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REVIEW

Markers of Renal Complications in Beta Thalassemia Patients with Iron Overload Receiving Chelation Agent Therapy: A Systematic Review

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Objective: The emerging renal complications in beta-thalassemia patients have raised the global exchange of views. Despite better survival due to blood transfusion and iron chelation therapy, the previously unrecognized renal complication remain a burden of disease affecting this population —the primary concern on how iron overload and chelation therapy correlated with renal impairment is still controversial. Early detection and diagnosis is crucial in preventing further kidney damage. Therefore, a systematic review was performed to identify markers of kidney complications in beta thalassemia patients with iron overload receiving chelation therapy.

Methods: Searches of PubMed, Scopus, Science Direct, and Web of Science were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to identify studies of literature reporting renal outcome in β-TM patients with iron overload and receiving chelation therapy. The eligible 17 studies were obtained.

Results: uNGAL/NGAL, uNAG/NAG, uKIM-1 are markers that can be used as predictor of renal tubular damage in early renal complications, while Cystatin C and uβ2MG showed further damage at the glomerular level.

Discussion and Conclusion: The renal complication in beta-thalassemia patients with iron overload receiving chelating agent therapy may progress to kidney disease. Early detection using accurate biological markers is a substantial issue that deserves further evaluation to determine prevention and management.

Keywords: thalassemia, iron overload, chelating agent, kidney, health

Introduction

Beta thalassemia is one of the most frequent haemoglobin disorders inherited in an autosomal recessive manner bringing about worldwide health problems, especially in the tropical belt. Southeast Asia accounts for about 50% of thalassemia carriers in the world. Beta-thalassemia results from reduced or lost-globin chain synthesis due to mutations in the beta-globin gene.[1,2] Indonesia, with more than 200 million people, has a beta thalassemia carrier frequency of 6–10%, becoming an issue to anticipate by the government. The high demand for blood transfusions and chelating therapy marks their linear effect on the improved prognosis of beta-thalassemia patients.[2]

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Despite a better survival rate due to supportive therapy, the beta-thalassemia population still have an increased risk for various complications and thus remains a challenge in affecting their quality of life. The four most common complications are cardiac, endocrine, hepatic, and renal.[3–7] The emerging renal complications reported in beta-thalassemia patients have been correlated with the nature of the disease (eg, chronic anemia, hypoxia), iron overload due to regular blood transfusions, and chelating therapy. Altered vascular resistance and increased renal plasma flow, hyperfiltration, and renal tubular dysfunction were some common mechanisms in diminished renal function of beta-thalassemia patients. Iron overload beta-thalassemia patients were found to have distinct markers of kidney injury such as serum beta2-M, urinary calcium/creatinine, urine 2-M/creatinine, urinary NAG, urinary NAGL, urinary a1-microglobulin, and urinary RBP.[8–11] Moreover, renal complications also occurred significantly in those who received chelating agent therapy.[3,10,12–14] This study aims to identify markers of renal complications in beta-thalassemia patients with iron overload and chelation agent therapy.

Methods

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Literature Search

A comprehensive search of the electronic literature was done using the online databases PubMed, Scopus, Science Direct, and Web of Science. We used the following search term: ([MeSH]beta-Thalassemia] OR (thalassemia) OR (thalassemia beta major) AND (renal outcome*) OR (renal complication*) OR (renal function*) OR (renal damage*) OR (kidney injury*) OR (kidney function*) from the Cochrane Collaboration's search strategy for randomized control trials. Our search approach does not use a filter and has no year restrictions. The first search on each database was done in March, and the final search was done on May 29, 2022. Figure 1 contains the PRISMA flow for literature search.

Eligibility and Study Selection

All randomized control trials, cohort studies, case-control studies, and cross-sectional studies reporting renal outcome in patients with TM connected to chelation therapy were considered. We only list publications written in English. Unrecoverable full text studies and duplicate research were eliminated. Authors EP and EDA carried out the search. The full text of any articles that satisfied the inclusion criteria was retrieved by three writers (PZR, SDS, and AEP) after they separately screened the title and abstracts. The eligibility of full text articles was examined by both writers. The Mendeley program, a free online tool for managing references, was used during the selection process to eliminate duplicate studies and analyze the abstract and full text.

Data Extraction

Data extraction was carried out by two reviewers (BAM, CW), and any differences were settled by team consensus. Using an excel predesign table, the studies that satisfied the relevance and eligibility of our aforementioned criteria were extracted. All of collected data were: 1) A summary of the studies that were included, including methodological information about the site, sample, interventions, outcomes, and results. 2) Baseline features of the studies. 3) Renal outcome or function related to the previously described use of chelation therapy.

Results

We finally screened and obtained 17 studies of literature comparing β-TM with iron overload and with chelation therapy. We summarize them in Tables 1 and 2. From this table, 3 studies stated that there were significant differences in uNGAL/NGAL,[10,11,15] and 5 studies stated that there were significant differences in uNAG/NAG,[11,16–19] 2 studies revealed significant differences in uKIM-1,[3,10] 5 studies stated significant differences in Cystatin C,[20–24] 3 studies showed

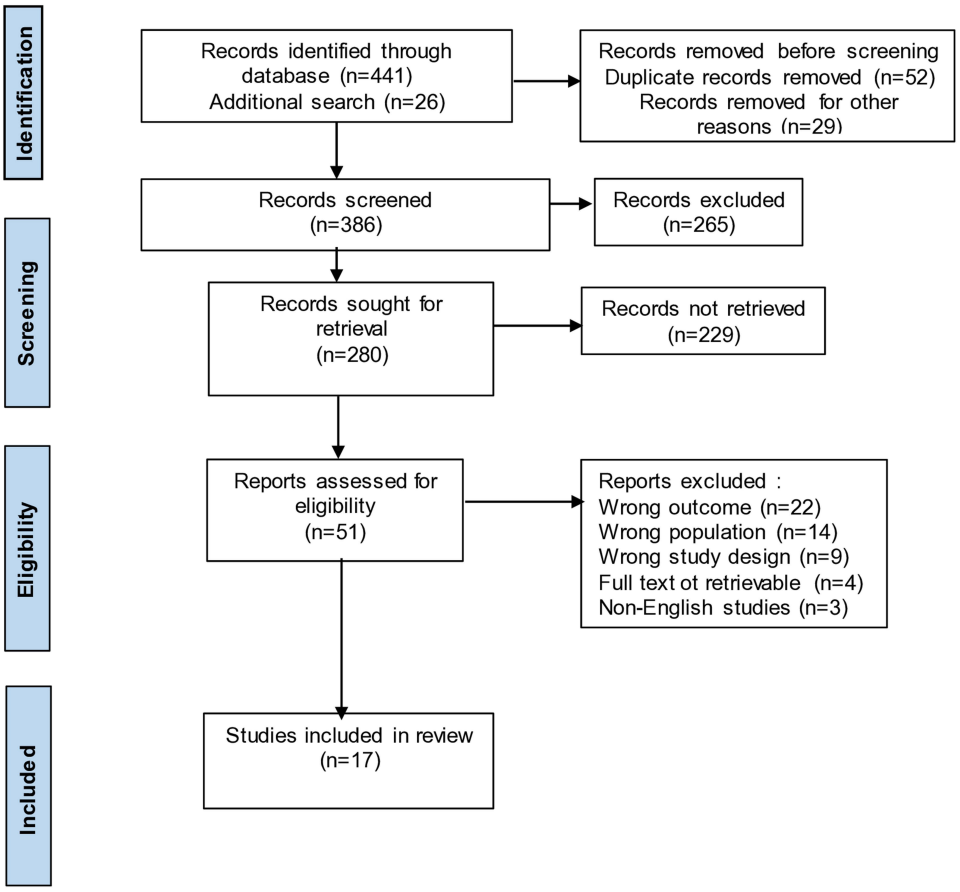

Figure 1 PRISMA flow chart.

a significant difference in uβ2MG[20,23,25] in beta thalassemia patients with iron overload and receiving chelating agents. Increase in uNGAL/NGAL; uNAG/NAG; uKIM-1; Cystatin C; This uβ2MG/β2MG is associated with early tubular and glomerular dysfunction. Three studies suggest that deferasirox is a chelating agent that causes an increase in uKIM-1, uNGAL, and u uβ2MG.[3,10,23]

Table 1 Chelation Therapy and Marker Reported from Study of Beta Thalassemia

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
1	Aldudak 2000[17]	2000	Cross-sectional	9.6 ± 5.0; 10 ± 4.7	Deferoxamine (70)	BUN
						S Cr
						S Na
						S K
						S Ua
						S Phosp
						Ccr

(*Continued*)

Table 1 (Continued).

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
						TRP
						uVolume
						uOsmolality
						uP/Cr
						uNAG/Cr
						uMDA/Cr
2	Smolkin 2008[16]	2008	Cross-sectional	10.8 ± 6.2; 11.2 ± 3.4; 10.2±4.5	Deferoxamine (n/a)	BUN
						Serum creatinine
						Serum uric acid
						GFR
						FENa
						FEK
						Urine Ca/Cr
						Uric acid excretion
						Tubular phosphorus reab
						Urine osmolality
						uNAG
						uNAG/Cr
3	Economou 2010[25]	2010	Case-control	13.66 ± 5.11; 12.66 ± 4.2	Deferasirox (28) group A	Serum creatinine
					Deferiprone + deferoxamine (14) group B	Urea
						Cystatin-C
						U Protein
						U Ca
						U FeNa
						u Phoshor, rabsorbtion
						uβ2 MG
						CrC
						eGFR

(*Continued*)

Table 1 (Continued).

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
4	Hamed 2010[5]	2010	Case-control	8.72±3.7; 8.4±4.1	Deferoxamine (34);	Cystatin-C
					w/o chelation (35)	Creatinine
						eGFRSchwartz
						Uric acid
						Calcium
						Inorganic phosphate
						Total antioxidant capacity
						Albumin/Cr
						NAG/Cr
						β2MG/Cr
						Inorganic phosphorus
						MDA/Cr
5	Mansi, 2013 (belum ada)	2013	Case-control		Deferoxamine (42)	Glucose
						Urea
						Creatinine
						Uric acid
						Sodium
						Potassium
						Chloride
6	Ali 2014[21]	2014	Cross-sectional	9.67± 1.35; n/a	Deferoxamine (62) group IA	Cystatin-C
					No chelating (38) group IB	Serum creatinine
					Control (50) group II	eGFRSchwartz
						CrC
						Albumin/Cr
7	Sen 2015[11]	2015	Cross-sectional	9.14 ± 4.4; 8.8 ± 4.0	Deferasirox (59)	U Na/Cr
						U K/Cr
						U Ca/Cr
						U P/Cr
						U Mg/Cr
						U Protein/Cr

(*Continued*)

Table 1 (Continued).

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
						U Uric acid/Cr
						uNAG/Cr
						uNGAL/Cr
						uKIM1/Cr
						uL-FABP/Cr
8	Behairy 2017[24]	2017	Case-control	10.41±3.86, 8.6±3.47	Deferoxamine (60%)	Urea
					Deferasirox (32.9%)	Creatinine
					Hydra (7.1%)	Urea/Cr
						Urine volume
						CrC
						Cystatin-C
						β2MG
						uAlbumin/Cr
						eGFRSchwartz
9	Bekhit 2017[19]	2017	Case-control	8.5 ± 3.5; n/a	Deferasirox (21)	S Urea
					Deferiprone (8)	S Cr
					Deferoxamine (3)	U Creatinine
						U Ca/Cr
						U uric acid
						GFR
						uNAG
10	Annayev 2018[23]	2018	Case-control	18.4 ± 11.8; n/a	Deferasirox (38)	FENa
					Deferiprone (8)	Na
					None (4)	K
						Ca
						P
						Mg
						U Ca/Cr
						Urea
						Creatinine

(*Continued*)

Table 1 (Continued).

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
						Albumin
						GFR based on age
						SCystatin-C
						uβ2 MG
11	ElAlfy 2018[20]	2018	Cross-sectional	12.8 ± 3.2	Deferoxamine (2)	Urea
					Deferasirox (9)	Uric acid
					Deferiprone (3)	Serum creatinine
					Combined (36)	Cystatin-C
						Urinary β2 microglobulin
						uAlbumin/Cr
						uβ2 M/albumin
12	Badelli 2019[10]	2019	Case-control	n/a	Deferoxamine (19)	GFR
					Deferasirox (21)	BUN
						Creatinine
						Cystatin-C
						GFR based on Cystatin
						uNGAL
						uKIM1
						uIL-18
						uCreatinine
						uAlbumin
						uNGAL/Cr
						uIL-18/Cr
						uKIM1/Cr
						uAlbumin/Cr
13	Fouad 2019[15]	2019	Case-control	29±9; 28±5	Deferasirox (11),	Albumin/Cr
					Deferipone(3)	eGFR
						NGAL
						uNGAL/Cr
14	Nafea 2019[3]	2019	Cross-sectional	14.7 ± 4.3	Deferasirox (26)	Serum K
					Desferoxamine (14)	Serum Na
					Deferiprone(26)	Serum Ca total

(*Continued*)

Table 1 (Continued).

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
						Seurm P
						Serum Mg
						Serum creatinine
						U K/Cr
						U Na/Cr
						U P/Cr
						U Mg/Cr
						Urinary creatinine
						eGFR
						U KIM-1/Cr
15	Bilir 2020[22]	2020	Cross-sectional	12.63 ± 4.58; 11.44 ± 4.37	Deferasirox (47)	Creatinin
						S Sodium
						S Potassium
						S Calcium
						S Phosphorus
						eGFR
						Cystatin-C
						Total antioxidant capacity
						Total oxidant capacity
						U Ca/Cr
						U Protein/Cr
						uβ2MG/Cr
						uRBP/Cr
						uNAG/Cr
						MDA/Cr
16	Capolongo 2020[45]	2020	Case-control	34 ± 12; 33 ± 14	Deferoxamine (40)	Serum creatinine
						eGFR
						S Na
						S K
						S Ca
						S Chlorine
						S Bicarbonate

(*Continued*)

Table 1 (Continued).

No.	Authors	Year of Publication	Study Type	Age (Years)	Chelation of Therapy (Number of Patients)	Markers Reported
						FENa
						U Ca
						U Phosp
						uAlbumin/Cr
						uOsmolarity
						uOsmolality
						pH
17	Mahmoud 2021[42]	2021	Case-control	9.58±4.07	Deferasirox (100)	Urea
						Creatinine
						eGFR
						U protein/Cr
						UNa/Cr
						UK/Cr
						UCa/Cr
						Uuric acid/Cr
						uNAG
						uNAG/Cr
						uKIM1
						uKIM1/Cr
						SCystatin-C
18	Tanous 2021[18]	2021	Cross-sectional	20.92± 9.7	Deferasirox (26)	Serum creatinine
					Deferiprone + deferoxamine (6)	Serum Na
					Deferoxamine (4)	Serum K
						Serum uric acid
						eGFR
						uNAG <12
						Abnormal uNAG (>12)
						Abnormal urine Ca/Cr (>0.14)
						Urine osmolality

Table 2 Result and conclusion from Study of Beta Thalassemia with Iron Overload and Receiving Chelation Agent Therapy

No	Authors	Results-Conclusions
1	Aldudak 2000	Administration of chelating agents in beta thalassemia patients actuates a damage to the proximal tubular kidney.
2	Smolkin 2008	In beta thalassemia patients, UNAG and UNAG/creatinine ratio markers can be used as markers to determine the frequency of transfusion and the effect of chelating agent therapy on ferritin levels.
3	Economou 2010	Glomerular and tubular dysfunction in iron overload beta thalassemia patients receiving chelating agents was observed through the elevation of cystatin C, proteinuria, hypercalciuria and beta2-microglobulin.
4	Hamed 2010	Chelating agents in beta thalassemia patients have been shown stimulate glomerular and tubular dysfunction.
5	Smolkin 2008	In beta thalassemia patients, UNAG and UNAG/creatinine ratio markers can be used as markers to determine the frequency of transfusion and the effect of chelating agent therapy on ferritin levels.
6	Mansi 2013	Kidney damage occurs in beta thalassemia patients receiving chelating agents characterized by increased urea, creatinine, uric acid, urinary sodium and potassium.
7	Ali 2014	Elevated cystatin C, serum creatinine, and serum ferritin and high uACR indicate kidney damage in beta thalassemia
8	Sen 2015	NAG and NGAL can be used as markers of renal injury in beta thalassemia patients experiencing iron overload and receive therapeutic chelating agents.
9	Behairy 2017	Cystatin-C and beta-2 microglobulin are specific and sensitive early biomarkers for monitoring glomerular and tubular dysfunction in children with beta-TM.
10	Bekhit 2017	NAG is excreted following renal damage, hence used as marker of the toxicity index in beta thalassemia patients receiving chelating agents.
11	Annayev 2018	Kidney damage was concluded after an increase in Cystatin C and beta microglobulin in beta thalassemia patients receiving iron chelating agents.
12	ElAlfy 2018	Iron overload in beta thalassemia patients with long-term use of chelating agents revealed differences in serum cystatin C, uACR, and urinary B2 microglobulin, and B2 microglobulin/albumin ratio values.
13	Badeli 2019	Administration of deferasirox led to kidney damage, characterized by an increase in uNGAL, inflammatory factors, sort of IL18, in beta thalassemia patients.
14	Fouad 2019	uNGAL levels, uNGAL/creatinine ratio, eGFR and urinary albumin creatinine ratio were distinctive between group with iron overload and added chelating agents.
15	Nafea 2019	UKIM-1 is a biomarker used to detect worsening eGFR in beta-thalassemia patients with iron overload and routine deferasirox.
16	Bilir 2020	Iron overload marked by high serum ferritin, is associated with proteinuria, increased cystatin C, and urinary protein/Cr in beta thalassemia patients routinely receiving chelating agents.
17	Capolongo 2020	The administration of chelating agents in patients with beta thalassemia iron overload induced renal tubular damage and required early detection to prevent further kidney damage.
18	Mahmoud 2021	Serum cystatin-C is a good predictive marker in the evaluation of glomerular dysfunction. Urine concentrations of NAG and KIM-1 represent sensitive, specific, and highly predictive early biomarkers for acute renal injury in patients with beta TM when subclinical kidney injury or dysfunction is expected before serum creatinine increases.
19.	Tanous 2021	The use of deferasirox for approximately 10 years induced the decline of eGFR and was negatively correlated with uNAG in beta thalassemia patients with iron overload.

Discussion

uNGAL/NGAL

The proximal tubule, distal tubule, and loop of Henle segments all contain epithelial cells that express the 25-kDa lipocalin iron-carrying protein known as neutrophil gelatinase-associated lipocalin (NGAL), which is released by active neutrophils.

Detection of NGAL can be done through serum or urine withdrawal. However, in renal tubular damage, NGAL is often upregulated.[26] NGAL is a low-concentration protein that binds iron-siderophore complexes and is found in a variety of cell types. NGAL is discharged in urine when proximal tubular damage inhibits the reabsorption or increase the synthesis. An abrupt increase in NGAL is brought on by acute kidney injury (AKI). High NGAL levels are also present in patients with other abnormalities, such as lupus nephritis, immunoglobulin A nephropathy, and urinary tract infections.[27,28] Significant relationships between urinary NGAL (uNGAL) and proteinuria were documented in chronic kidney disease.[29]

Recent case-control studies revealed that β -TM patients receiving deferasirox and regular blood transfusions had considerably greater levels of uNGAL and NGAL.[9] It is interesting to note that in β-TM patients, combined values of albumin/creatinin ratio and the uNGAL/creatinin ratio may be a more accurate predictor of kidney impairment and taken into account as potential indicators of renal failure. Additionally, as previously demonstrated, uNGAL somehow can predict renal function since it can estimate eGFR, evaluate the course of CKD, and serve as a surrogate measure for baseline eGFR.[30]

NGAL is highly associated with early renal complication regardless of the creatinine level, both in major and intermediate thalassemia.[31] In both young and adult beta-thalassemia patients, NGAL level elevates due to iron overload and prolonged use of chelating agents. Since renal injury might elevate NGAL to a significant level, it is wisely advised to routinely monitor the NGAL level. Another highlighted feature of NGAL is that it immediately elevates right after kidney injury, even before serum creatinine, urinary N-acetyl glucosaminidase, and 2-microglobulin levels are detected.

uNAG/NAG

Tubular damage is indicated by an increase in the level of N-acetyl-beta-d-glucosamine (NAG), a well-known biomarker for proximal tubular injury.[32] According to Aldudak et al, people with beta thalassemia had higher levels of the tubular damage indicators, such as NAG, malondialdehyde, and b2-microglobulin excreted in their urine.[17] In addition, Jalali et al showed that b-TM patients had significantly higher urine NAG levels than controls, with high NAG levels being the norm in most cases.[33] Besides, participants in Sen et al's study who had renal proximal tubular damage also showed significantly elevated levels of uNAG/Cr and uNGAL/Cr.[11]

The proximal tubular dysfunction that results from thalassemia itself may be caused by chronic hypoxia brought on by persistent anemia, by iron deposition, or by iron chelation.[4,19,23,34] According to some studies, the absence of a link between urine indicators and hemoglobin, haematocrit and ferritin levels may be due to very early tubular dysfunction, as seen by the rise of only NAG and NGAL, but not KIM-1, L-FABP, or urinary electrolytes.[11,19,34,35]

uKIM-1

A transmembrane protein called urinary human kidney injury molecule-1 (uKIM-1) is found in the proximal renal tubules within 24 hours of acute tubular necrosis after renal ischemia. Even while serum creatinine concentrations are unaffected by exposure to certain nephrotoxic drugs, urinary KIM-1 may still be detected.[36]

According to the findings of the Nafea et al study, young thalassemia patients receiving deferasirox therapy had evident subclinical nephrotoxicity when compared to patients receiving other chelation therapies. This was demonstrated by the statistically significantly higher levels of serum creatinine, eGFR, and UKIM-1/Cr. The serum levels of phosphorus, magnesium, creatinine, and blood sugar all showed a significant positive association with UKIM-1/Cr, however the blood hemoglobin level showed a significant negative correlation.[3]

According to Badeli et al's study results, the deferasirox group had significantly greater levels of uIL-18, uNGAL, uNGAL/CREA, uKIM-1/CREA, and BUN than the control group.[10] Deferasirox treatment led to partial necrosis in the renal tubules and increased urinary NGAL, Cystatin C, KIM-1, protein, and glucose production, as demonstrated by Sánchez González et al in an animal study.[37]

Cystatin C and uβ2MG

Cystatin C, not excreted by the renal tubules or reabsorbed into the serum, is a sensitive biomarker for glomerular filtration rate (GFR). All cells in the body continuously produce cystatin C and its production is unaffected by changes in age, sex, gender, or muscle mass. Cystatin C is a reliable and early marker of glomerular dysfunction in the pediatric

population.[22,36,38] A low-molecular-weight protein called urinary β2 microglobulin (u β2MG) is freely filtered by glomeruli, reabsorbed by renal tubules, and then eliminated. Due to its continual production, both are thought to be a more reliable endogenous measure of early glomerular filtration rate (GFR) affection than creatinine.[39] For monitoring glomerular and tubular dysfunction in kids with β -TM, β2MG is a sensitive early biomarker.[23,24] β2MG levels are very low in healthy people; it rises in inflammatory, immunologic, and cancerous conditions.[36] Other than that, Cystatin C and β2MG have strong correlation with age and creatinine clearance.[40] Early detection of glomerular disease will decrease the rate of renal failure and mortality.

Referring to a study by ElAllfy et al, thalassemia patients had significantly greater serum levels of cystatin C than healthy controls.[20] Positive correlations were found between serum cystatin C and indirect bilirubin, LDH and serum ferritin. Additionally, there was no connection between any of these indicators and the kidney function tests (serum creatinine, urea, and uACR) or between serum cystatin C and u2MG.[20] Elbedewy et al[41] and Mahmoud et al[42] showed a significant positive correlation between cystatin-C and serum ferritin and negative correlation with eGFR.

Behairy et al discovered that serum cystatin C and uβ2MG were negatively correlated with creatinine clearance, hemoglobin, and estimated GFR in children with β -TM while both markers were positively correlated with urea, creatinine, serum ferritin, UACR, duration of chelation therapy, and frequency of blood transfusion per year. As indicators for glomerular and tubular dysfunction, cystatin C and β2MG have good sensitivity and good specificity.[24]

Cystatin C and β2M, as well as serum ferritin and liver iron deposition were found to be significantly positively correlated, according to Kacar et al.[43] Serum ferritin levels were discovered to be associated with cystatin C and β2M levels by Uzun et al[44] found that serum ferritin is correlated with level of cystatin C and β2 M. The risk of glomerular and tubular dysfunction may increase with iron buildup in the body.

Conclusion

The renal complication in beta-thalassemia patients with iron overload receiving chelating agent therapy may progress to kidney disease. Early detection using accurate biological markers is a substantial issue that deserves further evaluation to determine prevention and management.

Ethics

This study was approved by Airlangga Hospital's ethical board with certificate number 024/KEP/2022. All analyses for the present study were based on previous published research, thus no patient consent was required.

Disclosure

The authors report no financial or other conflicts of interest in this review article.

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