Cystatin C as an Early Marker of Glomerular Dysfunction in Children with Beta Thalassemia Major

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ABSTRACT

Background and aim of work: *Reports investigating renal dysfunction in beta thalassemia major (β-TM) patients have been limited in number, mainly studying adult patients. Additionally, most of them had not assessed early markers of glomerular dysfunction such as cystatin C. Early identification of patients at high risk is of great importance as it may allow specific measures to be taken to delay renal impairment. The present work aimed to estimate the frequency of glomerular dysfunction in children with β-TM by using different markers and to correlate these markers to serum ferritin and iron chelation therapy.* ***Patients and Methods****: The study included one hundred patients with β-TM (Group I) which was subdivided into; groups: I-a included 62 patients (62%) with iron chelation therapy (deferoxamine) and group I-b included 38 patients (38%) without iron chelation therapy and Group II (control group) included fifty apparently healthy volunteers age and sex matched to the diseased groups. Members of the two groups were subjected to; history taking, clinical examination and laboratory investigations including determination of: Serum ferritin, albumin/creatinine ratio in urine, eGFR by both Schwartz formula and creatinine clearance; blood urea and serum creatinine and finally serum cystatin C.* ***Results:*** *Group I showed significant higher levels of Cystatin C, serum creatinine, serum ferritin, albumin /creatinine ratio in urine than group II. Furthermore, they had significantly lower eGFR and creatinine clearance than group II ($p<0.05$). Moreover, group I-a had significant lower eGFR and creatinine clearance than group I-b. Also, cystatin C had highly significant strong negative correlation with eGFR and creatinine clearance and significant strong positive correlation with serum ferritin. Finally, cystatin C had higher sensitivity and specificity than serum creatinine and creatinine clearance for small changes in GFR.* ***Conclusion:*** *Glomerular dysfunction in β-TM is not a rare complication so, the use of early markers such as cystatin C is useful for the early detection of small changes in GFR. Periodic renal assessment of those patients is mandatory where many of them may had hidden renal affection*
Keywords: *Glomerular dysfunction, β-thalassemia, Cystatin C*

INTRODUCTION

Beta thalassemia is the commonest type of thalassemia and usually produces severe anemia in their homozygous and compound heterozygous forms. The use of regular and frequent blood transfusion in thalassemia has improved life span and quality of life of the patients, but it leads to chronic iron overload[(1)].Unlike in the other organs, it is unclear whether kidney affection results solely from intravascular

hemolysis, chronic transfusion or as a complication of iron chelation therapy[2]. Patients with thalassemia are known to have severe cardiopulmonary, reticuloendothelial and other major systems dysfunction, but renal involvement has received little attention. Increased renal plasma flow and failure of urine concentration ability has been reported in adult subjects with Beta thalassemia since 1975[(3)]. Cystatin C is a small 13–kDa protein that is a member of the cysteine proteinase inhibitor family which is produced at a constant rate by all nucleated cells. Due to its small size it is freely filtered by the glomerulus, and is not secreted but is fully reabsorbed and broken down by the renal tubules. This means that the primary determinate of blood cystatin C levels is the rate at which it is filtered at the glomerulus making it an excellent GFR marker. A recent meta-analysis demonstrated that serum cystatin C is a better marker for GFR than serum creatinine [4].

AIM OF THE WORK: The present work aimed to estimate the frequency of glomerular dysfunction in children with β-TM by using different markers and to correlate these markers to serum ferritin and iron chelation therapy.

PATIENTS & METHODS

The present work was a cross-sectional study included one hundred patients with β-TM (Group I) which was subdivided into; group I-a involved 62 patients (62%) on regular chelation therapy (deferoxamine , 20-50 mg/kg body weight via subcutaneous pump infusions over 8-12 hours /night, for 5 days per week) and group I-b included 38 patients (38%) without chelation therapy.They had regular follow up in pediatric Hematology Outpatient's Clinic, Minia Children University Hospital. Informed consent was obtained from every case (his/ her legal guardians). They were 62 males and 38 females with an age ranged from 8-16 years.

Exclusion criteria: History suggestive of recurrent urinary tract infections & systemic diseases that affects the kidney, history of intake of nephrotoxic drugs and family history of hereditary renal diseases.

Another group included fifty apparently healthy volunteers; age and sex matched to the diseased group.They were collected from June 2010 to August 2011.

All groups were subjected to; thorough history taking, clinical examination. Morning fasting blood samples and urine specimens were provided from all the studied cases for different biochemical function profiles including simple urine analysis[(5)] and albumin/creatinine ratio in urine according to (National Kidney Foundation, [(6)]with a reference (female <3.5 mg/mmol, male <2.5 mg/mmol. [(6)], creatinine clearance[(7)]. Estimated glomerular filtration rate (eGFR) was calculated using Schwartz formula for children[(8)]: eGFR (ml/min/1.73 m^2) = height (cm) × constant/ serum creatinine (mg/dl), where height was expressed in "cm" and constants was 0.44 (for children <2 years) and 0.55 (for children ≥2 years). Renal dysfunction was defined as eGFR <90 ml/min/1.73 m^2. Complete blood Picture (CBC) was done by Sysmex apparatus and serum

ferritin (µg/dl) was estimated by ELISA[9]. Complete liver function tests [10] & renal function tests including blood urea with a reference ranges 3.0–6.0 mmol/l and serum creatinine were estimated spectrophotometrically [11]. The reference ranges of serum creatinine (female 40–90 µmol/l; male, 50–100 µmol/l). Serum cystatin C level was measured by quantikine human cystatin C immunosorbent assay (ELISA) kit with reference value: 0.80 - 0.90 mg/l [12,13].

Statistical Analysis [14]:

The data were coded and verified prior to data entry. The Statistical Package of SPSS version 13 for windows was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD). Comparison of different variables in various groups was done using student t-test and Mann -Whitney test for normal and non-parametric variable respectively. Chi square test (χ^2) was used to compare frequency of qualitative variables among the different groups. Pearson's and Spearman's correlation tests were used for correlating normal and non-parametric variables respectively. Multiple regression analysis was also performed to determine effect of various factors on a dependent variable. P-value > 0.05 (insignificant), P< 0.05 is significant and P < 0.01 is (highly significant).

RESULTS

Table (1) showed that group I patients had highly significantly higher percentage of positive consanguinity than group II (P<0.001). As regard anthropometric measurements, group I had statistically significant lower weight and height than group II where (P=0.04, 0.01respectively). Comparison between group I-a and group I-b as regard clinical findings showed that group I-a had significantly higher frequency of blood transfusion and splenomegaly than group I-b where (P=0.02 & 0.003respectively). Concerning laboratory parameters, table (3) showed that both group I-a and group I-b had highly significantly higher levels of serum cystatin C, serum creatinine, serum ferritin and albumin /creatinine ratio in urine than group II where (P<0.05). On the other hand, they had significantly lower eGFR by Schwartz, creatinine clearance than group II. Comparison between group I-a and group II-b demonstrated that group I-a had significantly lower eGFR by Schwartz and creatinine clearance than group I-b where (P=0.001 and 0.006 respectively). Figures 1&2 showed that there were statistically significant strong negative correlations between serum cystatin C, eGFR and creatinine clearance (r= -0.91, P= 0.001 & r= - 0.80, P= 0.005 respectively). On the other hand, serum cystatin C had highly significant strong positive correlation with serum ferritin (r=0.90, P=0.001), figure (3). Moreover, serum cystatin C had insignificant negative weak correlation with frequency of blood transfusion (r=-0.14, P=0.3), figure (4). Further, cystatin C had significant fair positive correlation with duration of chelation therapy (r=0.29, P=0.04), figure (5). ROC curve was done for serum cystatin C and serum creatinine

in thalassemia major patients and control groups and found that AUC for serum cystatin C was significantly higher than that for serum creatinine (92% versus 80%). Moreover, serum cystatin C had higher sensitivity and specificity than serum creatinine (66% versus 26%)(Table 4&Figure 6). Table (5) and Figure (7) showed that the area under the curve for serum cystatin C was significantly higher (0.84 ±0.03) than the area under the curve for creatinine clearance (0.35 ±0.05). Moreover, serum cystatin C had higher sensitivity and specificity than creatinine clearance (66% versus 62% and (92% versus 65% respectively).

Table (1): The demographic and anthropometric characteristics of β-thalassemia major patients and controls.

Parameter		**Group I, β- thalassemia major, (NO=100)**	**Group II, control (NO= 50)**	**P-value**
Age (years)	Mean ±SD	9.6±1.1	9.8±1.7	0.8
Gender No (%)	Male Female	62(62%) 38(38%)	30(60%) 20(40%)	0.5
Residence No (%)	Urban Rural	44(44%) 56(56%)	20(40%) 30(60%)	0.7
Consanguinity No (%)	Positive Negative	30(30%) 70(70%)	0(0%) 50(100%)	0.001**
Weight (kg)	Mean ±SD	18.05±5.2	24.7±3.4	0.04*
Height (cm)	Mean ±SD	99.9±18.9	120.9±16.6	0.01*
Body mass index (Kg/m^2)	Mean ±SD	16.9±3.9	18.6±1.3	0.07
HC (cm)	Mean ±SD	49.1±4.7	47.6±3.7	0.6
Systolic BP(mmHg	Mean ±S	96.5±12.1	94.2±13.4	0.4
Diastolic BP(mmHg)	Mean ±SD	56.2±15.06	61.1±8.5	0.08

**Significant* ***Highly significant*

Table (2): Comparison between β-thalassemia major patients subgroups as regarding clinical characteristics.

Parameter		**Patients subgroups**		**P- value**
		Group I-a, N=62 With chelation	**Group I-b, N=38 Without chelation**	
Age at onset of transfusion, (months)	Mean ±SD	7.8±3.2	8.7±2.6	0.07
Frequency of blood transfusion/year	Mean ±SD	11.3±1.9	9.4±4.03	**0.02***
Splenomegaly No (%)	+ve -ve	96(96%) 4(4%)	32(64%) 18(36%)	**0.003****
Splenectomy No (%)	+ve -ve	4(4%) 96 (96%)	2 (4%) 48 (96%)	0.3

**Significant* ***Highly significant*

Table (3): Comparison between β-thalassemia major subgroups and controls as regard some laboratory findings.

Parameter		**Group I-a, with chelation (N= 31)**	**Group I-b, without chelation (N= 19)**	**Group II Control (N=35)**	**P-value**		
					I-a Vs II	**I-b Vs II**	**I-a Vs I-b**
cystatin C (mg/dl)	Range Mean±SD	0.7-2 1.9±0.2	0.5-1.8 1.6±0.3	0.3-0.6 0.6±0.1	0.01*	0.01*	0.1
Serum creatinine (mg/dl)	Range Mean±SD	0.7-1.5 0.9±0.1	0.5-1.2 0.7±0.2	0.5-0.8 0.4±0.08	0.01*	0.01*	0.1
eGFR Schwartz (ml/min/1.73m^2)	Range Mean±SD	44-88.1 77.4±30.4	56-99 83.2±36.4	58.9-154 102.9±23.4	0.01*	0.04*	0.04*
Creatinine clearance (ml/min)	Range Mean±SD	33-134 34.2±5.9	40.3-135 46.3±6.05	88-133 89.7±2.1	0.001**	0.04*	0.04*
Serum ferritin (ng/ml)	Range Mean±SD	165-1210 1020.3±45.1	98-1001 995.09±35.5	12-76 15.3±2.5	0.001**	0.001**	0.9
Albumin/creatinine in urine(mg/mmol)	Range Mean±SD	1.1-112.8 67.8± 24.4	0.6-101.4 62.2±30.1	0.4-2.2 1.3±0.2	0.001**	0.02*	0.5

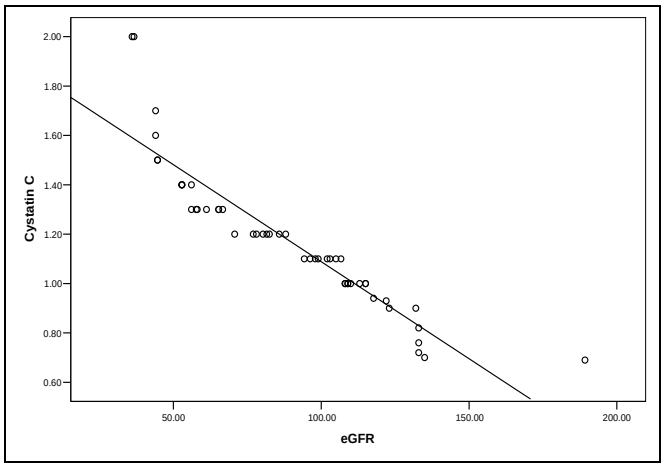
*Significant **Highly significant

Table (4): Diagnosis accuracy of reduced GFR from serum Cystatin C and serum creatinine among β-thalassemia major patients and control.

	Threshold value	**AUC Mean ±SD**	**Sensitivity**	**Specificity**	**95% CI**
Cystatin C , (mg/dl)	1.05	0.85 ±0.04	66%	92%	0.77-0.94
Serum creatinine , (mg/dl)	0.7	0.73 ±0.05	26%	80%	0.62-0.84

Table (5): Diagnosis accuracy of reduced GFR from serum Cystatin C and creatinine clearance among β-thalassemia major patients and control.

	Threshold value	**AUC Mean ±SD**	**Sensitivity**	**Specificity**	**95% CI**
Cystatin C, (mg/ml)	1.05	0.84 ±0.03	66%	92%	0.76-0.93
Creatinine clearance (ml/min)	113	0.35 ±0.05	62%	65%	0.24-0.47



r= -0.91 P= 0.001**

Figure (1): Correlation between serum Cystatin C (mg/dl) and e GFR in β-thalassemia major patients.

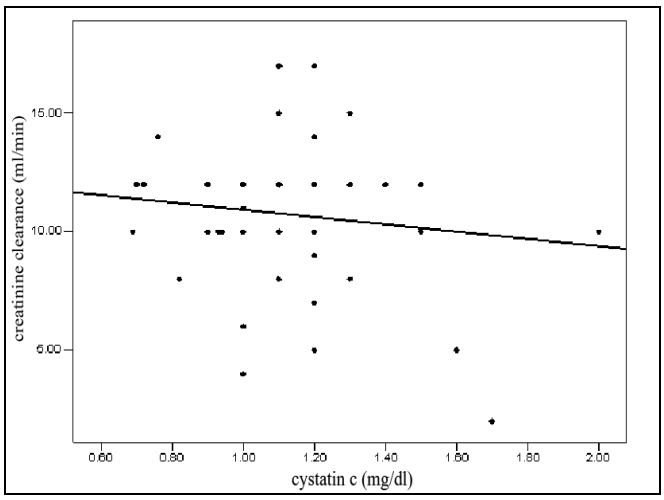
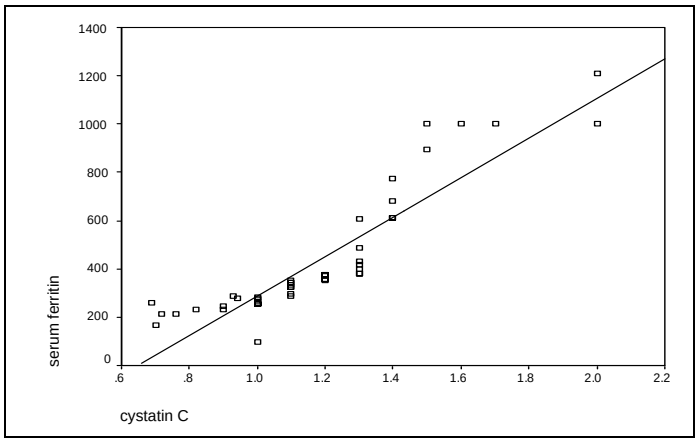


Figure (2): Correlation between serum Cystatin C (mg/dl) and creatinine clearance in β-thalassemia major patients.



r=0.90 p=0.001**

Figure (3): Correlation between Cystatin C and serum ferritin (mg/dl) in β-thalassemia major patients.

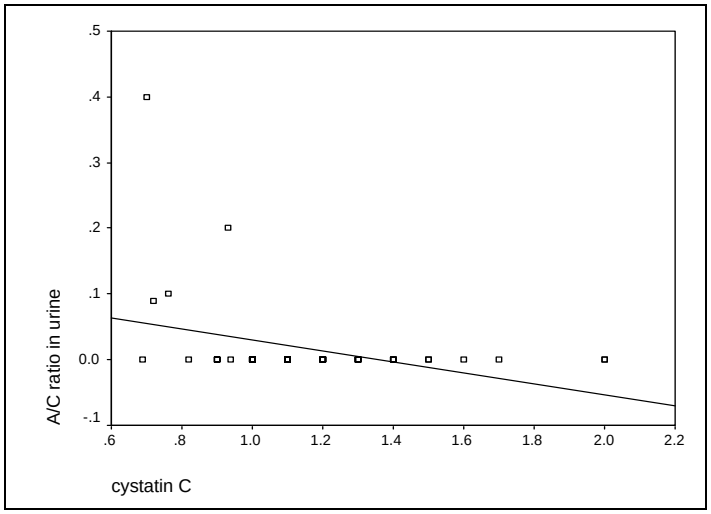


Figure (4): Correlation between serum Cystatin C and A/C ratio in urine in β-thalassemia major patients.

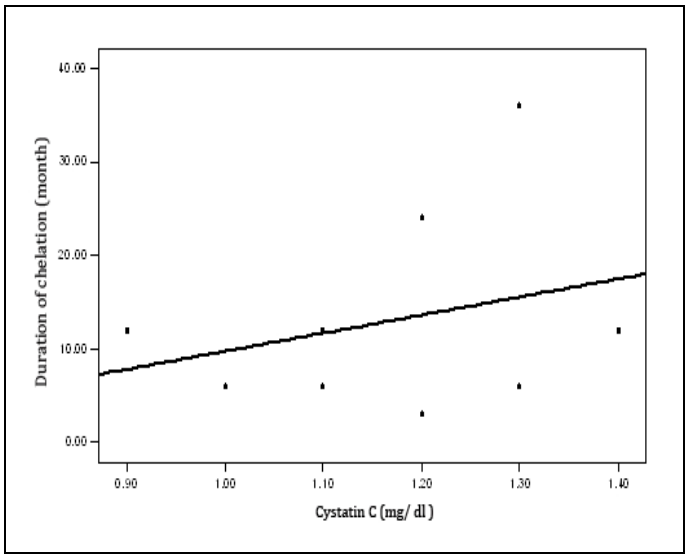


Figure (5): Correlation between serum Cystatin C and duration of chelation therapy (month) in β-thalassemia major patients.

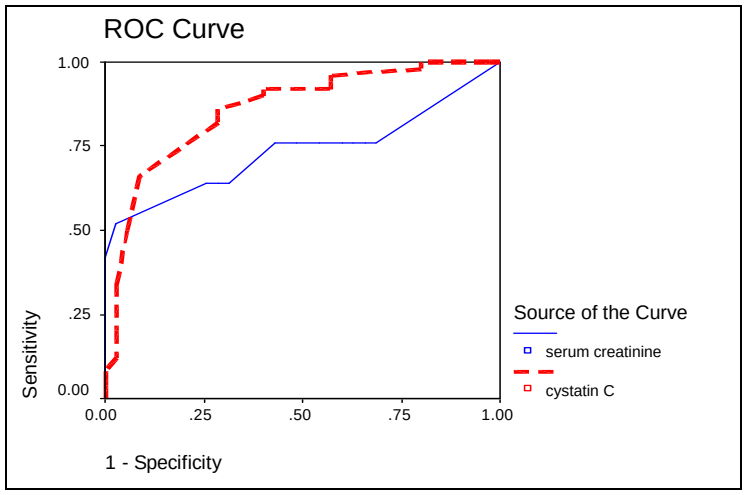


Figure (6): Receiver operating characteristic curve for serum Cystatine C and creatinine among β-thalassemia major patients and control.

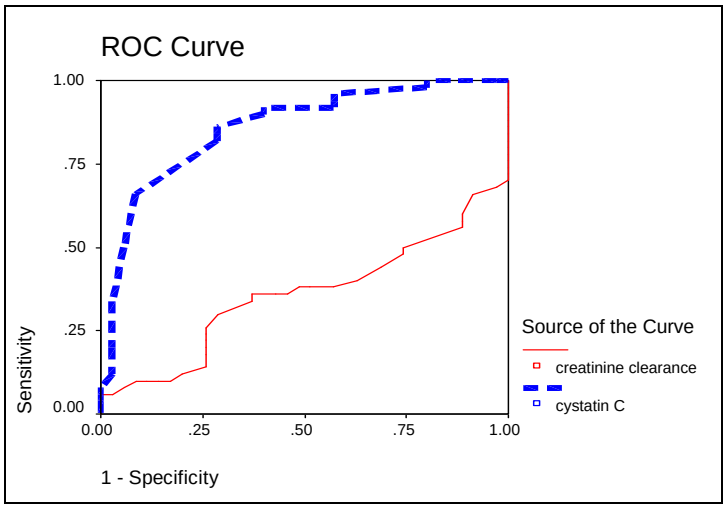


Figure (7): Receiver operating characteristic curve for serum serum Cystatine C and creatinine clearance among β-thalassemia major patients and control

DISCUSSION

Cardiac, pulmonary and endocrine complications in β-TM were well known and had evaluated by many researchers. It should be noted that less attention was paid to renal complications. Several investigations about renal involvement in adult β-TM patients had been done as those by **Koliakos et al., [15].**

The present study was designed to estimate the renal function in children with β-thalassemia by using different early markers including cystatin C and correlate these findings with different clinical and laboratory findings.

Concerning demographic data, the current study showed that β-TM patients had significantly higher frequency of positive consanguinity and 56% of them from rural areas.[16]

As regard some clinical data, the current study demonstrated that patients of group I-a had statistically significant higher frequencies of blood transfusion and splenomegaly (P=0.02 &0.003 respectively) (table 2).This could be explained by that patient of group I-a who were on chelation therapy had severe form of the disease with its subsequent clinical manifestations.

Concerning some laboratory data, the present study revealed that β-thalassemic patients whether on chelation therapy (group I-a) or without chelation therapy (group I-b) had statistically significantly higher levels of serum cystatin C, serum creatinine and serum ferritin than the control (P=0.01) for each of them. On the other hand, they had significantly lower eGFR and creatinine clearance than the control (P=0.01 & 0.04 and P=0.001&0.04 respectively), table (3). This could be explained by that renal

dysfunction in patients with β-TM was due to multifactorial including long standing anemia, chronic hypoxia and iron overload[15]. In addition, shortened red blood cells life span with rapid iron turnover and tissue deposition of excess iron and deferoxamine (DFO) therapy had been proved to be nephrotoxic and induce proximal tubular dysfunction by unknown mechanism[17]. These results were in agreement with the results obtained by **Grundy et al.,** [18] **and Hamed and El-Melegy** [19] who reported higher serum levels of serum cystatin C and serum creatinine and lower levels of creatinine clearance. In contrast to our findings**, Koliakos et al.,** [15] found normal serum creatinine and creatinine clearance in thalassemic patients who received subcutaneous deferoxamine treatment.

Concerning urinary findings the current study showed that group I-a and group I-b had statistically significant higher levels of albumin/creatinine ratio in urine than the control group (P=0.001&0.02 respectively). This could be explained by that albuminuria was attributed mainly to destruction of glomerular filtration membrane. Moreover, massive iron deposition in tissues results in increase of free radical production via Fenton reaction, leading to cell death by binding cell proteins and disturbing their production [20)&(21)]. Also, proteinuria could result from prolonged hyperfiltration, prostaglandin secretion and chronic anemia [22].

Comparison between group I-a and group I-b as regard some laboratory data showed that group I-a had significant lower eGFR and creatinine clearance than group I-b (P=0.04 for both).

Cystatin C is a 122-amino acid non-glycosylated low molecular weight (13 kDa) protein which inhibits cysteine proteases. Cystatin C is filtered by glomeruli, followed by tubular reabsorption and degradation resulting in excretion of a minute amount in the urine [23&4]. Concerning different correlations, the current study showed that serum cystatin C had statistically highly significant strong negative correlations with eGFR and creatinine clearance (r= - 0.91, P= 0.001& r= - 0.80, P= 0.005), figures 1& 2.This could be explained by that serum cystatin C shows a highly significant negative correlation with GFR. With a very simple formula; cystatin C gives a good estimate of GFR, more accurate and precise than other methods. Because biological variation is low, serum cystatin C gives also a good assessment of GFR changes during follow-up [24]. Further, cystatin C had statistically highly significant strong positive correlation with ferritin (r=0. 90, P=0.001), figure (3).This could be explained by that each 1 ml of packed red cells increases the body's iron load by 1 mg. Increased iron deposition coming from multiple life-long transfusions and enhanced iron absorption results in secondary hemosiderosis with secondary renal affection [25]. Moreover, serum cystatin C had statistically significant fair negative correlation with A/C in urine where (r=-0.36, P=0.01), figure (4).This could be explained by that **Katopodis et al.,** [26] who concluded that proteinuria and microalbuminuria may be related to prolonged

glomerular hyperfiltration and glomerulosclerosis. Also, serum cystatin C had significant positive fair correlation with duration of chelation therapy (r=0.29, P=0.04), figure 5. In the present study, serum cystatin C and creatinine values were measured as markers of GFR in β-TM patients and controls. ROC plots was done for serum cystatin C and serum creatinine to determine accuracy of serum cystatin C versus serum creatinine by plotted claimed sensitivity and specificity of β-TM patients and control. This test strongly suggested that serum cystatin C was indeed superior to serum creatinine for detection GFR as AUC was 0.85±0.04 for cystatin C versus 0.73±0.05 for serum creatinine with higher sensitivity and specificity (66%, 92%) versus (64%, 75%), table 4, figure 6**.** This finding was in agreement with the results obtained by **Larsson et al., [(27)]** who stated that plasma **c**ystatin C provided a better indication of changes of GFR than did serum creatinine. Furthermore, table 5 and figure 7 showed that AUC for serum cystatin C was significantly higher than that for creatinine clearance (0.85 ±0.04) versus (0.35 ±0.05) when compared β-TM patients and control groups. Also, sensitivity and specificity of serum cystatin C where higher than creatinine clearance (66%, 92%) versus (26%, 75%) respectively**.** This finding was in agreement with the finding obtained by **Finney et al., [(28)]** who demonstrated that serum cystatin C concentration was effectively constant by the 1st year of life, and remained constant throughout adulthood up to the age of 50 years rather than creatinine clearance. They also, suggested that serum cystatin C might offer a considerable advantage to pediatric nephrologists in detection of reduction of GFR.

Conclusion: From results of the present study it could be concluded that glomerular dysfunctions exists in children with β-TM. These abnormalities are mainly sub-clinical, so renal dysfunction may not be detected by routine tests. The need for early markers is recommended. Cystatin C is a promising early marker for monitoring glomerular dysfunction. In β-TM, the renal dysfunction may be partially explained by deferoxamine toxicity, so it is recommended to use alternative chelation drugs to avoid effects of deferoxamine on glomerular functions.

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يعتبر السيستاتين سى علامة مبكرة على خلل كبيبات الكلى فى الأطفال المصابين بأنيميا البحر المتوسط من النوع بيتا

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أنيميا البحر المتوسط من النوع بيتا (الثلاسيميا بيتا) هى الأكثر شيوعا من مرض الثلاسيميا وفقر الدم الشديد ولها عدة أشكال وراثية مختلفة؛ هذا ويعالج أكثر المرضى تضررا عن طريق نقل الدم المتكرر والذي أدى استخدامه بصورة منتظمة ومتكررة فى علاج مرض أنيميا البحر المتوسط إلى التحسن فى نوعية حياة هؤلاء المرضى.

يؤدى نقل الدم المتكرر إلى زيادة تركيز الحديد المزمن فى الأنسجة المختلفة بما فى ذلك القلب ، الكبد ، الغدد الصماء ، والكلى وغيرها من الأنسجة. وعلى عكس الأجهزة الأخرى ليس من الواضح ما إذا كان التأثير الذى يحدث للكلى ناتجا من انحلال الدم داخل الأوعية الدموية فقط ؛أم نتيجة لنقل الدم المزمن ومضاعفات العلاج بإستخلاب الحديد.

السيستاتين سى هو بروتين صغير ١٣ كيلو دالتون وهو عضو فى أسرة الانزيم المثبط بروتيناز السيستين الذى يتم إنتاجه بمعدل ثابت من قبل جميع الخلايا الأنويه؛ونظرا لصغر حجمه فإنه يتم تصفيته بحريه من قبل الكبيبات الكلويه ولا يفرز بل يعاد إمتصاصه وتكسيره بواسطه الأنابيب الكلويه؛ وحديثا يعد إستخدام السيستاتين سى لقياس معدل الترشيح بالكليه أفضل من إستخدام مستوى الكرياتينين بمصل الدم.

خلال هذا البحث تم دراسة مجموعتين: المجموعة الاولى: اشتملت ١٠٠ مريضا تم تشخيصهم مسبقا كمرضى بانيميا البحر المتوسط من النوع بيتا ، ثم قسمت هذه المجموعة الى قسمين: المجموعة الاولى (١- أ) شملت ٦٢مريضا بأنيميا البحر المتوسط الذين يعالجون بإستخلاب الحديد ، و المجموعة الاخرى (١- ب) شملت ٣٨مريضا بأنيميا البحر المتوسط الذين لا يعالجون بإستخلاب الحديد. المجموعة الثانيه : أشتملت على ٥٠ طفلا أصحاء ظاهريا ومتماثلين فى السن والجنس مع المجموعه الأولى. وقد خضعت كلتا المجموعتين الى :

١-التاريخ المرضى . ٢- الفحص الاكلينيكى. ٣ - الكشف الطبى والأشعه التلفزيونيه على البطن

٤- وبعض الإختبارات المعملية وشملت (صورة دم كامله ، وظائف كبد ، وظائف كلى، ومستوى السيستاتين سى بالدم، وإستخلاص الكرياتنين).

ومن خلال هذه الدراسه تم إستنتاج أن الأطفال المرضى بأنيميا البحر المتوسط يعانون من القصور الكلوى وهذا قد يكون نتيجه لفقر الدم المزمن ، وزيادة الفيريتين، والاكسدة المفرطة و سمية ديفيروكسامين ولكن هذا الخلل قد يكون بدون علامات سريريه و دون الحد الذى يمكن إكتشافه بواسطه الإختبارات الروتينيه لذا يعد السيستاتين سى علامة واعدة لرصد القصور الكلوى فى هذه الحالات لأنه وجد أن السيستاتين سى أكثر حساسية من الكرياتنين لتحديد أى تغير بسيط فى معدل الترشيح الكلوى.

بناء على نتائج هذه الدراسة نوصى بمتابعة وظائف الكلى في المرضى الذين يعانون من أنيميا البحر المتوسط ا للكشف عن القصور الكلوي في وقت مبكر حيث أن هذه المضاعفات ليست نادرة الحدوث.