iron reserve.⁽⁵⁾

Annual blood consumption was measured by calculating total intake of packed RBC in one year divided by body weight in kilograms, and the resultant unit is ml of packed RBC/ kg body weight/year, it had been regarded as a good indicator of iron overload, transfusion scheme and hypersplenism, in which amount in excess of 200 ml/kg/year is an indication for splenectomy.^(6,7)

Patients with thalassaemia major in the early transfusional period need to have serum ferritin levels determined every 1–2 months in order to have a baseline value of iron load to initiate iron chelation therapy which should be started when serum ferritin levels exceeds 1000 ng/ml and periodic monitoring of serum

ferritin every 3 months should be done for patients on iron chelation therapy.⁽⁸⁾

Aims of the study

- 1- To assess serum ferritin in transfusion dependent β -thalassaemic patients in Mosul.
- 2- To establish a correlation between serum ferritin and different clinical, biochemical, and haematological parameters.
- 3- To determine the efficacy of chelation therapy using desferrioxamine measured by serum ferritin.

Patients and methods

A total of 100 transfusion dependent β -thalassaemia patients attending at thalassaemic centre in Ibn-Al Atheer paediatric hospital in Mosul, 52% were males and 48% were females for regular blood transfusions from November 2007 to November 2008 were studied.

History and examination were done for all patients.

The patients were divided into three groups:

- 1- Patients with good compliance to desferrioxamine therapy (37 %) who took desferrioxamine at a dose of (20 mg/kg/day), four times weekly or more by subcutaneous infusion using a special pump.
- 2- Patients with poor compliance to desferrioxamine therapy (36%) who took less than four times weekly with variable dose either by subcutaneous infusion or by other route.
- 3- Patients who didn't receive desferrioxamine therapy at all (27 %).

No WBC filter was used in all of our patients.

Ten ml of venous blood were obtained from each patient immediately before the next blood transfusion.

Three ml were added to EDTA containing tubes and used for doing complete blood picture and blood film.

The remaining 7 ml of blood sample were collected in a plain tube for serum separation, serum is stored at - 20 degrees centigrade for estimation of serum ferritin and performing hepatitis screen later.

All investigations were done according to standard methods.⁽⁹⁾

Results

Age of patients was in the range of (2-29) years with a mean age of 8 years, 72% of patients were 10 years or younger.

Regarding weight for age distribution of our patients, compared to 5th % of the general population, 37% of our patients were found to be under weight ($p < 0.001$).

Regarding height for age distribution of thalassaemic patients, compared to 5th % of the general population 57% of patients in the study were found to be of short stature for age ($p < 0.001$).

Control for serum ferritin was done on 30 normal children and adults of the same age and sex of the patients and the mean of serum ferritin was found to be 28.66 ng/ml ranging between 8 and 144 ng/ml.

The mean value of serum ferritin in all 100 transfusions dependent β -thalassaemia patients was 1886.74 ng/ml with a range of 380 – 7990 ng/ml

For degree of association between serum ferritin and different parameters, it was found that increasing age of patients and number of blood transfusions to date were found to be associated with increased serum ferritin level.

Figure (1): Histogram shows age and sex distribution of our patients, age of patients was in the range of (2-29) years with a mean age of 8 years, 72% of patients were 10 years or younger.

Figure (2): Scatter diagram shows relation between serum ferritin and age of the patients, a positive correlation was established ($p < 0.02$) and ($r = 0.233$).

Figure (3): Scatter diagram shows a positive correlation between number of blood transfusions to date and increased serum ferritin, ($p < 0.001$) and ($r = 0.365$).

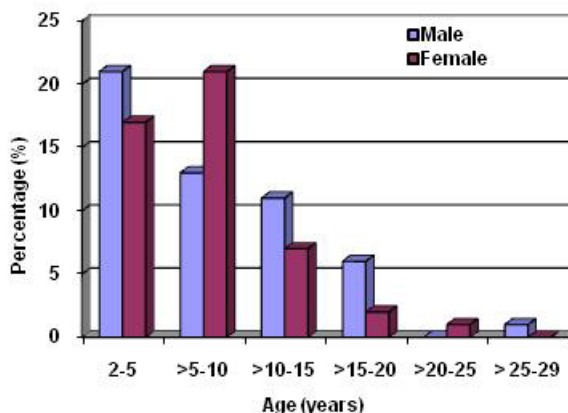


Figure (1): Histogram shows age and sex distribution of patients in the study.

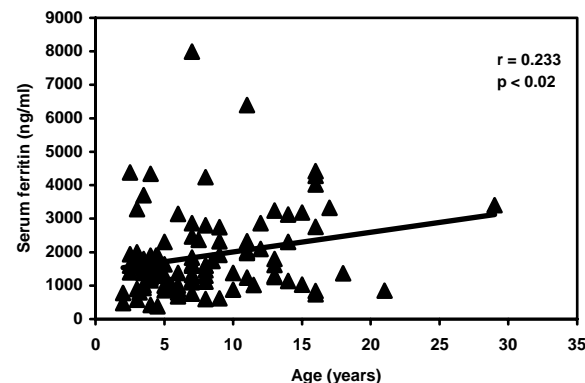


Figure (2): Scatter diagram shows relation between serum ferritin and age of patients in years.

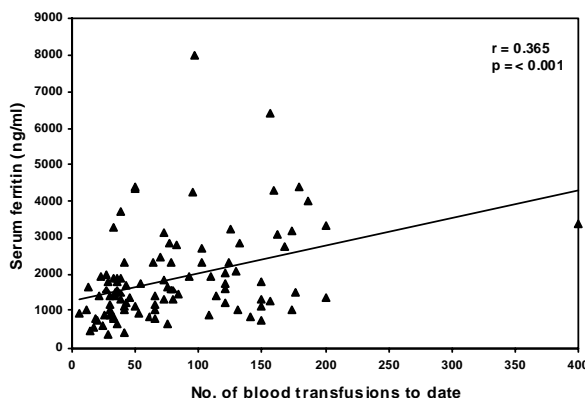


Figure (3): Scatter diagram shows relation between serum ferritin and number of blood transfusion to date.

Figure (4): Scatter diagram shows that increased annual blood consumption is directly associated with increased serum ferritin level ($p < 0.05$) and ($r = 0.212$).

Table (1): On grouping of patients according to serum ferritin level into 2 groups, those below 2500 ng/ml and those equal to or more than 2500 ng/ml and comparison between them, it was found that patients with serum ferritin equal to or above 2500 ng/ml were older than those below 2500 ng/ml, and had significantly short stature for their age when compared to patients with serum ferritin less than 2500 ng/ml.

Figure (5): Diagram shows distribution of patients compliance to desferrioxamine with regard to serum ferritin with higher serum ferritin in patients with poor compliance when compared to patients with good compliance ($p < 0.05$).

Mean serum ferritin in all patients using desferrioxamine was 2043 ng/ml with a mean

age of (9.44) years, and significantly ($P < 0.05$) higher than mean serum ferritin in patients not started using desferrioxamine with a very young age, the mean age was (3.4) years and serum ferritin mean was 1462.96 ng/ml.

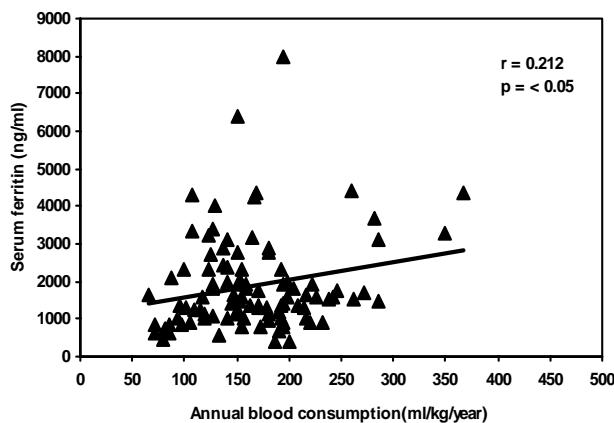


Figure (4): Scatter diagram between serum ferritin level and annual blood consumption.

Table (1): Grouping of patients with transfusion dependent β -thalassaemia according to S. ferritin level and comparison between their different parameters.

Parameters	Serum ferritin (ng/ml)		P-value
	< 2500 No. of patients (79) Range 380 – 2460 Mean \pm SD 1369.80 \pm 510.09	\geq 2500 No. of patients (21) Range 2740 – 7990 Mean \pm SD 3831.43 \pm 1285.31	
Age(years) Range Mean \pm SD	2 – 21 7.18 \pm 4.13	2.5 – 29 11.32 \pm 6.64	<0.001
Height for age growth retardation (short stature) No %	42 53.16	15 71.43	<0.001
Splenectomy No %	9 11.39	5 23.8	<0.001
Number of blood transfusions to date Range Mean \pm SD	5 – 200 67.72 \pm 46.69	96 – 156 131.33 \pm 84.53	<0.001
Annual blood consumption ml/kg/yr Range Mean \pm SD	65.47 - 285.38 159.63 \pm 51.46	106.38 - 367.92 185.54 \pm 77.14	<0.05

Independent samples T test was used.

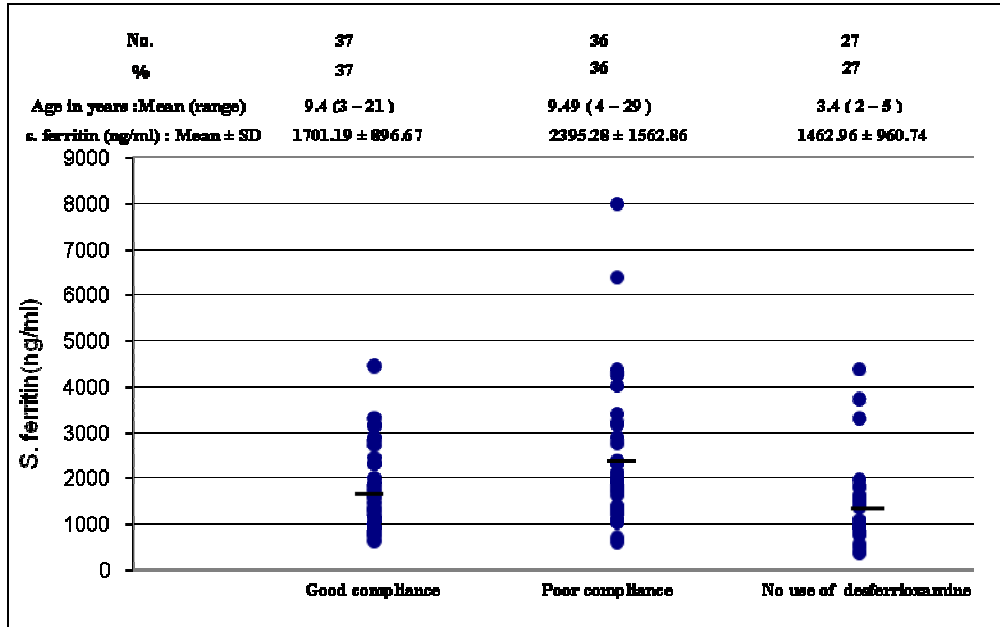


Figure (5): Distribution of patients compliance to desferrioxamine with regards to S. ferritin level (Total no. of patients on desferrioxamine was 73).

Regarding some of the complications, 2 male patients were diabetics, aged 16 and 29 years and both were splenectomised.

They were both on insulin, but their random blood glucose was within normal range, serum ferritin of one of them was 1740 ng/ml, the other patient serum ferritin was 3400 ng/ml.

Table (2): This table shows a statistically significant increased hepatitis C infection in our patients compared to normal Iraqi population ($p < 0.001$).

Table (2): Comparison of hepatitis between patients in the study and Iraqi population.

	Hepatitis B (HBsAg)	Hepatitis C (HCV Antibodies)	Concomitant Hepatitis B and C
Patients in the study %	1	16	1
Prevalence in Iraqi population (%)	2-3*	0.5*	0**

* Reference 10

** Reference 11

Discussion

Results of serum ferritin were significantly correlated with both advancing age of the patients (figure 2) and increased number of blood transfusion to date (figure 3) which is comparable to those of Shanna study.⁽¹²⁾

Carnelli et al and Cario et al studies also found that serum ferritin values correlates to total amount of blood transfusions.^(13,14)

Close to our results, Cario et al found that (75%) of patients younger than 10 years had serum ferritin less than 1800 ng/ml while (52%) of thalassaemic patients who were older than 10 years had serum ferritin above 2500 ng/ml.⁽¹⁴⁾

Short stature was found in 71.43% of transfusion dependent β -thalassaemia patients with serum ferritin equal or above 2500 ng/ml compared to (53.16%) of short stature in patients with serum ferritin below 2500 ng/ml, similar findings were repeated in Moayeri et al study who showed that short stature is common in thalassaemic patients with serum ferritin above 2000 ng/ml; he relates this to suboptimal chelation therapy leading to high serum ferritin level with iron deposition and damage to hypothalamic pituitary axis and growth failure.⁽¹⁵⁾

Also Shalitin et al suggested that a cutoff point of 3000ng/ml serum ferritin during the first decade of life predict final short stature.⁽¹⁶⁾

Mean serum ferritin is lower in patients with good compliance to desferrioxamine (DFO) when compared to patients with poor compliance ($p < 0.05$) (figure 4) indicating the beneficial effect of proper chelation therapy in reducing mean serum ferritin level.

The same was found by Kattamis et al⁽¹⁷⁾ and Richardson et al.⁽¹⁸⁾

Patients not started using DFO had significantly lower mean serum ferritin values 1462.96 ng/ml compared to both groups on DFO therapy those with good compliance to DFO (mean serum ferritin of 1701.19 ng/ml) and those with poor compliance to desferrioxamine therapy with a mean serum ferritin of 2395.28 ng/ml.

The probable cause for this lower mean serum ferritin value in the group of patients not started using desferrioxamine was the younger mean age of these patients compared to other groups on desferrioxamine therapy (3.4 years mean age of patients not use desferrioxamine versus 9.4 years in patients with compliance and 9.49 years in patients with poor compliance to desferrioxamine respectively).

Many studies showed that 2500 ng/ml serum ferritin is a cut point of prognosis with higher incidence of cardiac complication and shortened survival in those above 2500 ng/ml compared to those below 2500 ng/ml.^(19,20)

Short stature was found in 71.43% of transfusion dependent β -thalassaemia patients with serum ferritin equal or above 2500 ng/ml compared to 53.16% of short stature in patients with serum ferritin below 2500 ng/ml, similar findings were reported in Moayeri et al study who showed that short stature is common in thalassaemic patients with serum ferritin above 2000ng/ml, he relates this to suboptimal chelation therapy leading to high serum ferritin level with iron deposition and damage to hypothalamic pituitary axis and growth failure.⁽¹⁵⁾

In the current study splenectomised patients have higher ferritin mainly because those patients were older than non splenectomised

and received more units of total blood transfusion.

Annual blood consumption is significantly higher in transfusion dependent β -thalassaemia patients with serum ferritin above 2500 ng/ml when compared to those below 2500 ng/ml, because increased blood intake per body weight is associated with increased iron overload.

Because of early accelerated schedule for hepatitis B vaccination which starts at the time of registration in thalassaemic centre and administration of booster doses of hepatitis B vaccine, the prevalence of hepatitis B in our patients is even less than those of general population.

However, up to 16% of our patients were infected by hepatitis C.

This result was similar to that of Dawaj study on thalassaemic patients in Mosul 2007, where he found that 17% of patients had hepatitis C infection.⁽²¹⁾

These results of hepatitis C infection in thalassaemic patients were high when compared to 0.5 % incidence of hepatitis C in Iraqi population.⁽²²⁾

It appears clearly that the unavailability of vaccination to hepatitis C and the use of non screened blood bags during sanction against Iraq in the nineties of the previous century till 2003 increased the incidence of hepatitis C in our thalassaemic patients.

Conclusions

1. Growth retardation regards weight for age and height for age was found in 37% and 57% of our patients respectively.
2. Increasing age of the patients, number of blood transfusions to date and annual blood consumption were found to be associated with increased serum ferritin level.
3. By grouping patients into two groups those with serum ferritin below 2500 ng/ml and those with serum ferritin equal or above 2500 ng/ml, it was found that patients with serum ferritin equal or more than 2500 ng/ml were of shorter stature, had greater percentage of splenectomy, received higher number of blood transfusions and were of higher annual blood consumption

than patients with serum ferritin less than 2500 ng/ml.

4. Compliance of patients to chelation therapy was directly correlated to serum ferritin level with higher serum ferritin in patients with poor compliance.
5. Patients not using desferrioxamine had lower mean age and lower mean serum ferritin than patients using desferrioxamine.

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