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Renal dysfunction in patients with thalassaemia

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Summary

Little is known about the effects of thalassaemia on the kidney. Characterization of underlying renal function abnormalities in thalassaemia is timely because the newer iron chelator, deferasirox, can be nephrotoxic. We aimed to determine the prevalence and correlates of renal abnormalities in thalassaemia patients, treated before deferasirox was widely available, using 24-h collections of urine. We calculated creatinine clearance and urine calcium-to-creatinine ratio and measured urinary β_2-microglobulin, albumin, and protein. We used multivariate modelling to identify clinical, therapeutic, and laboratory predictors of renal dysfunction. One-third of thalassaemia patients who were not regularly transfused had abnormally high creatinine clearance. Regular transfusions were associated with a decrease in clearance ($P = 0{\cdot}004$). Almost one-third of patients with thalassaemia had hypercalciuria, and regular transfusions were associated with an increase in the frequency and degree of hypercalciuria ($P < 0{\cdot}0001$). Albuminuria was found in over half of patients, but was not consistently associated with transfusion therapy. In summary, renal hyperfiltration, hypercalciuria, and albuminuria are common in thalassaemia. Higher transfusion intensity is associated with lower creatinine clearance but more frequent hypercalciuria. The transfusion effect needs to be better understood. Awareness of underlying renal dysfunction in thalassaemia can inform decisions now about the use and monitoring of iron chelation.

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Keywords

thalassaemia; kidney; creatinine clearance; hyperfiltration; hypercalciuria; albuminuria; proteinuria; transfusion

The thalassaemia syndromes are a group of related haemolytic disorders that result from defective synthesis of haemoglobin and ineffective erythropoiesis. Transfusions of packed red blood cells are a mainstay of treatment for thalassaemia. Depending on the severity of thalassaemia, transfusions may need to be given regularly to maintain health or only sporadically in response to acute exacerbations. Iron overload is a consequence of both the transfused iron and increased intestinal absorption of iron from ineffective erythropoiesis. Chelation therapy is needed to prevent or reverse iron overload because there is no physiological mechanism to excrete iron. Thalassaemia and iron overload are known to affect many organ systems, such as the heart, lungs, liver, and endocrine glands.

Less is known about the effects of thalassaemia on the kidney. Abnormalities of renal function, such as increased renal plasma flow, decreased urine concentrating ability, and renal tubular acidosis, have been occasionally reported since 1975. (Mastrangelo *et al*, 1975; Shehab & Barakat, 1985) There are several recent reports of renal tubular dysfunction in patients with thalassaemia. (Sumboonnanonda *et al*, 1998, 2003; Aldudak *et al*, 2000; Koliakos *et al*, 2003; Mohkam *et al*, 2008; Sadeghi-Bojd *et al*, 2008; Smolkin *et al*, 2008) Anaemia and iron-mediated toxicity are the speculated causes of these abnormalities. Chelation therapy may also affect renal function in thalassaemia patients. Deferoxamine does not affect the kidneys unless it is given intravenously, especially at high doses. (Koren *et al*, 1989; Cianciulli *et al*, 1992, 1994) The newer oral iron chelator, deferasirox, can cause increases in serum creatinine, proteinuria, and even renal failure. (Vichinsky, 2008) Creatinine clearance is reported to be normal in thalassaemia, (Sumboonnanonda *et al*, 1998, 2003; Aldudak *et al*, 2000; Koliakos *et al*, 2003; Mohkam *et al*, 2008; Smolkin *et al*, 2008). However, all these reports estimated clearance by the Schwartz equation, (Schwartz *et al*, 1987) which can be inaccurate and does not correlate well with glomerular filtration rate (GFR) in other chronic anaemic states like sickle cell disease. (Schwartz & Work, 2009; Ware *et al*, 2010) Accurate measurements of creatinine clearance in patients with thalassaemia by timed urine collections are lacking. The relationship between creatinine clearance and abnormalities of tubular function, such as hypercalciuria, are also unknown.

The study of renal function abnormalities in thalassaemia is now timely, because of the increasing use of deferasirox. Underlying renal abnormalities could be a risk factor for deferasirox-related nephropathy. Therefore, we aimed to determine the prevalence of glomerular and tubular renal function abnormalities using timed urine collections and to evaluate the effects of genetic and laboratory factors, clinical complications, and regimens of transfusion and chelation. We hypothesized that regular transfusion therapy was associated with renal dysfunction.

Methods

Patient population

The Thalassemia Clinical Research Network (TCRN) comprises five thalassaemia centres in North America and their associated satellite sites. The TCRN conducted the Low Bone Mass Cross-sectional Observational Study (LBMCOS) that included a large group of patients (≥6 years of age) with all thalassaemia syndromes (thalassaemia major and intermedia). (Vogiatzi *et al*, 2009) This group of patients is well characterized, including data on genotype, transfusion status, chelation, iron burden, endocrinopathies, and other complications. The great majority of patients on chelation were treated with deferoxamine or deferiprone, because deferasirox was not widely clinically available at the time of the initial study. Patients in the LBMCOS also had 24-h urine collection to calculate urinary calcium excretion. The present study included all LBMCOS patients with complete urine collections for the calculation of creatinine clearance. As such, we only included patients whose urinary creatinine excretion rate was appropriate for age and gender within a range ≥10 but <40 mg/kg per day. We excluded patients who had missing urinary creatinine or calcium values and those who underwent stem cell transplantation. This study was approved by the TCRN Data and Safety Monitoring Board and by the ethical review boards of all TCRN institutions. A signed informed consent, and assent in case of a minor, was obtained.

Definitions and measurements

We classified patients by thalassaemia genotype (alpha or beta). Transfusion status was assigned by the number of transfusions received: ≥8 transfusion in the past year (regularly transfused or thalassaemia major); <8 transfusions in the past year; or not transfused in the past year. Clinical complications were ascertained by medical history and laboratory or radiographic studies as defined previously. (Vogiatzi *et al*, 2009, 2010).

Urine and serum samples were stored at −80°C and analysed as a batch at a central facility by previously described methods. (Vogiatzi *et al*, 2009, 2010) Blood urea nitrogen (BUN) and serum creatinine were classified according to standard normal ranges for age and sex. (Robertson & Shilkofski, 2005) Creatinine clearance was calculated from 24-h urine specimens using the standard formula: (U) × (V/P) × (1·73/BSA), where U = 24-h urine creatinine concentration V = (total volume of urine collected)/(hours of urine collection × 60 min); *P* = serum creatinine and BSA = body surface area (m^2). We classified creatinine clearance as low [<2 standard deviations (SDs) below average]; normal (within 2 SDs of average); or high (>2 SDs above average) based on normal values for age and gender [age 2–12·99 years: 133 ml/min per m^2 ± 27 (SD); age ≥13 and female: 126 ± 22; and age ≥13 and male: 140 ± 30]. (Hogg *et al*, 2003) For comparison, we also estimated each patient's GFR using the Schwartz equation. (Schwartz *et al*, 1987) We calculated the urinary calcium to creatinine ratio (U_{Ca}:U_{Cr}) using the formula: 24-h urinary calcium concentration 24-h urinary creatinine concentration. We classified U_{Ca}:U_{Cr} as normal (≤0·21) or high (>0·21). (Matos *et al*, 1997) Urinary β_2-microglobulin was classified as detectable or not. Urinary albumin content was expressed as mg/g creatinine, and total urinary protein excretion was expressed as mg/m^2 per h; both measures were calculated from 24-h urine collections.

Statistical analysis

Continuous variables were summarized as means, SDs, and ranges. Categorical variables were summarized as percentages. To test the effects of age, race, and gender on renal outcomes, we used regression/analysis of variance (ANOVA) by considering the outcomes as continuous variables. Race was not found to have an effect, but all further models controlled for both age and gender. We considered creatinine clearance and U_{Ca}:U_{Cr} as both continuous and binary outcomes (high vs. normal for creatinine clearance and U_{Ca}:U_{Cr}; low vs. normal for creatinine clearance only). Logistic regression (SAS PROC LOGISTIC) was used for categorical outcomes, and generalized linear models (SAS PROC GLM) were used for continuous outcomes. Models were fit for the following predictors: regular transfusion status (yes/no), serum transferrin receptor concentration, serum ferritin concentration, alpha thalassaemia (yes/no), beta thalassaemia (yes/no), heart disease (yes/no), cirrhosis (yes/no), hepatitis C (yes/no), hypothyroidism or hypoparathyroidism (yes/no), hypogonadism (yes/no), failure to thrive (yes/no), diabetes mellitus (yes/no), vitamin D deficiency (yes/no), fasting glucose concentration, and dietary calcium intake. Multivariate models were fit using predictors significant in bivariate analysis. Sub-group analysis by chelator type (deferasirox vs. non-deferasirox) was also performed.

Analyses were generally exploratory with the aim of describing observed patterns in the data. Corrections for multiple comparisons were not made, and alpha ≤0·05 was considered to be statistically significant. All analyses were performed using SAS (version 9.1.3, SAS Institute, Cary NC, USA).

Results

Characteristics of patients

We identified 216 eligible patients. 51·4% were female. The mean age was 23·2 years (range 6·1–75·4). Eighty-five patients (39%) were children (<18 years of age) and 131 (61%) were adults (≥18 years of age). 188 had beta-thalassaemia major or beta-thalassaemia intermedia, 14 had Hb H or Hb H-CS, 13 had E-beta-thalassaemia, and 1 had homozygous alpha thalassaemia major. 180 subjects were regularly transfused (≥8/year) and 36 were not. The mean Hb concentration for regularly transfused patients was 100 g/l compared to 91 g/l for those not regularly transfused. Patients were treated with the following iron chelators: deferoxamine (*N* = 157), deferasirox (*N* = 17), and deferiprone (*N* = 2).

Blood urea nitrogen and serum creatinine

The mean (±SD) values of BUN and serum creatinine were 5·4 ± 1·6 mmol/l and 48·6 ± 16·8 μmol/l, respectively. Most patients had values of BUN and creatinine that were in the normal range. Twenty-five had a BUN above the upper limit of normal for age, which were mostly mild elevations (mean BUN 8·2 mmol/l). Two had a creatinine above the upper limit of normal for age and sex: a 12-year-old female (88·4 μmol/l) and a 23-year-old male (123·8 μmol/l). The BUN of regularly transfused patients was modestly, but significantly, higher than those not regularly transfused (5·5 vs. 4·8 mmol/l, *P* = 0·01). The serum creatinine was 49·5 ± 15·9 μmol/l for regularly transfused patients and 44·2 ± 18·6 μmol/l for those not regularly transfused, but this was not statistically different (*P* = 0·07).

Creatinine clearance

Creatinine clearance was significantly associated with age: clearance decreased by 0·7 ml/min per 1·73 m^2 for every year of increasing age ($P = 0·02$). In the subset of patients >30 years of age ($n = 75$), there was no association between clearance and age (P = 0·53). Clearance was not associated with gender ($P = 0·91$) or race ($P = 0·47$). Table I shows the distribution of creatinine clearance by diagnosis and transfusion status. Among all patients, 7·8% had a low creatinine clearance, 71·3% had a normal clearance, and 20·8% had a high clearance (for their age and gender). Among patients who were not regularly transfused (<8 transfusions/year), 36·1% had a high creatinine clearance, whereas 17·8% of regularly transfused patients (≥8 transfusions/year) had a high creatinine clearance. 8·3% of regularly transfused patients had a low creatinine clearance. Table II compares the creatinine clearance of regularly transfused patients to those not regularly transfused. Regularly transfused patients had significantly lower creatinine clearance than those not regularly transfused ($P = 0·004$). Among regularly transfused patients, the creatinine clearance was lower in adults than children (137·5 vs. 155·5; $P = 0·03$).

A multivariate logistic regression model controlling for age and sex showed that the only significant predictors of high creatinine clearance were non-regular transfusion status, increased serum transferrin receptor concentration, and increased dietary calcium intake (Table III). Not predictive of high creatinine clearance were the specific thalassaemia diagnosis, serum ferritin, serum glucose, body mass index, and any of the clinical complications or endocrinopathies. If we excluded the patients ($N = 17$) receiving deferasirox from the model, the significant predictors of high creatinine clearance were non-regular transfusion status and increased serum transferrin receptor concentration (Table III). A multivariate logistic regression model found no significant predictors of a low creatinine clearance (*versus* normal).

We also assessed the agreement between GFR calculated by the Schwartz equation and from timed measurements of urinary creatinine clearance. The mean difference between both methods was 30 ml/min per 1·73m^2 ($P < 0·001$). The correlation concordance coefficient was 0·62, indicating only moderate agreement. The Schwartz formula mostly overestimated GFR, especially for lower values.

Urinary calcium excretion

U_{Ca}:U_{Cr} was significantly associated with gender (females 0·18 *versus* males 0·15; $P = 0·04$) but not age ($P = 0·95$) or race ($P = 0·53$). There was also no association between U_{Ca}:U_{Cr} and age ($P = 0·14$) in the subset of patients >30 years of age ($P = 75$). The distribution of U_{Ca}:U_{Cr} by diagnosis and transfusion status is shown in Table I. Among all patients, 71·3% had a normal U_{Ca}:U_{Cr}, and 28·7% had a high ratio (hypercalciuria). Among patients who were not regularly transfused, 11·1% had a high U_{Ca}:U_{Cr}. In contrast, 32·2% of regularly transfused patients had a high U_{Ca}:U_{Cr} (hypercalciuria). Table II compares the U_{Ca}:U_{Cr} of regularly transfused patients to those not regularly transfused. Regularly transfused patients had significantly higher U_{Ca}:U_{Cr} than those not regularly transfused ($P < 0·0001$). U_{Ca}:U_{Cr} was significantly negatively correlated with creatinine clearance ($r = −0·24$, $P = 0·0004$).

A multivariate logistic regression model showed that the only significant predictors of a high U_{Ca}:U_{Cr} (hypercalciuria) were regular transfusion status and decreased serum trans- ferrin receptor concentration (Table III). Not predictive of high U_{Ca}:U_{Cr} were the specific thalassaemia diagnosis, serum ferritin, serum glucose, dietary calcium intake, body mass index, and any of the clinical complications or endocrinopathies. If we excluded the patients (*N* = 17) receiving deferasirox from the model, the only significant predictor of a high U_{Ca}:U_{Cr} was non-regular transfusion status (Table III). Vitamin D deficiency as a binary (yes/no) variable was not associated with high U_{Ca}:U_{Cr}, but as a secondary analysis we categorized serum 25-hydroxy-vitamin D levels as: <11, 11–30, and >30 ng/ml. Vitamin D levels >30 (but not 11–30) were associated with an increased odds of a high U_{Ca}:U_{Cr} compared to vitamin D levels <11 (OR 4·1, 1·3– 13·1).

Urinary β_2-microglobulin, albumin, and protein

Urinary β_2-microglobulin was detectable in only seven patients (4%), all of whom were regularly transfused, but there was not a statistically significant association with transfusion status (*P* = 0·60). Albuminuria was found in 102 patients (59%) with a mean of 26·2 (SD 56·2) mg/g creatinine. Greater albuminuria was associated with increasing age in all patients (*N* = 102, *P* < 0·001), but not in the subset >30 years of age (*N* = 75; *P* = 0·07). Similarly, higher total proteinuria was associated with increasing age in all patients (*N* = 102, *P* = 0·007), but not in the subset >30 years of age (*N* = 75; *P* = 0·49). Table II shows the distribution of urinary albumin content and total urinary protein excretion by transfusion status for only those patients who had detectable urinary albumin or protein. Detectable urinary albumin was not associated with regular transfusion status (*P* = 0·40). Similarly, neither the degree of urinary albumin (*P* = 0·82) nor degree of total protein (*P* = 0·45) differed significantly by regular transfusion status. Only one patient had macroalbuminuria (>300 mg/g creatinine), and he was in the regular transfusion group; all others had microalbuminuria (≤300 mg/g creatinine).

A multivariate logistic regression model showed that the only significant predictors of detectable urinary albumin were increased serum transferrin receptor concentration, decreased serum ferritin concentration, and failure to thrive (Table III). Not predictive of detectable urinary albumin were regular transfusion status, the specific thalassaemia diagnosis, serum glucose, dietary calcium intake, and any of the clinical complications or endocrinopathies besides failure to thrive. If we excluded the patients (*N* = 17) receiving deferasirox from the model, the only significant predictor of detectable urinary albumin was serum transferrin receptor concentration (Table III). A multivariable linear regression model showed that the log of total urinary protein concentration was positively associated with serum transferrin receptor concentration (Table III); none of the other covariates was predictive. Even if we excluded the patients (*N* = 17) receiving deferasirox, the log of total urinary protein concentration was positively associated with serum transferrin receptor concentration (Table III).

Discussion

This study found that renal hyperfiltration was common in patients with thalassaemia. One-third of patients who were not regularly transfused had an abnormally high creatinine clearance. Higher intensity of transfusions was associated with lower creatinine clearance. For most regularly transfused subjects, creatinine clearance was in the normal range, but 8% had an abnormally low clearance. We also found that hypercalciuria is common. Almost one-third of patients with thalassaemia have hypercalciuria (high U_{Ca}:U_{Cr}), and a higher intensity of transfusions was associated with a greater frequency and degree of hypercalciuria. Albuminuria was present in the majority of patients, but it was not consistently associated with the intensity of transfusion therapy.

Several authors have reported abnormalities of renal tubular function in patients with thalassaemia major and intermedia, such as proteinuria, hypercalciuria, and hyperphosphaturia as well as increased urinary excretion of markers of tubular injury, such as *N*-acetyl-β-D-glycosaminidase, malondialdehyde, and β_2-microglobulin. (Sumboonnanonda *et al*, 1998, 2003; Aldudak *et al*, 2000; Koliakos *et al*, 2003; Mohkam *et al*, 2008; Sadeghi-Bojd *et al*, 2008; Smolkin *et al*, 2008) Our findings of hypercalciuria, albuminuria, proteinuria, and excretion of β_2-microglobulin are in accordance with prior reports of renal tubular dysfunction. However, these studies all reported normal GFR. (Sumboonnanonda *et al*, 1998, 2003; Aldudak *et al*, 2000; Koliakos *et al*, 2003; Mohkam *et al*, 2008; Smolkin *et al*, 2008) In contrast, we found that hyperfiltration was common and that chronic transfusion therapy was associated with a decrease in creatinine clearance. This discrepancy might be explained by the fact that we measured creatinine clearance by 24-h urine collection, while prior reports only estimated clearance by the Schwartz equation. We found that the Schwartz equation agreed only moderately with measured creatinine clearance in thalassaemia patients, so we recommend that it not be used in future studies of renal function in thalassaemia.

Hyperfiltration could be a consequence of chronic anaemia, similar to that observed in young children with sickle cell anaemia. (Allon, 1990) In thalassaemia, however, there is no concurrent vaso-occlusive damage to the renal medulla. The decrease in creatinine clearance that we found to be associated with regular transfusions and bone marrow suppression (lower serum transferrin receptor) might result from alleviation of anaemia. Transfusion-related decreases in creatinine clearance and increases in U_{Ca}:U_{Cr} might also represent iron-mediated glomerular and tubular injury. We did not find a correlation between serum ferritin and creatinine clearance or U_{Ca}:U_{Cr}, but ferritin may be too poor a marker of iron burden for this purpose. Other studies have shown renal tubular abnormalities to be related to duration of chelation, duration of transfusions, the amount of transfused iron, and magnetic resonance imaging measurements of body iron. (Koliakos *et al*, 2003; Sumboonnanonda *et al*, 2003; Mohkam *et al*, 2008; Smolkin *et al*, 2008) Others have also reported that the degree of tubular abnormalities is correlated with the degree of anaemia. (Smolkin *et al*, 2008) These findings and the presence of markers of oxidative damage to tubules (Sumboonnanonda *et al*, 1998, 2003; Aldudak *et al*, 2000; Koliakos *et al*, 2003; Mohkam *et al*, 2008; Sadeghi-Bojd *et al*, 2008; Smolkin *et al*, 2008) argue for a role of anaemia and iron in the renal dysfunction in thalassaemia. Haemolysis, rather than anaemia *per se*, might contribute to

renal dysfunction through the release of free haem and iron or by decreasing nitric oxide bioavailability, but we did not measure any markers of haemolytic rate in this study to investigate this hypothesis.

The main limitation of our study was that it was a cross-sectional analysis. We did not follow individual subjects over time, so we cannot conclude that regular transfusions caused the changes in renal function reported here. However, a causal association is supported by fact that serum transferrin receptor concentration is also associated with measures of renal function. These two independent predictors, transfusion status and serum transferrin receptor, reciprocally reflect the intensity of transfusion and bone marrow suppression of the patient. That is, we found that a higher number of transfusions (regular transfusion status) and greater bone marrow suppression (lower serum transferrin receptor concentration) were both associated with a decrease in creatinine clearance and an increase in hypercalciuria. Another limitation is that we studied a relatively small number of patients who were not regularly transfused ($N = 36$, 20% of our sample), so this sample may not have been representative of the larger population. Nevertheless, we report here the largest study to date of renal function in patients with thalassaemia. We also did not obtain a “gold standard” measurement of GFR, such as the clearance of inulin, iothalamate, or iohexol. Unlike past studies in thalassemia, however, we did not simply use spot urine specimens or estimate clearance by the Schwartz equation. Instead we measured creatinine clearance by 24-h urine collection, and to improve the accuracy of this technique we only included patients whose urinary creatinine excretion rate was appropriate for age and gender. We also controlled for potentially confounding factors in multivariate models. Finally, our chelated study population was predominantly treated with deferoxamine or deferiprone, so our findings probably do not represent the nephrotoxic effects of the newer oral agent, deferasirox, which was given to a small number of patients ($N = 17$). Even if we exclude these patients from key multivariable models, the overall conclusions of this study remain unchanged.

In summary, renal hyperfiltration, hypercalciuria, and albuminuria are common in thalassaemia patients. Higher transfusion intensity is associated with lower creatinine clearance but more frequent hypercalciuria. Further research is needed to understand the causes of glomerular and tubular injury in thalassaemia, but awareness of underlying renal dysfunction can inform decisions now about the use and monitoring of nephrotoxic agents, such as deferasirox.

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Appendix

The following TCRN sites and investigators contributed to the study (listed in alphabetical order): Children's Hospital, Boston: Ellis Neufeld, MD, PhD, Principal Investigator, Melody Cunningham, MD, Co-Principal Investigator; Children's Hospital of Philadelphia: Alan R. Cohen, MD, Principal Investigator, Janet L. Kwiatkowski, MD, Co-Principal Investigator, Catherine S. Manno, MD, Coinvestigator, Marie Martin, RN, Nurse Coordinator, Debra Hillman, Regulatory Affairs Coordinator, Gail M. Jackson, CDT, Nutrition Assessment Program Coordinator, Maria J. Henwood-Storto, DO, Endocrinologist; Shannon H. Fourtner, MD, Endocrinologist; Children's Hospital & Research Center Oakland: Elliott Vichinsky, MD, Principal Investigator, Dru Foote, NP, Study Coordinator, Eun-Ha Pang, Study Coordinator, Zahra Pakbaz, MD, CCD, Certified Clinical Densitometrist, Selma Holden, Study Coordinator; Toronto General Hospital: Nancy Olivieri, MD, Principal Investigator; U.T. Southwestern Medical Center: Charles T. Quinn, MD, MS, Coinvestigator, Leah Adix, CCRP, Clinical Research Associate; Weill Medical College of Cornell University: Patricia J. Giardina, MD, Principal Investigator, Robert W. Grady, PhD, Coinvestigator, Jeffrey E. Mait and Dorothy Kleinert, NP, MPH, MA, Study Coordinators, Irina Chaikhoutdinov and Gladys Cintron, Data Coordinators, Sylvia Hom, DXA Technician, Hospital for Special Surgery; National Heart, Lung, and Blood Institute: Kathryn Hassell, MD, Project Officer; Data Coordinating Center, New England Research Institutes: Sonja McKinlay, PhD, Principal Investigator, Felicia Trachtenberg, PhD, Senior Statistician, Lisa Virzi, RN, MS, MBA, Project Director.

Table I

Creatinine clearance and urinary calcium to creatinine ratio by diagnosis, age group, and transfusion status.

		Creatinine clearance (ml/min/m^2)		Calcium to creatinine ratio	
Diagnosis	***N***	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
All Patients, *N* = 217					
β-thalassemia (≥8/year)★	163	140·6 ± 50·0	32·47–423·5	0·18 ± 0·10	0·01–0·57
β-thalassaemia (<8/year)†	17	191·0 ± 73·8	77·8–324·1	0·12 ± 0·07	0·01–0·30
β-thalassaemia (none)‡	8	178·0 ± 68·7	93·2–287·3	0·13 ± 0·11	0·03–0·34
Hb H disease	8	150·6 ± 52·3	68·3–235·4	0·09 ± 0·06	0·04–0·22
Hb H-Constant Spring	6	141·3 ± 46·9	70·78–214·3	0·16 ± 0·15	0·01–0·37
E-β-thalassaemia (≥8/year) ★	3	187·0 ± 98·6	128·0–300·9	0·14 ± 0·08	0·06–0·21
E-β-thalassaemia (<8/year)†	8	181·3 ± 93·5	89·2–349·8	0·12 ± 0·11	0·01–0·31
E-β-thalassaemia (none) ‡	2	166·9 ± 48·2	132·9–201·0	0·09 ± 0·09	0·03–0·16
Homozy. α-thalassaemia	1	140·1	–	0·26	–
Children (<18 years), *N* = 85					
β-thalassemia (≥8/year)★	57	148·9 ± 41·6	75·0–244·8	0·17 ± 0·12	0·01–0·57
β-thalassaemia (<8/year)†	4	235·1 ± 64·2	180·4–311·5	0·10 ± 0·03	0·06–0·13
β-thalassaemia (none) ‡	6	166·6 ± 61·1	93·2–241·8	0·16 ± 0·12	0·05–0·34
Hb H disease	7	150·1 ± 56·4	68·3–235·4	0·09 ± 0·06	0·04–0·22
Hb H-Constant Spring	4	157·2 ± 40·7	118·7–214·2	0·18 ± 0·17	0·01–0·37
E-β-thalassaemia (≥8/year) ★	1	300·9	–	0·14	–
E-β-thalassaemia (<8/year)†	4	245·6 ± 89·6	155·6–349·8	0·09 ± 0·15	0·01–0·31
E-β-thalassaemia (none) ‡	2	166·9 ± 48·2	132·9–201·0	0·09 ± 0·09	0·03–0·16
Adults (≥18 years), *N* = 131					
β-thalassemia (≥8/year)★	106	136·1 ± 53·7	32·5–423·5	0·18 ± 0·10	0·02–0·47
β-thalassaemia (<8/year)†	13	177·4 ± 73·5	77·8–324·1	0·13 ± 0·08	0·01–0·30
β-thalassaemia (none) ‡	2	212·3 ± 106·1	137·2–287·3	0·04 ± 0·01	0·03–0·05
Hb H disease	1	154·0	–	0·12	–
Hb H-Constant Spring	2	109·5 ± 54·8	70·8–148·3	0·11 ± 0·13	0·02–0·20

Br J Haematol. Author manuscript; available in PMC 2014 December 01.

		Creatinine clearance (ml/min/m^2)		Calcium to creatinine ratio	
Diagnosis	***N***	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
E-β-thalassaemia (≥8/year) ★	2	130·1 ± 3·0	128·0–132·2	0·14 ± 0·11	0·06–0·21
E-β-thalassaemia (<8/year)†	4	116·9 ± 36·5	89·2–168·4	0·16 ± 0·07	0·10–0·24
Homozy. α-thalassaemia	1	140·1	–	0·26	–

★ ≥8 transfusions per year.

† <8 transfusions per year.

‡ Not transfused in past year.

Table II

Measurements of renal function by transfusion status.

	Regular transfusion status					
	Yes (≥8 transfusions/year)			No (<8 transfusions/year)		
Measurement	***N***	**Mean ± SD**	**Range**	***N***	**Mean ± SD**	**Range**
Creatinine Clearance (ml/min per 1·73m^2)	180	143·8 ± 54·3	32·47–423·5	36	173·4 ± 65·0	68·3–349·8
U_{Ca}:U_{Cr} (ratio)	180	0·18 ± 0·10	0·01–0·57	36	0·10 ± 0·08	0·01–0·34
Urinary Albumin (mg/g creatinine)	84	27·8 ± 61·2	3·3–522·2	18	18·6 ± 20·2	4·1–95·2
Total Urinary Protein (mg/m^2/h)	147	3·5 ± 4·2	0·3–30·7	27	3·2 ± 1·7	1·0–8·8

Table III

Multivariate regression models of creatinine clearance, urinary calcium to creatinine ratio (U_{Ca}:U_{Cr}), urinary albumin, and total urinary protein by chelation group.

	All chelators†		No deferasirox‡	
Model and significant predictors★	**OR**	**95% CI**	**OR**	**95% CI**
Model: High creatinine clearance (vs. normal)				
Regular transfusion status (yes vs. no)	0·39	0·17–0·88	0·42	0·18–0·94
Serum transferrin receptor	1·03	1·01–1·05	1·03	1·01–1·05
Dietary calcium intake (mg)	1·00	1·00–1·01		
Model: High U_{Ca}:U_{Cr} (vs. normal)				
Regular transfusion status (yes vs. no)	3·72	1·24–11·2	3·54	1·17–10·7
Serum transferrin receptor	0·98	0·95–0·99		
Model: Detectable albumin (vs. not detectable)				
Serum transferrin receptor	1·04	1·01–1·06	1·03	1·01–1·06
Serum ferritin	0·81	0·67–0·98		
Failure to thrive (yes vs. no)	0·48	0·24–0·95		
	β	*P*	β	*P*
Model: Total protein (log-transformed)				
Serum transferrin receptor	0·015	<0·0001	0·016	<0·0001

★All models controlled for age and gender.

†All patients, regardless of iron chelator, were included.

‡Patient receiving deferasirox (*N* = 17) were excluded from the analyses.

OR, odds ratio; 95% CI, 95% confidence interval