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Comparison of The Effects Of Deferasirox And Deferoxamine On Uric Acid And Renal Function In Patients with Beta Thalassemia

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ABSTRACT

Objective: Beta thalassemia is the most common congenital hemolytic anemia in all over the world. It is characterized by a profound ineffective erythropoiesis making regular blood transfusions is essential for survival, while a serious problem of iron overload arise due to inability of human body to excrete accumulated iron of blood transfusion which is a lethal health problem that can be managed by iron chelators. Iron overload may occur in kidney after blood transfusion. The objective of this study is to evaluate the effects of iron chelators on markers of renal function in transfusion dependent β- Thalassemic patients who were treated with either deferasirox(DFX) or deferoxamine (DFO)

Methods: In this cross-sectional study, the total number of subjects participated was 164 (patients and controls) with age range (3-21) years old divided into 108 patients with homozygous β- thalassemia major. The patients were subdivided into: The DFO group (54 patients) were used Deferoxamine and the DFX group (54 patients) were used Deferasirox. The remaining 56 were enrolled as apparently healthy subjects (Control). Blood samples were collected from each patient and control subject at the thalassemic Center of ibn Al-Atheer Teaching Hospital in Nineveh Province, Iraq. The Parameters tested in this study, included laboratory measurements of serum ferritin, renal function tests (serum urea, serum creatinine and creatinine clearance) and serum uric acid. Descriptive characteristics (weight
, height, and body mass index) were also collected during interviews with patients and controls with their relatives.

Results: Results illustrated a significant difference is present between the means of serum ferritin, ($p<0.001$), creatinine clearance($p<0.01$) and creatinine ($p<0.05$) for patient group on DFO and control group. In addition, a significant difference is present between the means of serum ferritin, uric acid ($p<0.001$), urea ($p<0.05$) for patients' group on DFX and control group. A significant difference is present in serum ferritin ($p<0.001$), urea, creatinine clearance, uric acid ($p<0.01$), creatinine ($p<0.05$) between the two patient groups (DFO and DFX).

Conclusion: It was concluded from this study that changes in renal function markers in patients with β-thalassemic patients may be attributed to chronic anemia, iron overload as well as to deferoxamine or deferasirox therapy. These changes could have any long-term effects in β- thalassemic patients. In addition, the same urine markers did not correlate with age, indicating that chronic anemia or treatment with either deferoxamine or deferasirox are not related to renal dysfunction in β-thalassemic patients.

Keywords: Beta-thalassemia, renal function, uric acid, iron overload, deferasirox , deferoxamine.

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INTRODUCTION

Beta-thalassemia is a severe genetic blood disorder caused by a mutation in the β-globin gene leading to the excessive destruction of red blood cells and resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals.[1] It is prevalent in Mediterranean country and Middle East (including Iraq) Treatment approaches include correction of anemia, suppression of erythropoiesis and inhibition of iron absorption from gut. Iron overload is a serious problem of continuous blood transfusion, which is lethal for β-thalassemia patient's tissues and organs. It is managed by administration of iron chelators in order to remove transiently available (labile) iron pools from plasma or within the cells [2] Patients with β-thalassemia should start iron chelation treatment once they have had 10- 20 transfusions or when serum ferritin levels increase above 1000 ηg/ml. Two iron chelators approved by the USA and FDA were available and were mostly used to chelate and excrete excess iron. Deferoxamine is used parentally or subcutaneously (s.c.) while Deferasirox is used orally. both of them are used by patients at Thalassemic Center in Ibn Al-Atheer Teaching Hospital. [1,2]

SUBJECTS, MATERIALS AND METHODS

The study project was approved by postgraduate committee at College of Pharmacy and Research Ethical Committee of Nineveh Health Directorate. It was carried out in collaboration with the medical staff of Thalassemia Center of Ibn Al- Atheer Teaching Hospital in Nineveh Province, Mosul, Iraq. Blood samples of thalassemic patients collected as a part of routinely work in this center. It is a cross- sectional, single-center investigation study.

Subjects

The total number of subjects enrolled in this study was 164 . 108 of them were patients with homozygous β-thalassemia major and the remaining 56 were enrolled as controls of apparently healthy subjects.

I. Patients

One hundred and eight patients with age range between (3-21) years old diagnosed as β-thalassemia major, having received multiple blood transfusion and having chronic iron overload with serum ferritin greater than 1000 ηg/ml. Patient's samples subdivided into:

1. DFO group include 54 patients (30
2. DFX group include 54 patients (31 males & 23 females) use Deferasirox with mean ±

S.D. of age 10.05 ± 3.3 years old.

II. Controls

Total number of non-thalassemic subjects (Control group) was 56 samples (36 males & 20 females), collected from healthy individuals with age range match to those of patients. Having mean ± S.D. of 11.8 ± 5.3 years old.

Diagnosis Criteria

Patients already diagnosed by physicians at the center as having β- thalassemia major depending on hemoglobin variants test using high performance liquid chromatography (HPLC). All patients have increased level of fetal hemoglobin (HbF) up to 80-98% and reduced level of normal hemoglobin (HbA) to about 2 – 10%

The parameters measured in this study, included tests for serum ferritin; renal function tests (serum urea, serum creatinine, creatinine clearance) and serum uricacid. Descriptive features (weight, height, and body mass index), were also determined during an interview with each patient and control .

Inclusion criteria

- Patients having β-thalassemia major diagnosed in the hospital depending on hemoglobin variants test by hemoglobin electrophoresis.
- Age range between 3 - 21 years old of both sexes.

Exclusion criteria

- Patients on chelation therapy for period of less than 3 months.
- Patients with active infection, hepatitis B or C.
- Patients receiving medications for other disease as diabetic mellitus or cardiac disease.
- Patients with hematologic disorder as Alpha thalassemia, Sickle cell anemia and sideroblastic anemia.
- Patient with a history of possible hepatic or renal impairments.

Collection of Data

The main source of data is directly obtained from all the studied subjects by the investigator himself during interviews with them or their relatives.

Approximately 5 ml of venous blood samples from each individual of the studied groups were collected via cannula directly to vacutest tubes, which is a routinely work done by nursing staff in the Thalassemia Center. The blood samples were then placed in the incubator at 37°C for 15–30 min to enable blood coagulation to occur. The blood samples then centrifuged for 5 min at 4500 rpm in order to obtain serum samples. The serum was separated and then put in aliquots (small tubes), and finally deep freeze at–20°C.

Determination of Serum Ferritin, Urea, Creatinine, Creatinine Clearance and Uric Acid

Serum ferritin level was determined by an enzyme-linked assay method using Chemwell 2910 device, which is automated for quantitative test with a kit of Ferritin AccuBind® ELISA - Monobind Inc. [3] Serum urea level was measured by enzymatic method, using a Reflotron urea strips supplied by Roche Diagnostics GmbH (Mannheim, Germany). [4] Serum creatinine was tested by Chemwell T full automated open system utilizing enzymatic assay. [5] Creatinine Clearance was calculated according to the Shull *et. al.* (Shull *et. al.,* 1978). [6] Serum uric acid measured by using a Reflotron uric acid strips supplied by Roche Diagnostics GmbH (Mannheim, Germany). [7]

Ethical Approval

The study was conducted in accordance with the ethical principles that have their origin in the Research Ethical Committee of Nineveh Health Directorate . Patients and controls were granted verbal and analytical approval before the sample was taken. For all patients and controls, the participation was voluntary and confidential. The study protocol and the subject information and consent form were reviewed and approved by local ethics committee at Ibn Al-Atheer Teaching Hospital in Nineveh Province, Iraq.

Statistical Analysis

Standard statistics was performed by windows 10 operating system with statistical program SPSS version 20 to analysis of collected data, and the outcome results of SPSS typed using Microsoft office 2013 (Word and Excel).

Data presented as mean ± standard deviation (S.D.) and analyzed byusing the following statistical methods. [8]

1. Standard descriptive statistical methods were used to determine the mean, standard deviation (SD), number (No.) and percentage (%).
2. Mann Whiteny U test to compare between subdivisions of each group due to incompatible number of subjects, and data presented as mean rank.
3. ANOVA test used to compare between more than two groups.
4. Chi square test to compare between non-parametric percentages.
5. The statistical results considered significant at $p<0.05$.
6. Scattered/Dot. and Histogram used for drawing graphs.

RESULTS

The outcomes of the present study data shows varying degrees of differences in the studied parameters with variable degrees of significant and correlations between groups and subgroups.

Descriptive Features of Subjects

Table.1 shows a non-significant difference in age between patients and controls but the same table shows significant difference for height ($p<0.05$), weight ($p<0.001$) and body mass index ($p<0.001$) between patients and controls.

Table.1 : Comparison of Age, Height, Weight and BMI between patients and Control

Parameters	Mean ± S.D.		P value
	Total Patients (N=108)	Control (N=56)	
Ages (years)	11.4 ± 4	11.8 ± 5.3	**NS**
Height (cm)	131.4 ± 15.3	139.6 ± 29.4	**< 0.05**
Weight (kg)	30.9 ± 10.5	43.9 ± 21.8	**< 0.001**
BMI	**17.3 ± 2.5**	**21 ± 4.2**	**< 0.001**

Analysis performed by independent-samples t-test

- ***Serum Ferritin***

The means of serum ferritin significantly increased for both DFO group and DFX group ($p<0.001$) when compared with control group (Table 2 and 3 and Figure 1).
The comparison between means of serum ferritin levels for DFO group and DFX group shows significant increase for DFO group ($p<0.001$) (Table 4 and Figure.1).
Table.5 shows significant difference in serum ferritin levels ($p<0.001$) between mild, moderate and sever degrees of iron overload levels.
The comparison for Age and gender in each of patient's subgroups (DFO group and DFX group respectively) shows non-significant differences (Table.6 and.7).

- ***Serum Urea***

The means of serum urea for DFO group shows non-significant difference when compare with control group (Table 2 and Figure 2). while the means of serum urea for DFX group shows significant increase when compare with Control group ($p<0.05$) (Table 3 and Figure2).
In addition, a comparison between the means of DFO group with DFX group shows a significant increase in serum urea levels for DFX group ($p<0.01$) (Table 4, and Figure 2).

- ***Serum Creatinine (Cr.)***

The means of serum creatinine levels for DFO group show a significant decrease ($p<0.05$) when compare with control group (Table 2 and Figure 3) while the means of serum creatinine for DFX group shows a non-significant difference when compare with Control group (Table 3 and Figure 3).
In addition, a comparison between the means of DFO group with DFX group shows a significant increase in serum creatinine levels for DFX group ($p<0.05$) (Table 4, and Figure 3).
There is non-significant differences found between means of creatinine in groups of iron overload degrees (Table 5).
The comparison for Age and gender in each of patient's subgroups (DFO group and DFX group respectively) shows non-significant differences (Table 6 and 7).

- ***Creatinine Clearance (Cr.cl.)***

The means of creatinine clearance for DFO group shows significant increase ($p<0.01$) when compared with control group (Table 2and Figure 4) while the means of creatinine clearance for DFX group shows a non-significant when compared with Control group (Table 3 and Figure4).
In addition, a comparison between the means of DFO group with DFX group shows a significant increase in creatinine clearance levels for DFO group ($p<0.01$) (Table 4, and Figure 4).
Iron overload degrees groups shows a significant difference ($p<0.01$) in the means of creatinine clearance (Table 5).

Serum Uric Acid (UA)

Table 2 and Figure 5 shows a non-significant difference between DFO group and Control group, while DFX shows significant decrease ($p<0.001$) when compared with Control group (Table 3 and Figure 5).DFO group shows higher significant level of uric acid mean than that of DFX group ($p<0.01$) (Table 4 and Figure 5).A non-significant difference in serum uric acid levels between degrees of iron overload groups (Table 5).

Table .2: Comparison of studied parameters between patient's group on DFO and Control

Parameters	Mean ± S.D.		P value
	DFO Group (N=54)	Control Group (N=56)	
Ferritin (ηg/ml)	3891 ± 1845	26.4 ± 19.7	**< 0.001**
Urea (mg/dl)	24.6 ± 4.3	25.1 ± 5.8	**NS.**
Creatinine (mg/dl)	0.45 ± 0.14	0.54 ± 0.25	**< 0.05**
Cr.cl. (ml/min/1.73m^2)	172 ± 83.6	132.6 ± 48	**< 0.01**
Uric acid (mg/dl)	**4.3 ± 1.24**	**4.5 ± 1.36**	**NS.**

Analysis performed by using independent-samples t-test

Table .3: Comparison of studied parameters between patient's group on DFX and Control

Parameters	Mean ± S.D.		P value
	DFX Group (N=54)	***Control Group (N=56)***	
Ferritin (ηg/ml)	2212 ± 1485	26.4 ± 19.7	**< 0.001**
Urea (mg/dl)	27.4 ± 6.6	25.1 ± 5.8	**< 0.05**
Creatinine (mg/dl)	0.52 ± 0.15	0.54 ± 0.25	**NS.**
Cr.cl.(ml/min/1.73m^2)	125 ± 66.4	132.6 ± 48	**NS.**
Uric acid (mg/dl)	**3.54 ± 1.23**	**4.5 ± 1.36**	**< 0.001**

Analysis performed by using independent-samples t-test

Table .4: Comparison of studied parameters between DFO and DFX group.

Parameters	Mean ± S.D.		P value
	DFO Group (N=54)	***DFX Group (N=54)***	
Ferritin (ηg/ml)	3891 ± 1845	2212 ± 1485	**< 0.001**
Urea (mg/dl)	24.6 ± 4.3	27.4 ± 6.6	**< 0.01**
Creatinine (mg/dl)	0.45 ± 0.14	0.52 ± 0.15	**< 0.05**
Cr.cl.(ml/min/1.73m^2)	172 ± 83.6	125 ± 66.4	**< 0.01**
Uric acid (mg/dl)	**4.3 ± 1.24**	**3.54 ± 1.23**	**< 0.01**

Analysis performed by using independent-samples t-test

Table .5: Studied biochemical parameters in different iron overload degrees (mild, moderate, sever) in patients depending on ferritin levels

Parameters	Mean ± S.D.			P value
	Ferritin level <2500 Mild (N=46)	***Ferritin level 2500-5000 Moderate (N=49)***	***Ferritin level >5000 Sever (N=13)***	
Ferritin (ηg/ml)	1411±560	3612±647	6743±1388	**0.001****
Urea (mg/dl)	27.9±6.8	24.6±4.5	24.6±4	**0.05***
Creatinine (mg/dl)	0.51±0.14	0.46±0.14	0.48±0.16	**NS.**
Cr.cl.(ml/min/1.73m^2)	124±51	163±86	178±106	**0.05***
Uric acid (mg/dl)	**3.6±1.2**	**4±1.2**	**4.4±1.4**	**NS.**

Analysis performed by using ANOVA test
*significant difference exist at ($p<0.05$) level of significant
**highly significant difference exist at ($p<0.001$) level of significant

Table.6: Comparison of the studied parameters for patient's subgroup on DFO and patient's subgroup on DFX between <12 years and ≥12	*DFO group Mean Rank*	*P value*	*DFX group Mean Rank*	*P value*

years old. Parameters	<12 years (N=17)	≥12 years (N=37)		<12 years (N=39)	≥12 years (N=15)	
Ferritin (ηg/ml)	23.3	29.4	NS.	25.2	33.3	**NS.**
Urea (mg/dl)	30.2	26.2	NS.	27.1	28.5	**NS.**
Creatinine (mg/dl)	28.7	26.9	NS.	28.7	24.3	**NS.**
Cr.cl.(ml/min/1.73m^2)	14.6	33.4	< 0.001	22.6	40.2	**< 0.001**
Uric acid (mg/dl)	**21.5**	**30.2**	**NS.**	**25.9**	**31.4**	**NS.**

Analysis performed by Mann-Whitney test

Table.7: Comparison of the studied parameters for patient's subgroup on DFO and DFX between males and females.

Parameters	DFO group Mean Rank		P value	DFX group Mean Rank		P value
	Male (N=30)	**Female (N=24)**		**Male (N=31)**	**Female (N=23)**	
Ferritin (ηg/ml)	27.3	27.6	NS.	26.5	28.7	**NS.**
Urea (mg/dl)	32.6	21.1	< 0.01	25.8	29.7	**NS.**
Creatinine (mg/dl)	28.8	25.7	NS.	28.9	25.5	**NS.**
Cr.cl.(ml/min/1.73m^2)	26	29.2	NS.	25.8	29.7	**NS.**
Uric acid (mg/dl)	**27.8**	**27**	**NS.**	**31.6**	**21.9**	**< 0.05**

Analysis performed by Mann-Whitney test

- ***Correlation between Serum Ferritin and other parameters***

There is no significant correlation between serum ferritin level and serum urea, creatinine, creatinine clearance and uric acid for both DFO and DFX groups (Table 8 and 9) respectively.

Table.8: Correlations between serum ferritin level and studied parameters for DFO.

Parameters	Serum Ferritin Level (N=54) DFO group	
	r value	P value
Urea (mg/dl)	-0.019	**NS.**
Creatinine (mg/dl)	0.019	**NS.**
Cr.cl.(ml/min/1.73m^2)	0.188	**NS.**
Uric acid (mg/dl)	**-0.003**	**NS.**

Table.9: Correlations between serum ferritin level and studied parameters for DFX group

Parameters	Serum Ferritin Level (N=54) DFX group	
	r value	P value
Urea (mg/dl)	-0.154	**NS.**
Creatinine (mg/dl)	0.082	**NS.**
Cr.cl.(ml/min/1.73m^2)	0.071	**NS.**

Uric acid (mg/dl)	**0.067**	**NS.**

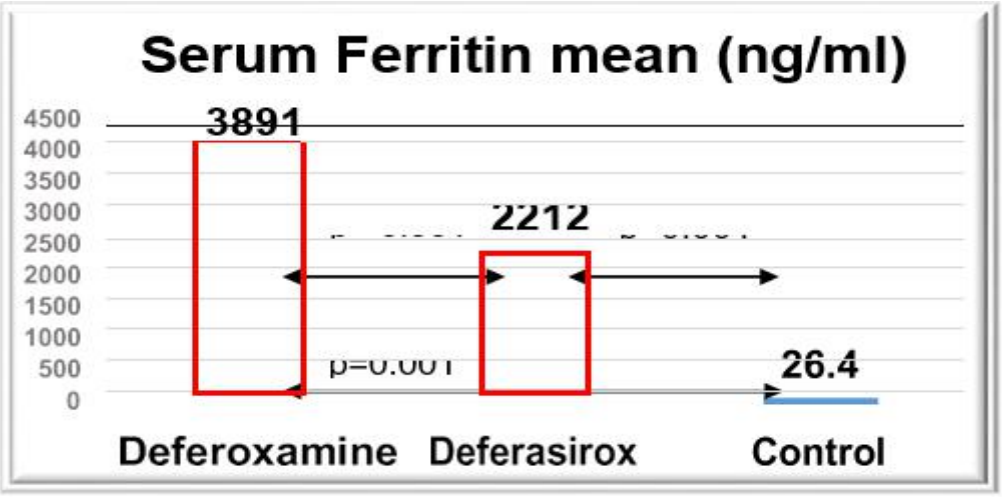

Figure (1): Mean of serum ferritin for the DFO group, DFX group and Control group

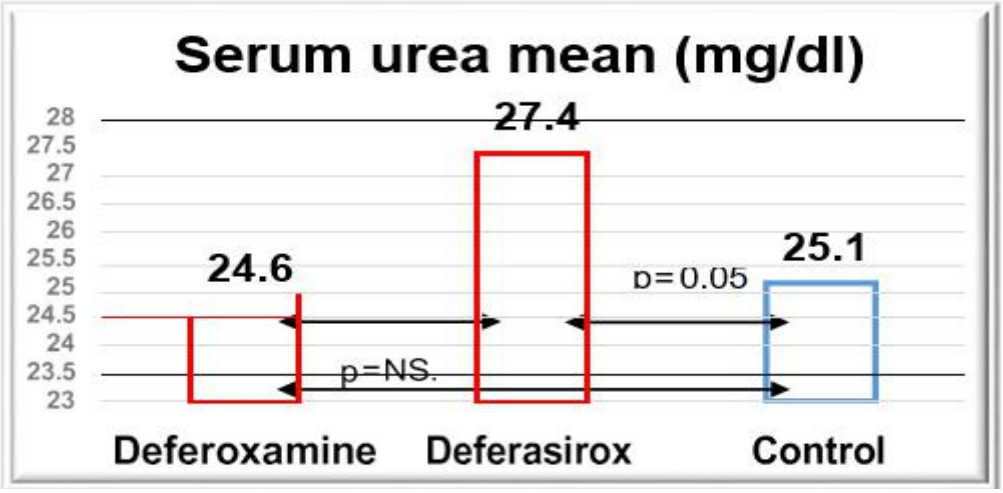

Figure (2): Mean of serum urea for the DFO group, DFX group and Control group

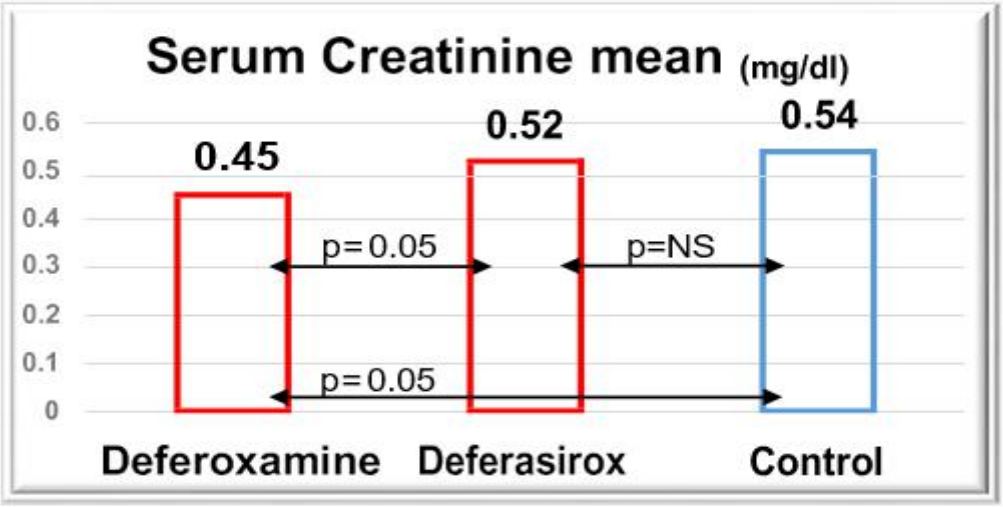

Figure (3): Mean of serum creatinine for the DFO group, DFX group and Control group

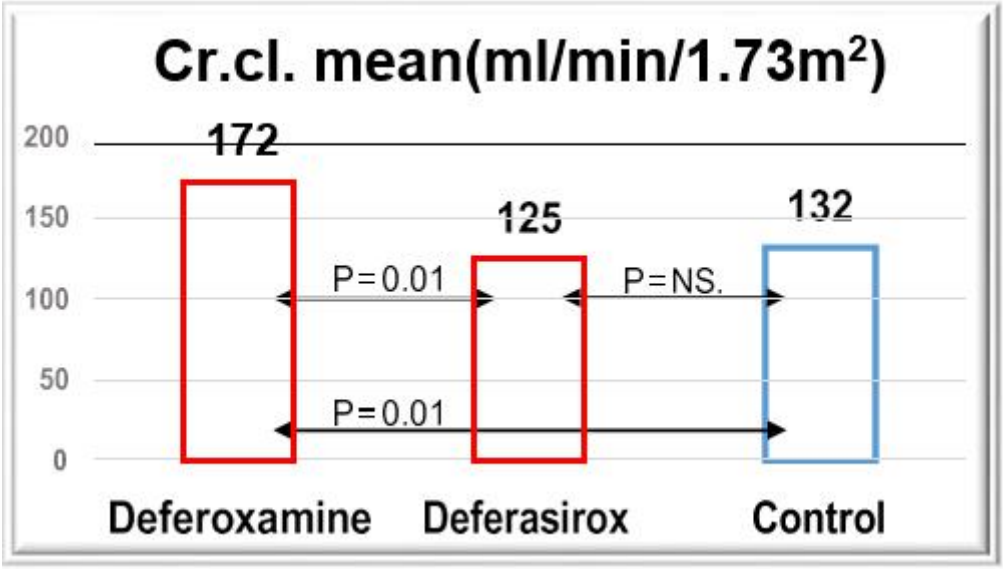

Figure (4): Mean of creatinine clearance for the DFO group, DFX group and Control group

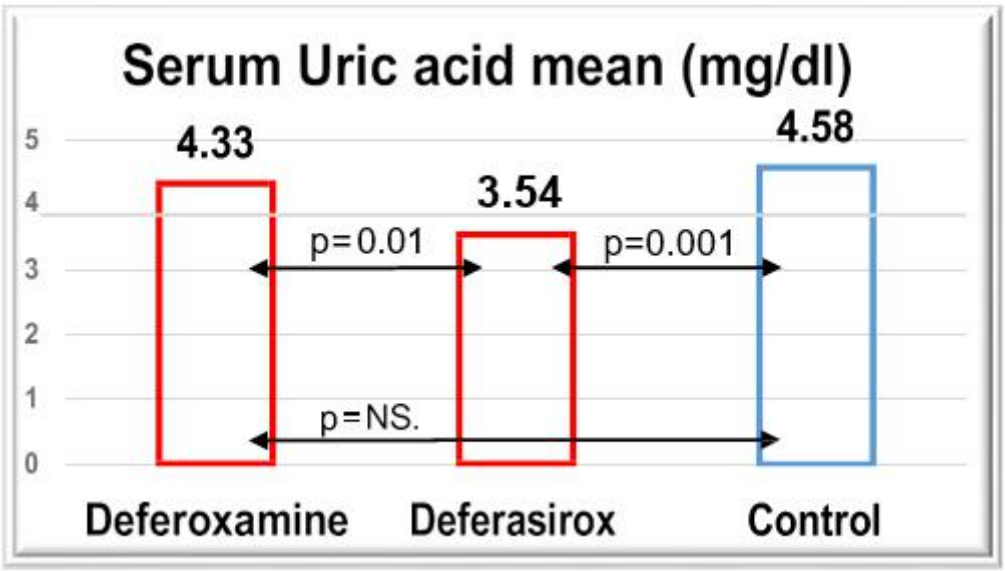

Figure (5): Mean of serum uric acid for the DFO group and DFX group.

DISCUSSION

Beta thalassemia is the most common congenital hemolytic anemia due to partial or complete loss of β-globin chain synthesis that is characterized by severely ineffective erythropoiesis requiring regular red blood cell (RBC) transfusions to sustain life. Iron chelating agents reduce the tissue damages by chelate iron and excrete it out of the body. Without successful iron chelation therapy, patients with transfusional iron overload are at risk f or iron accumulation in vital organs such as liver and heart.

Descriptive Features of Subjects

Finding of height, weight and body mass index, shows significantly lower means at (*p<0.05*, *p<0.001* and *p<0.001*) respectively between all patients when compared with healthy controls. (Although there are non- significant differences between their ages).These may be due to the disease itself, iron overload, blood transfusion, chelation, some food restriction, nausea and vomiting that may contribute to decrease appetite and muscle mass with consequent growth retardation.

Saxena, (2003) supported that thalassemic patients are short, have low rate of growth with low BMI, which related to low hemoglobin and high ferritin levels and sub-optimal iron chelation therapy. [9]

Serum ferritin used as an indirect measure of iron and it is not an accurate means of iron overload assessment but it gives a fairly good idea of the trend of iron loading.[10,11] The result shows significant differences (*p<0.001*) when comparing means of serum ferritin of both patients groups with that of control group (Tables 2 and 3 , Figure 1) which is usual and cleared in many studies due to ineffective erythropoiesis and subsequent blood transfusion with increase diet iron absorption.[12,13] By comparing the mean of serum ferritin levels for DFO group versus that for DFX group, a significant difference (*p<0.001*) was found (Table 4 and Figure 1).The mean serum urea in the present study was within normal range for both DFO & DFX groups of β-thalassemia patients. These results were compatible with study of Al Haddad *et. al.,* (2012) and Shfik *et. al.,* (2011) who studied some biochemical characteristics of transfusion dependent thalassemic children at public

hospitals in Gaza city and shows significantly deteriorated liver and kidneys function tests in patients as compared to controls.[14,15]

The present study found that levels of serum urea for DFX and DFO groups show significantly increased levels (*P<0.01* and *P<0.05*) respectively when compared with control group. The above results were found compatible with study of Mansi *et. al.,* (2013) who studied the serum urea and creatinine levels in β-thalassemia major that underwent periodical blood transfusion and they were on DFO as chelating agent.[16]

Their results revealed a significant increase in serum urea level in patients group compared to control group even though it is still within normal range. They found that elevated levels of renal

Table 7 shows a significant increase in the mean of serum urea level by comparing gender subgroups in DFO group (*p<0.01*) and non-significant in DFX group. The results of present study found that DFO group shows significant decrease in the mean serum creatinine level when compared with control group (*p<0.05*) (Table 2 and Figure 7) which may be related to the lower body mass index, due to growth retardation and lower muscle mass, usually encountered in β-thalassemia patients.[17]

This result was in agreement with that stated by Jafari *et. al.,* (2011); Younus *et. al.,* (2012), who found a significant decrease in the level of serum creatinine in β-thalassemia patients compared to healthy subjects, and concluded that there was no evidence of renal tubular and glomerular damage in β-thalassemia patients as demonstrated by the results of their studies.[18,19]

Whereas, the mean of serum creatinine for DFX group shows a non- significant variation when compared with the Control group as in (Table 3 and Figure 7) but has a significant increase (*p<0.05*) in the mean of serum creatinine when compared with DFO group (Table 4 and Figure 7).

The results of the present study shows a non-significant difference for creatinine regarding degree of iron overload that is consistent with the result of Fathi *et. al.,* (2013) who shows a non-significant increase for group using Deferasirox according to different ranges of elevated serum ferritin.[20]

In the present study creatinine clearance shows significant increase with age for DFO and DFX groups occur as calculation of creatinine clearance depend on age. Renal function tests were evaluated by Marouf *et. al.,* (2006) for patients with sickle cell anemia, they found hyper-filtration (considered above 140 ml/min/1.73 m^2) measured on the basis of serum creatinine in MDRD and Cockcroft-Gault formula.[21] In present study creatinine clearance calculated for β-thalassemia according to shull *et. al.* equation that shows significant increase in the mean of Cr.cl[6] compared with the control group indicating hyper-filtration which agree with the results of Malaki *et. al.,*
(2011) who considered hyper-filtration as maladaptation of renal glomerular hemodynamic function to the insults to the kidneys in general.
Therefore, serum creatinine alone cannot yield this information for the evaluation of patients having renal dysfunction.[22,23]

In the present study, the result found that serum uric acid shows a non- significant variation between the means of DFO group and Control group (Table 2 and Figure 9).This finding is in accordance with Smolkin *et. al.,* (2008) when they studied renal functions in patients with β-thalassemia major and with thalassemia intermedia.
[24] They show a non-significant difference between patient and control group and reported that the main findings were hyperuricosuria without hyperuricemia which could be due to rapid erythrocyte turnover in combination with decreased reabsorption of filtered uric acid from the damaged proximal tubules. In addition, they assumed that iron deposition in the renal tubule may not be removed properly by deferoxamine. In addition, they concluded that renal tubular function was impaired in β-thalassemia major and thalassemia intermedia, but this impairment is not detected by routine biochemical tests[25]

CONCLUSIONS

Higher ferritin levels were found in serum of both patients groups as compared to control group due to blood transfusion. The renal function tests were lower in patients group compared to control group. It is concluded from this study that changes in renal function in patients with β- thalassemic patients can be attributed to chronic anemia, iron overload as well as to deferoxamine or deferasirox use. These changes would have any long-term effects on the patients. In addition, the same urine markers did not correlate with age, indicating that chronic anemia or deferoxamine or deferasirox treatment are not related to renal dysfunction in β-thalassemic patients.

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