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Glomerulotubular function in transfusion-dependent thalassemia children: a prospective cohort study

Henny Adriani Puspitasari[1*], Ludi Dhyani Rahmartani[2], Diashati Ramadhani Mardiasmo[3], Pustika Amalia Wahidiyat[2], Eka Laksmi Hidayati[1]

[1]Division of Nephrology, Department of Child Health, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[2]Division of Hematology-Oncology, Department of Child Health, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[3]Medical Technology Cluster, Indonesia Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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ABSTRACT

Introduction: Thalassemia is the most common hemoglobinopathy in Indonesia. Chronic anemia, iron overload, and treatment with iron chelating agents are factors that contribute to kidney dysfunction in children with transfusion-dependent thalassemia (TDT). Urine neutrophil gelatinase-associated lipocalin (uNGAL) and urine albumin-creatinine ratio (uACR) are markers of glomerular and tubular damage.

Objectives: To analyze the glomerulotubular function in TDT children.

Patients and Methods: This prospective cohort study recruited 40 TDT children aged ≤18 years old from thalassemia transfusion outpatient clinic, Dr. Cipto Mangunkusumo general hospital, Jakarta, Indonesia between February and June 2021. Disease history, treatment, and anthropometry were obtained during enrollment (T0). Blood and urine samples were taken at enrollment (T0) and at 1 (T1), 2 (T2), and 3 (T3) month follow-up appointments. Data analyzed were iron chelating agent, ferritin, hemoglobin, estimated glomerular filtration rate (eGFR), uNGAL, uACR levels.

Results: We observed kidney hyperfiltration in more than 30% of the participants. Transfusion volume was the most dominant factor for eGFR (β = -0.974, *P* = 0.022) and uNGAL (β = 0.872, *P* = 0.015). A low-proportion of albuminuria was found with duration of disease as the predominant factor (β = -0.946, *P* = 0.000). Deferiprone (DFP) and deferasirox (DFX) showed comparable association with all kidney biomarkers.

Conclusion: The findings of this study indicate glomerular hyperfiltration in TDT children as the main early sign of glomerulotubular function impairment. In addition, a small proportion of proteinuria was also found in our study. Thus, both biomarkers should be part of long term kidney follow up in TDT children.

Original

Implication for health policy/practice/research/medical education:
This study investigated the glomerulotubular function in children with TDT using kidney biomarkers uNGAL, uACR, and eGFR. The findings implied the need of long term kidney follow up in all TDT children.

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Introduction

Thalassemia is an inherited autosomal recessive blood disorder that results in ineffective erythropoiesis. Globally, approximately 270 million people are carriers for the thalassemia genetic defect, and around 23 000 children are born with beta thalassemia major every year (1). Indonesia is one of the countries in the "thalassemia belt" due to its high prevalence. Dr. Cipto Mangunkusumo general hospital (CMGH), Indonesia's national thalassemia centre, treats 600-700 patients per month. The Indonesian pediatric society—hematology oncology work group unit recorded 10 555 children with thalassemia in 2019 (2). This number is most likely lower than the actual number of cases in the population, as there are still numerous

***Corresponding author**: Henny Adriani Puspitasari, Email: henny.adriani01@ui.ac.id

undiagnosed cases each year. Although lung, heart, and endocrine complications of thalassemia are well described in the literature, kidney complications have received less attention (3).

Chronic anemia, iron overload, and iron chelating agents are factors that cause kidney dysfunction (4). Chronic anemia and hypoxia have been associated with oxidative stress, lipid peroxidation, and apoptosis, which lead to tubular injury and can cause a decrease in glomerular filtration rate (GFR) over time. The quality of life of children with thalassemia major can be improved with regular blood transfusions; however, repeated transfusions lead to chronic iron overload in the heart, liver, and various other tissues (5). Autopsies from patients with beta thalassemia major found hemosiderin deposits in the proximal, distal, and terminal tubules (6). These iron deposits induce reactive oxygen species production, resulting in tubular injury (4). Therefore, patients with transfusion-dependent thalassemia (TDT) require iron chelating agents to remove excess iron from their bodies. There are three commonly used iron chelating agents; deferoxamine, deferiprone (DFP), and deferasirox (DFX). Deferoxamine is administered as a subcutaneous infusion, whereas DFP and DFX are administered orally. DFP and DFX are therefore less invasive and convenient and are therefore preferred. It has been established that DFX has nephrotoxic side effects and is related to tubular damage, acute kidney injury, electrolyte acid-base disorders, and abnormal urinary findings (7).

Glomerular injury in thalassemia is assessed with GFR and urine albumin-creatinine ratio (uACR) (8). Studies have found glomerular hyperfiltration in 20% to 40% of thalassemia cases (9). Decreased estimated GFR (eGFR) is uncommon in pediatric thalassemia patients, but a 10-year follow-up study found eGFR<90 mL/min/1.73 m^2 in 18.5% of adult thalassemia patients (10). Albuminuria is assessed uACR, which reflects endothelial permeability and dysfunction. A study of pediatric thalassemia patients found that elevated uACR occurred in 24% and 47% of patients (11). Urine neutrophil gelatinase-associated lipocalin (uNGAL), expressed by proximal tubule epithelial cells, is an excellent biomarker for detection of early tubular injury. Upon nephrotoxic and/or ischemic injury, its levels are elevated. Several studies have demonstrated that uNGAL markedly increased 2-6 hours after cardiac surgery in children who subsequently developed acute kidney injury, and uNGAL also predicted contrast-induced nephropathy in children undergoing cardiac catheterization (12-14).

Objectives

The aim of this study was to analyze glomerulotubular function in children with TDT using kidney biomarkers uNGAL, uACR, and eGFR as well as associating factors. We hypothesize that children with TDT will have decreased glomerulotubular function.

Patients and Methods

Study design

This prospective cohort study was conducted at the thalassemia transfusion outpatient clinic, CMGH, Jakarta, Indonesia, between February and May 2021.

This study recruited 40 children in who were 18 years old or under, diagnosed with TDT, and treated with an iron chelating agent (DFP or DFX) for at least 12 months. The exclusion criteria included patients with end-stage kidney disease (eGFR<15 mL/min/1.73 m^2), those undergoing dialysis treatment and/or liver dysfunction prior to enrollment. All participants underwent three months of consecutive follow-up. Sample size was calculated using coefficient correlation formula.

Data collection

History of disease, treatment details, and anthropometry measurements were obtained during enrollment (T0). Blood and urine samples were taken four times: at enrollment (T0) and at 1 month (T1), 2 month (T2), and 3 month (T3) follow-ups. A venous blood sample (2 ml) was collected by a phlebotomist and sent to the CMGH laboratory to test for ferritin at enrollment, serum hemoglobin at T0-T3, and serum creatinine at T0–T3. Hemoglobin was tested using the cyanide-free spectrophotometry method with a Sysmex XN-3000 (Sysmex, Japan). Ferritin was tested using the chemiluminescence microparticle immunoassay method, and creatinine was tested using the enzymatic creatininase method; both used Abbot Architect ci8200 (Abbot, Illinois, IL, USA). A minimum of 10 mL of urine was collected and sent to the Prodia Laboratory in a cooler box to test for uNGAL at enrollment and uACR at T0–T3. Urinary NGAL was examined using the ELISA method with a QUANTIKINE Immunoassay (R&D Systems, Minneapolis, MN, USA; NGAL Immunoassay).

Variable definitions

The eGFR was calculated with the modified Schwartz formula (15). Glomerular hyperfiltration was defined as eGFR>150 mL/min/1.73 m^2. Albuminuria or abnormal uACR was defined as uACR >30 mg/g. Decline in eGFR was defined as eGFR <90 mL/min/1.73 m^2 (16). Nephrotic range proteinuria was defined as uACR >300 mg/g (17). Abnormal uNGAL was defined as uNGAL >150 ng/mL. Severe hemochromatosis was defined as ferritin >2500 ng/mL (18). Ferritin levels were only obtained at baseline as it is usually only tested every 3 months.

Statistical analysis

All of the statistical analyses were performed using IBM SPSS Statistics for Macintosh, version 21.0, released in 2012 (IBM Corp., Armonk, NY, USA). Categorical data were presented as a percentage, whereas normal and non-normally distributed data were presented as mean ± standard deviation (SD) and median (minimum–

maximum), respectively. The normality test was carried out using the Shapiro–Wilk test. Bivariate analysis of categorical datasets was conducted with Fisher's exact test. Bivariate analyses of categorical and numerical datasets were conducted with the unpaired t-test (normal distribution) or the Mann–Whitney U test (non-normal distribution). Statistical significance was achieved when $P < 0.05$. The correlation test was performed with Pearson correlation. Pearson's correlation coefficient (r) values greater than 0 indicated a positive association and values less than 0 indicated a negative association. A multivariate analysis was carried out using linear multiple regression (backwards method). Subsequent analysis comparing DFP and DFX group are available in supplementary material.

Results

Patient characteristics

We recruited 40 children with TDT who were undergoing treatment with DFP or DFX. The median age at the time of diagnosis was 9.5 (1-120) months. The patients received blood transfusions 19 (10-54) times per year, and 78.9% of the patients had severe hemochromatosis (Table 1).

Table 1. Baseline characteristics

Characteristics	Total (n=40)
Age (months), median (min-max)	168 (96–228)
Gender, No. (%)	
Male	19 (47.5)
Female	21 (52.5)
Weight (kg), mean (SD)	36.6 (9.7)
Height (cm), mean (SD)	144.2 (13.0)
Age at time of diagnosis (months)	9.5 (1–120)
Duration of disease (months), mean (SD)	140.3 (51.2)
Number of blood transfusions per year, median (min-max)	19 (10–54)
Chelation therapy, No. (%)	
DFP	20 (50)
DFX	20 (50)
Hb T0 (g/dL), median (min -max)	8.5 (5.9–10.5)
Ferritin T0 (ng/mL), median (min-max)	5719.2 (49.9–19273.2)
Ferritin T0 >2500 (ng/mL), No. (%) (n=38)	30 (78.9)

Kidney biomarker profile

Table 2 presents the distribution of the uNGAL, uACR, and eGFR of the participants. We observed a small proportion of patients with albuminuria and no patients with uACR >300 mg/g. However, kidney hyperfiltration was evident in more than 30% of the participants across all time points. Only one patient exhibited abnormal uNGAL (>150 ng/mL). There were 3/40 (7.5%) patients with eGFR <90 mL/min/1.73 m^2 (Table 2) since enrollment, two of which had eGFR <60 mL/min/1.73 m^2. There was only one patient with persistent albuminuria during the first 2 months of follow-up.

Various factors such as age, duration of disease, frequency and volume of transfusions per year, dose of chelating agent, ferritin, hemoglobin levels and their association with kidney biomarkers were evaluated using Pearson's correlation. Higher uNGAL was associated with older age ($r = 0.329$, $P = 0.038$). The older the patient ($r = -0.390$, $P = 0.015$) and the longer the duration of disease ($r = -0.453$, $P = 0.004$), the lower the eGFR. Ferritin and hemoglobin levels did not correlate with any kidney biomarker levels.

Table 3 presents a multivariate analysis that was carried out using kidney biomarker as the dependent variables and variable with $P < 0.250$ based on bivariate analysis. Transfusion volume was the most dominant factor that influenced both eGFR ($\beta = -0.974$, $P = 0.022$) and uNGAL ($\beta = 0.872$, $P = 0.015$). For uACR, the most dominant factor was duration of disease ($\beta = -0.946$, $P = 0.000$).

The relationship between urinary kidney biomarkers can be found in Figures 1 and 2. Urinary NGAL taken at baseline had a significant inverse correlation with eGFR across the 3 months of follow-up (T0 $r = -0.478$, $P = 0.003$; T1 $r = -0.455$, $P = 0.003$; T2 $r = -0.445$, $P = 0.004$; T3 $r = -0.453$, $P = 0.004$).

On the contrary, Figure 2 shows a positive correlation between uNGAL and uACR at the second follow-up (T2 $r = 0.452$, $P = 0.003$).

Table 2. Kidney biomarker profile across time

	T0	T1	T2	T3
Median uNGAL (ng/mL), (min-max)	13.0 (0.72-171.0)	N/A	N/A	N/A
Median uACR (µg/mgCr), (min-max)	3.8 (0-91.2)	5.4 (0-82.6)	5.3 (0-61.4)	6.0 (0-193.0)[a]
Median eGFR (mL/min/1.73 m^2), (min-max)	152.8 (25.3-210.6)	144.6 (25.3-210.6)	140.5 (25.3-210.6)	137.3 (25.3-210.6)[b]
Proportion of Abnormal uACR µg/mgCr, (%)	7.5	10	7.5	8.6[a]
Proportion of eGFR > 150 mL/min/1.73 m^2, (%)	52.5	45.0	37.5	34.2[b]

uNGAL: urine neutrophil gelatinase-associated lipocalin; uACR: urine albumin-creatinine ratio; eGFR: estimated glomerular filtration rate.
[a] n=35; [b] n=38.

Table 3. Multivariate analysis of kidney biomarkers with selected variables

Independent variable	Model	Unstandardized coefficient		Standardized beta	*P* value
		B	SE		
eGFR	(Constant)	239.621	60.528		0.000
	Transfusion frequency	3.873	1.979	0.800	0.061
	Transfusion volume	-0.013	0.005	-0.974	0.022
	Ferritin	-0.002	0.002	-0.280	0.199
	Hemoglobin	-7.818	5.816	-0.273	0.190
	R^2	0.208			
uACR	(Constant)	-53.962	44.002		0.230
	Age	0.866	0.209	0.831	0.000
	Duration of disease	-0.782	0.168	-0.946	0.000
	Hemoglobin	4.654	3.893	0.167	0.242
	R^2	0.484			
uNGAL	(Constant)	6.942	12.752		0.590
	Transfusion frequency	-3.350	1.322	-0.888	0.016
	Tranfusion volume	0.009	0.004	0.872	0.015
	Ferritin	0.003	0.001	0.379	0.025
	R^2	0.244			

uNGAL; urine neutrophil gelatinase-associated lipocalin, uACR; urine albumin-creatinine ratio, eGFR; estimated glomerular filtration rate.

Glomerular hyperfiltration and albuminuria

A comparison between the DFP and DFX groups showed no difference in all biomarkers at all time points. However, in the DFX group, the eGFR was higher across all time points (Table 4). The proportion of patients with hyperfiltration and albuminuria were higher in children treated with DFX compared to children receiving DFP however, these findings were not supported statistically. Upon further analysis, albuminuria was not found in children with hyperfiltration state nor without.

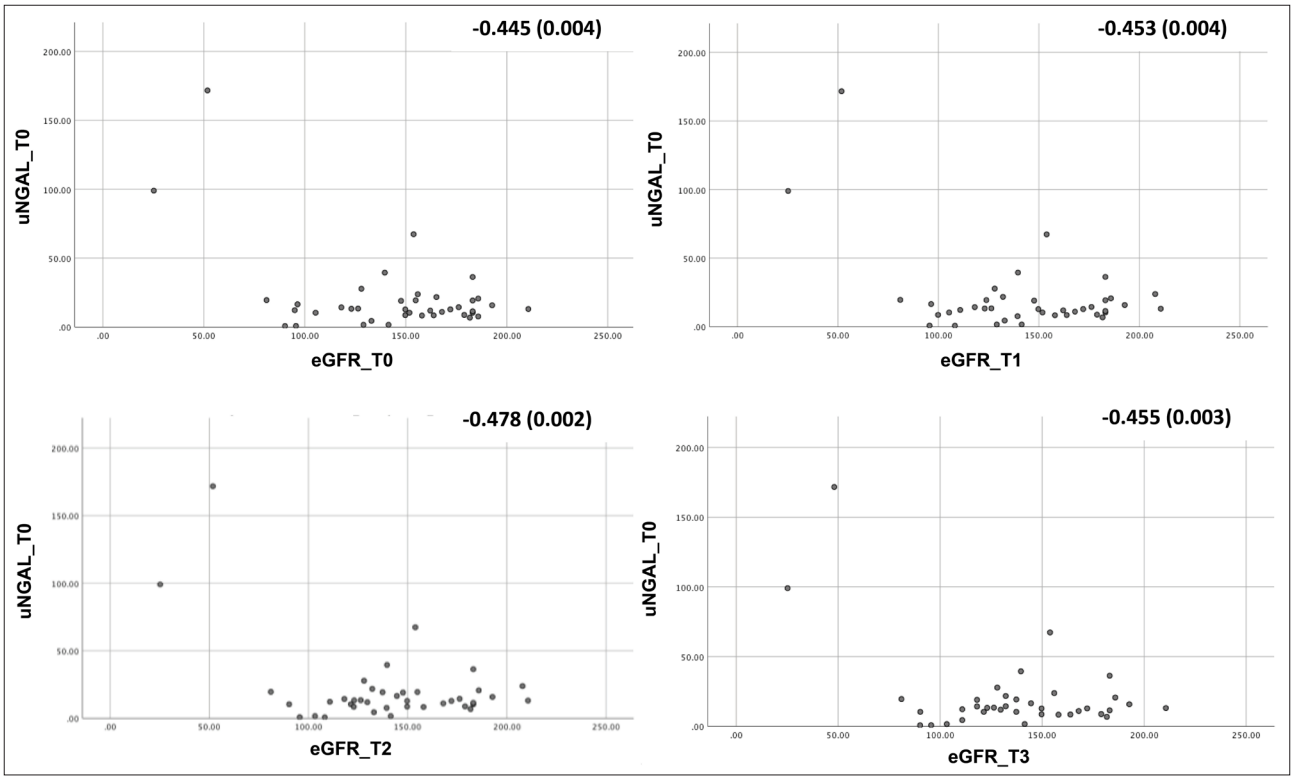

Figure 1. Significant inverse correlation between eGFR and uNGAL was found at T0 (A), T1 (B), T2 (C) and T3 (D). Data was analysed using Pearson correlation and presented as *r* (*P* value).

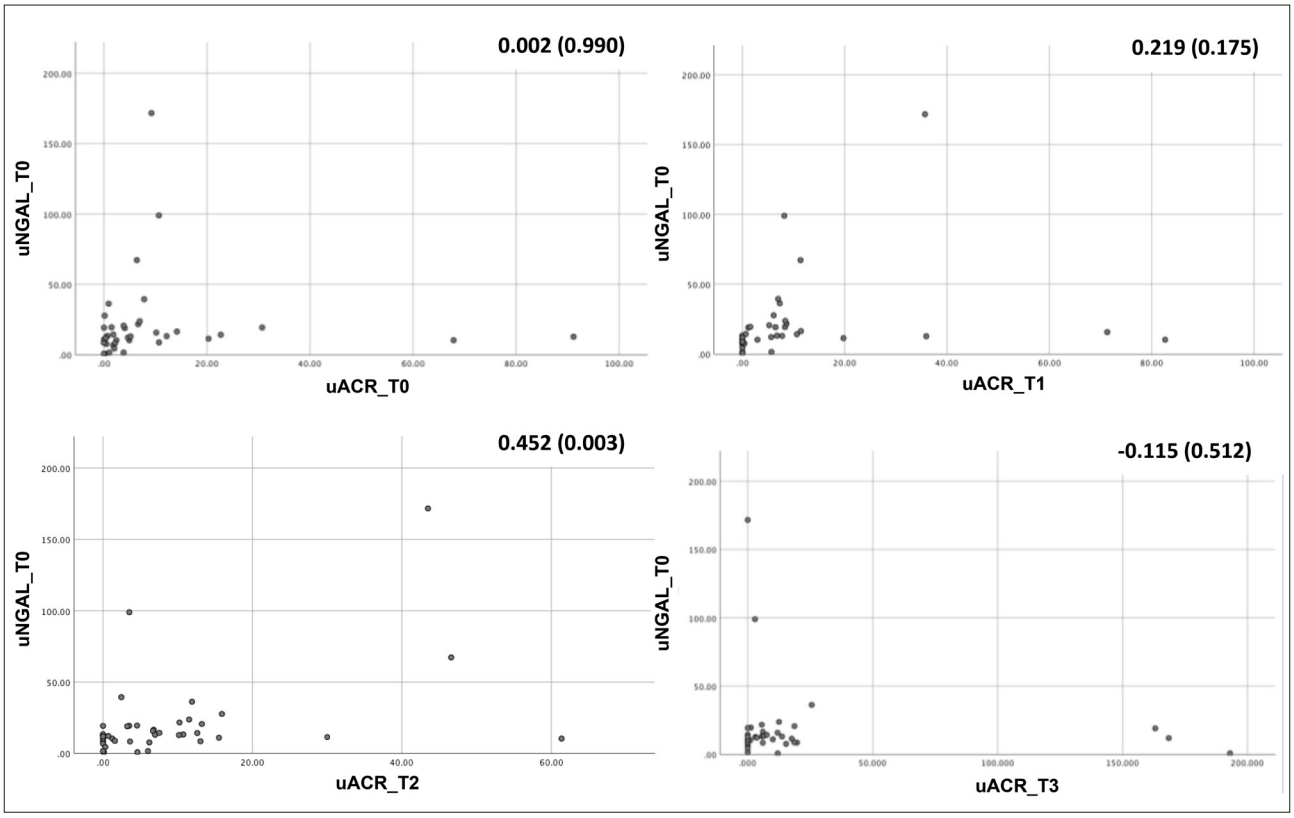

Figure 2. Significant positive correlation between uACR and uNGAL at T2 (C). Data was analysed using Pearson correlation and presented as *r* (*P* value).

Discussion

Kidney involvement in children with TDT is caused by several mechanisms, including chronic anemia, iron overload, and nephrotoxic effects of iron chelating agents (7). Our study found eGFR decline in 7.5% of children with TDT and none had nephrotic range proteinuria. Kidney hyperfiltration was found in more than one-third of our participants. Proportion of eGFR decline is similar to a previous study performed in Malaysia, which showed that 7.4% of pediatric TDT patients had an eGFR of <90 mL/min/1.73 m^2, and 3.3% had nephrotic range proteinuria. That same study observed 25.85% of glomerular hyperfiltration in their patients, slightly less than our findings (19).

Our patients received 19 (10–54) blood transfusions per year, and 78.9% of the patients had severe hemochromatosis (Table 1). The Malaysian study found that 55.6% of pediatric TDT patients had a serum ferritin

Table 4. Kidney biomarkers of patients who received DFP and DFX

	DFP (n=20)	DFX (n=20)	*P* value
uNGAL (ng/mL), median (min-max)			
T0	12.9 (1.61–171.7)	13.0 (0.72–67.29)	0.766[a]
eGFR (mL/min/1.73 m^2), mean (SD)			
T0	137.9 (44.1)	150.9 (36.1)	0.313[b]
T1	135.8 (44.2)	149.3 (36.6)	0.297[b]
T2	136.8 (43.7)	145.2 (35.9)	0.510[b]
T3	131.3 (43.4)[c]	140.4 (35.6)	0.489[b]
uACR (mg/g), median (min-max)			
T0	2.9 (0.0–30.7)	3.9 (0.0–91.2)	0.755[a]
T1	5.6 (0.0–35.7)	4.1 (0.0–82.6)	0.562[a]
T2	3.6 (0.0–43.5)	7.1 (0.0–61.4)	0.248[a]
T3	4.6 (0.0–168.5)[d]	7.6 (0 0 - 193.0)[e]	0.323[a]

[a] Mann-Whitney; [b] Unpaired *t* test; [c] n=18; [d] n=16; [e] n=19.
uNGAL; urine neutrophil gelatinase-associated lipocalin, uACR; urine albumin-creatinine ratio, eGFR; estimated glomerular filtration rate.

level over 2000 µg/L. Their study observed an association between longer duration of transfusion (months) and abnormal kidney function (19). Similarly, our study found inverse correlations between duration of disease and age with eGFR.

Urinary NGAL is a potential biomarker to screen for kidney dysfunction and thus may identify patients who are likely to have impaired kidney function. In our study, we only tested uNGAL at enrollment as it hypothesized that uNGAL levels rise earlier after kidney injury compared to creatinine levels. One study showed higher levels of uNGAL-to-creatinine ratio (uNGAL/Cr) in pediatric patients with beta thalassemia major compared to healthy children (22.1 ± 18.5 versus 11.5 ± 6.17, $P=0.01$) (20). However, uNGAL was found to be normal in all of our participants except one. This may indicate that even with hypoxemia and iron overload there was no proximal tubular injury which led to normal levels of uNGAL. In our study, mean ferritin level was 5719.2 ng/mL and we found no correlation between ferritin levels and uNGAL. We assume there may be another mechanism involved in upregulation of NGAL, apart from iron overload. Interestingly, uNGAL correlates with decline in eGFR in our study which may indicate the need for a repeated uNGAL testing and longer follow up duration.

Proteinuria is established as one of the kidney biomarkers that is linked to progression of kidney disease. One study reported significantly higher proteinuria, measured by urine protein-to-creatinine ratio, in patients with beta thalassemia major compared to healthy children (0.13 ± 0.09 and 0.07 ± 0.04, respectively; $P<0.001$) (20). Nephrotic range proteinuria, measured by uACR, was not evident in any of our patients. Only less than 10% of participants showed non-nephrotic range albuminuria during follow-up. However, there were few missing urine samples at the end of the study due to the surge of COVID-19 cases, which halted patient follow-up at the thalassemia clinic. Other studies reported that proteinuria could be explained by impaired proximal tubular reabsorption, which may be caused by severe iron overload in tissues, which triggers reactive oxygen radical production and leads to cellular injury (21,22). Moreover, previous studies have also provided strong clinical evidence consistent with proximal tubular injury in beta thalassemia major (6). A better indicator of tubular dysfunction are low molecular weight proteins, however we did not test for this. Consistent with normal NGAL results in our patients, nephrotic range albuminuria was not detected which indicated intact proximal tubular function.

In a previous study, no correlations were reported between urinary markers-to-creatinine ratios (uNAG/Cr, uNGAL/Cr, uKIM-1/Cr, and uL-FABP/Cr) and patient age at diagnosis, transfusion frequency, age at first transfusion, and duration of illness (20). The current study determined that older age and longer duration of disease were correlated with higher uNGAL, which reflects abnormal kidney function. We did not find a correlation between hemoglobin levels and kidney biomarkers. Hypoxia results in tubulointerstitial damage, loss of peritubular capillaries, and interstitial fibrosis, which leads to apoptosis or epithelial-mesenchymal transdifferentiation. The progression of kidney damage continues, with end-stage kidney disease as the endpoint (23).

Based on our multivariate analysis, we found the most dominant factor that influenced both eGFR and uNGAL was transfusion volume. Higher transfusion volume leads to higher amount of iron deposition and iron overload has been linked with proximal tubular dysfunction as Koliakos et al reported a positive correlation between ferritin levels and biomarker urine n-acetyl-beta-d-glucosaminidase (uNAG) (24). Longer duration of disease has been linked with longer exposure to glomerular membrane damage which we hypothesise leads to proteinuria. Thus, explains its correlation with uACR.

As hypothesized, the underlying mechanism of kidney injury caused by iron chelators is not only because of the nephrotoxicity of the drug but also due to "over-chelation", which leads to a relative reduction of iron and a decrease in GFR (25). DFX has more kidney-related adverse effects, such as proteinuria, increased serum creatinine, and, rarely, kidney failure (26). However, no significant differences were found in uNGAL, uACR, and eGFR levels between the DFP and DFX groups in the present study. Interestingly, we found a higher proportion of children with hyperfiltration and albuminuria in the DFX group. Statistical significance may not have been established due to the small sample size.

When we looked at the relationships among kidney biomarkers, we found an inverse correlation between uNGAL and eGFR. Nishida et al found a significant correlation between uNGAL and degree of proteinuria in pediatric patients with chronic kidney disease from different etiologies (27). However, our study found that uNGAL was correlated with uACR only at the second month follow-up. We assume that uACR may increase at a slower rate than uNGAL after kidney injury. Therefore, uNGAL may have detected kidney injury earlier than uACR.

More than 30% of our study population showed glomerular hyperfiltration. Brenner et al proposed a glomerular hyperfiltration hypothesis as a pathomechanism leading to glomerular sclerosis and end-stage kidney disease in an individual (28). Maladaptation within glomerular hemodynamics results in hyperfiltration and progressive excretion of albumin in the urine. At first, this population shows a "normal" GFR, but they are actually already in a state of hyperfiltration. The continuous process will then develop into kidney dysfunction (hypofiltration). Thus, in our study we found, increase correlation between duration of disease with eGFR. Chronic anemia and

previous splenectomy in hemoglobinopathy patients have been proposed to increase renal blood flow and change intrarenal hemodynamics (8,9). There were no participants with a history of splenectomy in this study. No association between hyperfiltration and albuminuria was identified in our study; this is probably due to the short follow-up duration.

Conclusion

The findings of this study indicate glomerular hyperfiltration in TDT children as the main early sign of glomerulotubular function impairment. In addition, a small proportion of proteinuria was also found in our study. Thus, both biomarkers should be part of long term kidney follow up in TDT children.

Limitations of the study

We acknowledge the limitations of our study. The number of patients was small, so further validation from other pediatric centers is required. In addition, close monitoring and longer follow-up are needed to assess glomerulotubular function in children with thalassemia.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author.

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Authors' contribution

Conceptualization: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani.
Data curation: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani, Diashati Ramadhani Mardiasmo.
Formal analysis: Henny Adriani Puspitasari, Eka Laksmi Hidayati, Diashati Ramadhani Mardiasmo.
Investigation: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani.
Methodology: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani.
Project administration: Henny Adriani Puspitasari.
Resources: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani, Diashati Ramadhani Mardiasmo.
Supervision: Eka Laksmi Hidayati, Pustika Amalia Wahidiyat.
Validation: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani, Eka Laksmi Hidayati, Pustika Amalia Wahidiyat.
Visualization: Diashati Ramadhani Mardiasmo.
Writing–original draft: Diashati Ramadhani Mardiasmo.
Writing–review and editing: Henny Adriani Puspitasari, Ludi Dhyani Rahmartani, Eka Laksmi Hidayati, Pustika Amalia Wahidiyat, Diashati Ramadhani Mardiasmo.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was conducted in accordance with the Declaration of Helsinki and approved by the Faculty of Medicine of Universitas Indonesia Ethics Committee (Ethical code# KET-1235/UN2.F1/ETIK/PPM.00.02/2020). Informed consent was obtained from the parents of the participants priot to the study as well as participants aged 12–18 years old. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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