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Early Detection of Renal Dysfunction in Thalassemia Children by Measuring Urinary N-Acetyl-Beta-D-Glucosaminidase (NAG)

Dr. Mohammed Jamal Uddin[1*], Dr. A.B.M Ali Hasan[2], Dr. Sanchoye Bhowmick[3], Dr. Tahmina Rahman Sarna[4], Dr. Sahifa Nazia[5], Dr. Shakil Mahmood[6]

[1]*Associate Professor, Department of Paediatrics, Kumudini Women's Medical College & Hospital, Mirzapur, Tangail, Bangladesh.*

[2]*Associate Professor, Department of Paediatrics, Kumudini Women's Medical College & Hospital, Mirzapur, Tangail, Bangladesh.*

[3]*Research Physician, Child Health Research Foundation, Bangladesh.*

[4]*Medical Officer (NRD division), Icddrd, Bangladesh.*

[5]*Medical Officer, Dr. M. R. Khan Shishu Hospital and Institute of Child Health, Dhaka, Bangladesh.*

[6]*Associate Professor, Department of Biochemistry, Gonoshasthay Samaj Vittik Medical College, Dhaka, Bangladesh.*

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Corresponding Author:** ***Dr. Mohammed Jamal Uddin, *Associate Professor, Department of Paediatrics, Kumudini Women's Medical College & Hospital, Mirzapur, Tangail, Bangladesh.*
Email: *jamalsomc@yahoo.com*

Abstract:

Background: *Renal tubular and or glomerular dysfunctions may occur in children with thalassemia without clinical features of renal impairment or a decrease in eGFR. Renal injury is still an underestimated complication in thalassemia patients. Early detection of this morbidity allows for delay in the progression of kidney damage and therefore reduces renal impairment.*

Objective: *The present study was done to determine early renal dysfunction in thalassemia children by measuring urinary NAG excretion and its correlation with routine renal biochemical markers.*

Methods: *This case-control study was conducted in the Department of Pediatrics, Kumudini Women's Medical College & Hospital, Mirzapur, Tangail, Bangladesh from June 2023 to July 2024. We included 50 children diagnosed with thalassemia who were on regular blood transfusion as the cases and 50 healthy children as the control group. Routine renal function tests, serum calcium, phosphorus, and urinary NAG (N-acetyl-β-D-glucosaminidase) levels were measured and statistically compared and P value <0.05 was considered significant.*

Results: *Our study showed urinary NAG excretion was significantly higher in thalassemia children than in healthy controls (P <0.001). We found glomerular filtration rate (GFR) was lower in 48% of thalassemia patients, Serum creatinine was higher in 34% of patients and increased urinary uric acid excretion in 46% of patients. We found a significant positive correlation between urinary NAG and serum creatinine, serum ferritin, urinary uric acid, age of the patients, and duration of the disease and found a significant inverse relation with hemoglobin and serum calcium.*

Conclusion: *Glomerular and tubular dysfunctions exist in thalassemia children. As early renal dysfunction may not be detected by routine renal function tests, the use of early markers is needed. Urinary NAG excretion can be considered a reliable index of tubular toxicity and a possible predictor of proteinuria in thalassemia children.*

Keywords: *Thalassemia, Renal dysfunction, Urinary NAG.*

1. INTRODUCTION

Thalassemia syndrome, a genetic hemoglobin disease, causes decreased or absent globin chain formation [1]. The most common pathology is the deficiency of alpha and beta globin chains, which are known as alpha and beta thalassemia, respectively [2]. A point mutation in the globin chain results in Hb-E formation that reduces the binding capacity of alpha and beta chains [3].

According to the report of the World Health Organization in 2018, almost 5.2% of people worldwide are carriers of thalassemia [4]. They also reported that the risk of giving birth to children with a hemoglobin disorder is present among 1.1% of couples worldwide and 2.7/1,000 fetuses were already affected [4]. In Bangladesh, there is population-based research on hemoglobinopathies. That is why data on the prevalence of hemoglobin disorders is lacking [5]. It is presumed from various research that around 3% and 4% of the Bangladeshi population are carriers of β Thalassemia and Hb E respectively [6]. Being an autosomal recessive disorder and following those carrier percentages in society, it is presumed mathematically that almost 33 out of every 10,000 babies are born with β/β or Hb E/β thalassemia every year [6]. However, the prevalence of carrier states might differ by area, ranging from 2.9 to 8.1% for thalassemia and from 2.4 to 16.5% for HbE carriers [7]. In high-income countries, children with thalassemia may survive longer but in low-income countries, most of them die before reaching their fifth birthday [4].

The number of patients suffering from thalassemia (beta major and HbE -beta) with different levels of severity is estimated to be approximately 60,000–70,000 in Bangladesh [8]. 33.1% of under-five children and 26% of adult women were anemic [9]. Among them, 10.7% of children and 7.1% were found to be suffering from Iron deficiency anemia [9]. The rest of them probably have other causes such as other dietary deficiency or congenital hemoglobin disorder [9].

The average life expectancy of patients suffering from thalassemia is around 30 years [10-12]. Due to regular screening for Iron overload, prescribing newer iron chelators, adopting new measures for safe blood transfusion, and the availability of bone marrow transplantation, the prognosis has improved to a great extent in developed countries [13]. In lower socioeconomic countries bone marrow transplantation is still not available [14]. Gene therapy is a potential cure option for this disorder but it is still not applicable widely due to its high cost [15]. Chronic anemia and hemolysis, ineffective erythropoiesis, and secondary iron overload due to repeated transfusion contribute to the pathology of thalassemia. [16,17]. Chronic anemia may be accountable for hepatosplenomegaly [18,19], congestive cardiomyopathy [20,21], and retardation of growth and development [22]. Breakdown of hemoglobin along with its consequence and hypercoagulable state results in pulmonary hypertension and thromboembolic disorder [23,24]. It also leads to excess absorption of iron in the intestine [25] and the development of extramedullary hematopoietic pseudotumor and osteoporosis [26,27]. Following the continuous breakdown of red corpuscles and anemia, oxygen delivery at the tissue level is reduced [28]. As renal cells are of various types, their resistance to reduced oxygen tension is also different [29].

Among them, the tubular cells are most sensitive to oxidative stress [30]. Hypoxia and anemia in tubulo interstitial cells cause reduced renal function, increased cell death, and cell injury which ultimately results in renal fibrosis and glomerulosclerosis [31]. Furthermore, hypoxia also induces endothelial activation, followed by leukocyte stasis and blocking blood flow to peritubular capillaries, ultimately leading to loss of capillary structure and exacerbating hypoxia and loss of nephrons [32]. Early death with cardiac, endocrine, and hepatic failure due to excessive iron deposition as a result of frequent blood transfusion is now a well-established fact [33] but information about renal involvement is still scarce [34]. Clinical manifestations of renal dysfunction or a decrease in GFR may not be manifest in children with beta-thalassemia major despite the presence of proximal renal tubular dysfunction [35]. Therefore, it is of utmost importance to identify at-risk patients for developing renal impairment [36]. Early identification will help to prevent or reverse renal impairment [37].

N-acetyl-beta-D-glucosaminidase (NAG) is a high-molecular-weight lysosomal enzyme that remains stored in the lysosomes of renal epithelial cells of proximal tubule [38]. Glomerular filtration of NAG is prevented as it has a larger molecular mass [39]. Being the most active glycosidase in tubular cells of the kidney has made NAG one of the earliest markers of renal tubular damage [40]. Any acute or chronic injury to proximal tubular cells of the kidney or the presence of nephrotoxic compounds excretion of NAG in urine [41]. Therefore, NAG can be a useful marker to recognize tubular cell damage early in the case of thalassemia patients. In recent years few studies published, representing amino aciduria [42], proteinuria [43], low urine osmolarity, and excess secretion of the proximal tubule damage markers, such as NAG activity in thalassemia patients [44]. As per our concern, no study has been done in

Bangladesh regarding renal involvement in thalassemia patients. Hence the aim of our study was early recognition of the proximal tubular and glomerular dysfunction in thalassemia Children by measuring urinary excretion of NAG and correlating the urinary NAG level with other clinical and laboratory findings.

2. METHODS

This case-control study was conducted in the Department of Pediatrics, *Kumudini Women's Medical College & Hospital, Mirzapur, Tangail, Bangladesh* from June 2023 to July 2024. We included 50 children diagnosed with thalassemia who were on regular blood transfusion as the cases and 50 healthy children as the control group. These are the following criteria to be eligible for enrollment as our study participants: a) Children aged between 1 to 16 years b) Children diagnosed with thalassemia c) Children who were on regular blood transfusion with or without chelating therapy d) Parents who were willing to participate were included in the study and

a) Children with other hemoglobinopathies such as sickle cell anemia b) Children with Type 1 diabetes mellitus c) Children on diuretics therapy, and anti-epileptic drugs d) Children with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD, etc.) were excluded from our study.

Data Collection: An informed written consent for participation was obtained. Full medical history and thorough physical examinations were done on all study subjects. Just before blood transfusion, venous blood and fresh midstream urine samples were collected for hematological and biochemical analysis. eGFR was calculated by using the Schwartz formula and expressed in (ml/ min/1.73 m2). Urinary N-Acetyle-Beta-D-Glucosaminidase (urinary NAG) was determined by colorimetric assay and the result was expressed in units per gram of urinary creatinine.

Statistical Analysis: All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation; qualitative data was expressed as frequency distribution and percentage. The data were analyzed using the student t-tests, chi-square (X^2) test, and Fisher's exact test. A p-value <0.05 was considered as significant. Statistical analysis was performed by using SPSS 22 (Statistical Package for Social Sciences) for Windows version 1

3. RESULT

Table 1. *The demographic and anthropometric characteristics of study subjects*

Parameters	Case n=50 (%)	Control n=50 (%)
Sex distribution		
Male	28(56%)	24(48%)
Female	22(44%)	26(52%)
Age distribution		
1-5 years	13(26%)	9(18%)
6-10 years	30(60%)	31(62%)
11-16 years	7(14%)	10(20%)
Mean ±SD	7.94(±4.34)	8.12((±3.26)
Anthropometry		
Weight in kg (Mean ±SD)		
Male	22.16±9.66	23.43±6.45
Female	19.08±6.45	21.63±5.84
Height in cm (Mean ±SD)		
Male	114.2±22.92	117.3±20.58
Female	108.7±13.04	110.6±12.73
Duration of disease in years		
Mean ±SD	6.9(±4.4)	

Table 1 shows that out of 50 thalassemic patients, 28 were males (56%) and 22 were females (44%). 24 (48%) males and 26 (52%) females belonged to control group. The mean age of the patients and controls were 7.94(±4.34) years and 8.12((±3.26) years respectively. The mean weight of the male and female patients was 22.16 ± 9.66 kg and 19.08±6.45 kg whereas among the controls the mean weight was 23.43±6.45 kg and 21.63±5.84 kg respectively, the mean height of

the male and female patients was 114.2±22.92 cm and 108.7±13.04 cm while the mean height of the male and female controls was 117.3±20.58 cm and 110.6±12.73 cm. The mean duration of the disease was 6.9(±4.4) years.

Table 2. *Laboratory parameters of the patients*

Parameters	Mean±SD
Hb% (gm/dl)	6.46±0.94
Serum ferritin (ng/ml)	1564.94203.1
Serum creatinine (mg/dl)	0.65±0.35
Serum urea	27.6±7.8
Serum Calcium (mg/dl)	7.7±0.82
Serum phosphate(mg/dl)	5.04±0.62
Urinary Ca^{+2} (mg/dl)	108.71428.33
Urinary uric acid (mg/dl)	1043.83±106.6
Urinary NAG((µ/gm)	158.6±22.52
eGFR ml/min/1.73m^2	
Sex	
Male	91.05 ±17.87
Female	82.27±15.50

Table 2 shows that all patients were on regular blood transfusion, the mean hemoglobin of the patients was 6.46 ± 0.94 g/dl, the mean Serum creatinine was 0.65±0.35 mg/dl, and serum creatinine was higher in 34% of patients but still within normal limit. Urinary uric acid was 1043.83 106.6 mg/dl, urinary uric acid was increased in 46% of patients. The mean urinary NAG of the patients was 158.6±22.52 µ/gm, NAG was increased in 62% of patients, and mean eGFR of the males and females were 91.05 ±17.87 ml/min/1.73m2 and 82.27±15.50 ml/min/1.73m2 respectively. Among of all patients, 48% of them had eGFR below the normal reference value.

Table 3. *Comparisons of urinary NAG levels among cases and controls groups.*

Parameters (Unit)	Case (n=50) Mean ± SD	Control (n=50) Mean ± SD	*P*-value
NAG (µ/gm)	155.6±22.52	55.8±14.23	P< 0.001

In table 3, we found that urinary NAG was significantly (p-value <0.001) higher in thalassemia patients than in healthy controls.

Table4. *Correlation between urinary NAG level and Demographic characteristics among thalassemia patients.*

	Urinary NAG level		
Demographic characteristics	**r**	***P*-value**	**Sig**
Age	0.33	0.01	s
Weight	0.04	0.77	ns
Height	0.06	0.65	ns
Duration of disease	0.29	0.03	s

Table 4 shows that a significant positive correlation was found between the urinary NAG and the age of the patients and duration of disease (p-value <0.01 and <0.03) respectively.

Table5. *Correlation between urinary NAG level and laboratory parameters among thalassemia patients.*

	Urinary NAG level		
Kidney functions	**r**	***P*-value**	**Sig**
Serum creatinine (mg/dl)	0.28	0.04	s
Serum Urea	0.14	0.2	ns
Serum ferritin (ng/ml)	0.28	0.05	s
Urinary Ca^{+2} (mg/dl)	0.02	0.85	ns
eGFR (ml/min/1.73m)	0.14	0.3	ns
Urinary uric acid (mg/dl)	0.34	0.01	s
Hb% (gm/dl)	0.44	0.001	ns
Serum phosphate(mg/dl)	0.27	0.5	ns
Serum Calcium (mg/dl)	0.28	0.04	s

Table 5 shows that a significant positive relationship between urinary NAG and serum creatinine, serum ferritin, and urinary uric acid (p-value 0.04, 0.05, and 0.01 respectively) was found while there was an inverse relationship with hemoglobin (Hb) and serum calcium (p-value 0.001 and 0.04 respectively). No significant correlation was found between urinary NAG, eGFR, and urinary calcium.

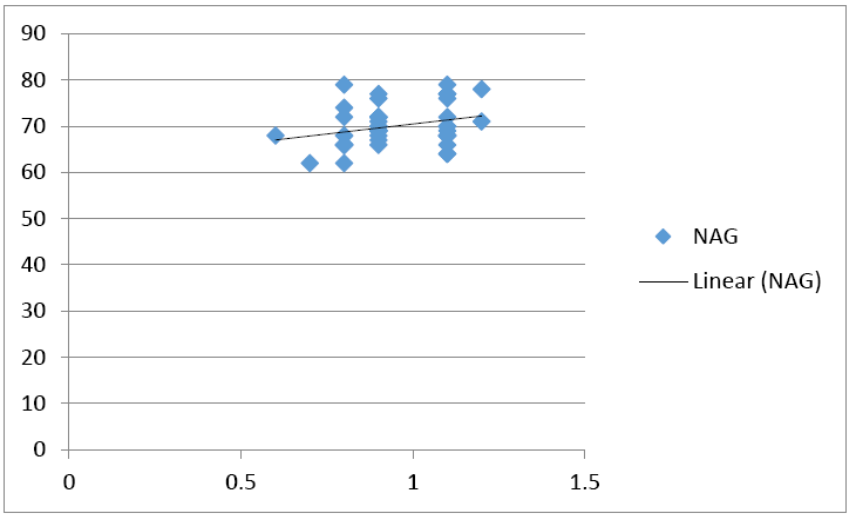

Figure 1. *Correlation between urinary NAG with serum creatinine.*

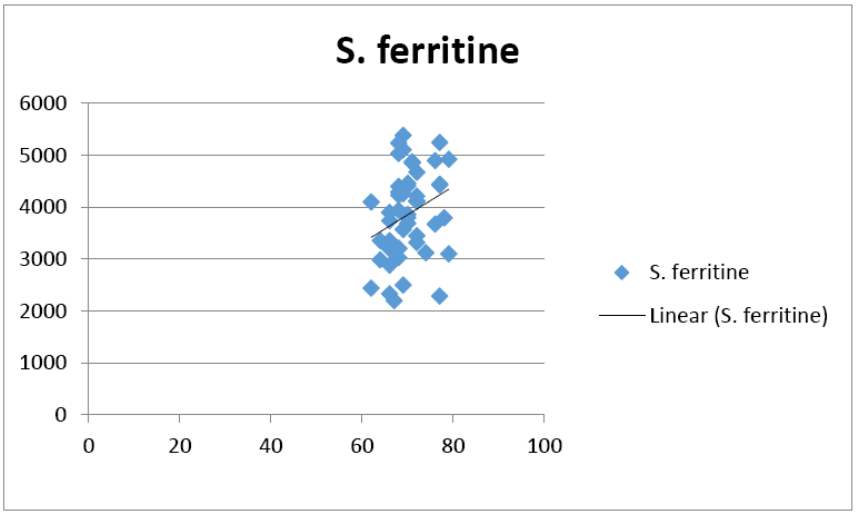

Figure 2. *Correlation between urinary NAG with serum ferritin*

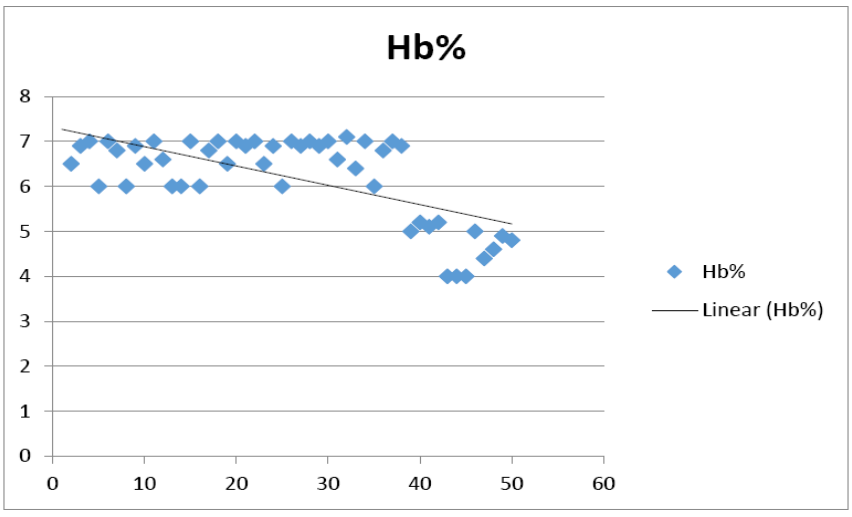

Figure 3. *Correlation between urinary NAG with Hemoglobin (Hb%)*

4. DISCUSSION

The survival of thalassemia patients has significantly improved in recent decades [45]. With the increasing of survivors, some previously unrecognized complications have been detected. Renal impairment is one of these morbidities [46]. Renal injury is still an underestimated complication in thalassemia patients [47]. Chronic anaemia and hypoxia, iron overload from repeated blood transfusion, and specific iron chelators are the main factors in the pathogenesis of renal dysfunction [44,48]. Renal involvement in thalassemia patients increases with the age of the patients and the duration of blood transfusions that may manifest as both tubular and glomerular dysfunction [49,50].

Tubular dysfunction may occur even prior starting of any symptom or sign of renal insufficiency [51]. Routine biochemical markers like serum creatinine and blood urea nitrogen (BUN) cannot detect early renal involvement before clinical features of renal impairment are observed, hence early and novel biomarkers of renal involvement in thalassemia patients are very important [52]. In recent decades several novel biomarkers such as serum cystatin C, urine N-acetyl-ß-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), beta 2 microglobulin, alpha 1 microglobulin, liver type fatty acid binding protein (LFABP) and retinol-binding protein (RBP) have been proposed to improve diagnosis and monitoring of early renal impairments among thalassemic patients [31-33]. In this study, we have observed urinary NAG activities as novel biomarkers for the detection of early renal dysfunction in children with thalassemia.

In this study, we found a significant ($P < 0.001$) increase in mean urinary NAG in thalassemic patients (158.622.52) in comparison to controls (55.8 ± 14.23). Several studies have found significant differences ($P<0.001$) in the mean value of urinary NAG activity between thalassemic patients and control groups [49,53,54]. Sen V et al [52] and Hashemieh M et al [55] also reported high urinary NAG activities in thalassemia patients.

Our study showed that 62% of thalassemia patients had increased urinary NAG, which was similar to other studies by Bekhit OEL et al (55.6%) [56], Jalali A et al (58.6%) [49] and Tantawy AA et al (58.1%) [42] NAG activity was found to be normal in the control group in this study. Jalali A et al [49] also observed normal NAG activity in non-thalassemic children. The increase of urinary NAG is due to tubular dysfunction and tubular proteinuria and not secondary to loss of glomerular selectivity as urinary NAG is not of plasmatic origin and is not filtered through the glomeruli [57] and is a sensitive and reliable index of proximal tubular toxicity [38] and a possible indicator of proteinuria [58].

Serum creatinine was increased in 38% of thalassemia patients in our study whereas Bekhit OEL et al [56] study showed that 40% of thalassemia patients had increased serum creatinine. In our study the mean serum creatinine level was (0.65±0.35) mg/dl but still within normal limit and those in Bekhit OEL et al [56] was (0.52 ± 0.15) mg/dl. In this study urinary uric acid was increased in 49% of patients, Bekhit OEL et al [56] also found urinary uric acid was increased in 40% of thalassemia children. Increased urinary uric acid may be due to reduced reabsorption of filtered uric acid from damaged renal tubules in combination with rapid erythrocyte turnover [59]. This study showed eGFR lower in females (82.27±15.50 ml/min/1.73m^2) than males (91.05 ±17.87 ml/min/1.73m^2) which is similar to a study done by Waseem F. et al [60]. eGFR was found lower than the normal reference value in 56% of thalassemia patients in our study whereas Waseem F.et at [60] found eGFR was lower in 42.6% of thalassemia patients. Similarly, eGFr was also found to be reduced significantly by Mahmoud AA et al [53].

In this study, we found a significant positive correlation between urinary NAG and age of the patients ($P <0.01$), duration of disease ($P <0.03$), serum creatinine ($P < 0.04$), serum ferritin ($P <0.05$), and urinary uric acid ($P < 0.01$). A similar finding was found in studies done by Bekhit OEL et al [56], Sen V et al [52], Mohkam M et al [61], and Jalali A et al [49]. This may be due to the iron overload from repeated blood transfusions [47]. In this study, we also found a significant inverse relation between urinary NAG and hemoglobin ($P <0.001$) and S. calcium level ($P <0.001$). Chronic hypoxia caused by reduced hemoglobin levels results in tubular dysfunction [36]. There was no significant correlation observed between urinary NAG and eGFR, blood urea, and urinary

calcium in thalassemia patients in our study. Jalali et al. also observed no significant correlation between NAG and eGFR change [49].

5. LIMITATIONS OF THE STUDY

Our study was a single-center study. We took a small sample size due to our short study period. No correlation was observed between urinary NAG and chelation therapy. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

6. CONCLUSION AND RECOMMENDATIONS

Glomerular and tubular dysfunctions occur in children with thalassemia major but these abnormalities are not detected early by routine biochemical markers (blood urea, serum creatinine), So, the use of early markers is needed. Urinary NAG excretion can be considered a possible predictor of proteinuria and a reliable index of tubular toxicity as we found a positive correlation between urinary NAG level and serum creatinine, urinary uric acid, and serum ferritin. Urinary NAG may be one of the novel biomarkers for early tubular dysfunction.

So further study of periodic assessment of renal function with a prospective and longitudinal study design including a larger sample size needs to be done to detect hidden renal dysfunction by using novel biomarkers.

REFERENCES

[1] Sanchez-Villalobos M, Blanquer M, Moraleda JM, Salido EJ, Perez-Oliva AB. New insights into pathophysiology of β-thalassemia. *Front Med (Lausanne)*. 2022; 9:880752. doi:10.3389/ fmed. 2022.880752

[2] Polprasert C, Wongprachar P, Suksusut A, et al. Comprehensive screening for coexisting heterozygous α0-thalassemia in hemoglobin E trait. *Hematology*. 2020;25(1):276-9. doi: 10.1080/16078454.2020.1786972

[3] Trakarnsanga K, Thongsin N, Metheetrairut C, Tipgomut C, Poldee S, Wattanapanitch M. Genetic correction of haemoglobin E in an immortalised haemoglobin E/beta-thalassaemia cell line using the CRISPR/Cas9 system. *Sci Rep*. 2022;12(1):15551. doi:10.1 038/s41598-022-19934-7

[4] World Health Organization (WHO). Global epidemiology of hemoglobin disorders and derived service indicators. Available from: https://www.who.int/bulletin/volumes/86/6/06-036673/en/. Accessed 2020 Jan 11.

[5] Hossain MS, Raheem E, Sultana TA, et al. Thalassemias in South Asia: clinical lessons learnt from Bangladesh. *Orphanet J Rare Dis*. 2017;12(1):93.doi:10.1186/s13023-017-0643-z

[6] National Guidelines on Thalassaemia management for physicians. Safe Blood Transfusion & Thalassaemia Management, Hospital Services Management and Directorate General of Health Services. 2019.

[7] Khan WA, Banu B, Amin SK, Selimuzzaman M, Rahman M, Hossain B, et al. Prevalence of beta thalassemia trait and Hb E trait in Bangladeshi school children and health burden of thalassemia in our population. *DS (Child) HJ*. 2005;21(1):1-7.

[8] Mandal PK, Maji SK, Dolai TK. Present scenario of hemoglobinopathies in West Bengal, India: An analysis of a large population. *Int J Med Public Health*. 2014;4(4):496-9.

[9] Rahman S, Ahmed T, Rahman AS, et al. Determinants of iron status and Hb in the Bangladesh population: the role of groundwater iron. *Public Health Nutr*. 2016;19(10):1862-74. doi:10.1017/S13689 80 015003651

[10] Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ*. 2008; 86:480-7.

[11] Ansari-Moghaddam A, Adineh HA, Zareban I, Mohammadi M, Maghsoodlu M. The survival rate of patients with beta-thalassemia major and intermedia and its trends in recent years in Iran. *Epidemiol Health*. 2018; 40:e2018048. doi:10.4178/epih.e2018048

[12] Dhanya R, Sedai A, Ankita K, et al. Life expectancy and risk factors for early death in patients with severe thalassemia syndromes in South India. *Blood Adv*. 2020;4(7):1448-57. doi:10.1182/blooda dvances.2019000760

[13] Farmakis D, Giakoumis A, Angastiniotis M, Eleftheriou A. The changing epidemiology of the aging thalassaemia populations: A position statement of the Thalassaemia International Federation. *Eur J Haematol*. 2020;105(1):16-23. doi:10.1111/ejh.13410

[14] Ali S, Mumtaz S, Shakir HA, et al. Current status of beta-thalassemia and its treatment strategies. *Mol Genet Genomic Med*. 2021; 9(12):e1788. doi:10.1002/mgg3.1788

[15] Ikawa Y, Miccio A, Magrin E, Kwiatkowski JL, Rivella S, Cavazzana M. Gene therapy of hemoglobinopathies: progress and future challenges. *Hum Mol Genet*. 2019; 28(R1): R24-R30. doi:10.1093/hmg/ddz172

[16] Colah R, Gorakshakar A, Nadkarni A. Global burden, distribution and prevention of β-thalassemias and hemoglobin E disorders. *Expert Rev Hematol*. 2010;3(1):103-17. doi: 10.1586/ehm.09.74

[17] Makis A, Voskaridou E, Papassotiriou I, Hatzimichael E. Novel therapeutic advances in β-thalassemia. *Biology (Basel)*. 2021; 10(6):546. doi:10.3390/biology10060546

[18] Choudhry VP. Thalassemia Minor and Major: Current Management. *Indian J Pediatr*. 2017; 84(8):607-11. doi:10.1007/s12098-017-2325-1

[19] Au TY, Benjamin S, Wiśniewski OW. Is the role of hepcidin and erythroferrone in the pathogenesis of beta thalassemia the key to developing novel treatment strategies? *Thalassemia Reports*. 2022;12(3):123-34. doi: 10.3390/thalassrep12030017

[20] Berdoukas V, Coates TD, Cabantchik ZI. Iron and oxidative stress in cardiomyopathy in thalassemia. *Free Radic Biol Med*. 2015;88(Pt A):39.doi:10.1016/j.freeradbiomed.2015.07.019

[21] Zhang H, Zhabyeyev P, Wang S, Oudit GY. Role of iron metabolism in heart failure: From iron deficiency to iron overload. *Biochim Biophys Acta Mol Basis Dis*. 2019; 1865(7):1925-37. doi:10.1016/ j.bbadis.2018. 08.030

[22] Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A systematic review and meta-analysis of stature growth complications in β-thalassemia major patients. *Ann Glob Health*. 2021;87(1):48. doi:10.5334/aogh.31 84

[23] Haw A, Palevsky HI. Pulmonary hypertension in chronic hemolytic anemias: Pathophysiology and treatment. *Respir Med*. 2018;137:191-200. doi:10.1016/j.rmed.2018. 02.020

[24] Fonseca AC, Silva DP, Infante J, Ferro JM. Cerebrovascular complications of anemia. *Curr Neurol Neurosci Rep*. 2021;21(10):51. doi:10.1007/s11910-021-01141-y

[25] Gupta R, Musallam KM, Taher AT, Rivella S. Ineffective erythropoiesis: anemia and iron overload. *Hematol Oncol Clin North Am*. 2018;32(2):213-21. doi:10.1016/j.hoc.2017. 11.009

[26] Bhardwaj A, Swe KM, Sinha NK, Osunkwo I. Treatment for osteoporosis in people with ß-thalassemia. *Cochrane Database Syst Rev*. 2016;3:CD010429. doi:10.1002/14651858.CD010429.pub2

[27] Pellegrino F, Zatelli MC, Bondanelli M, et al. Dual-energy X-ray absorptiometry pitfalls in thalassemia major. *Endocrine*. 2019; 65(3): 469-82. doi:10.1007/s12020-019-02003-x

[28] Machogu EM, Machado RF. How I treat hypoxia in adults with hemoglobinopathies and hemolytic disorders. *Blood*. 2018; 132 (17):1770-80. doi:10.1182/blood-2018-03-818195

[29] Heyman SN, Khamaisi M, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia response and the progression of chronic kidney disease. *Am J Nephrol*. 2008; 28(6):998-1006.

[30] Liu BC, Tang TT, Lv LL, Lan HY. Renal tubule injury: a driving force toward chronic kidney disease. *Kidney Int*. 2018;93(3):568-79. doi:10.1016/j.kint.2017.09.033

[31] Shaw I, Rider S, Mullins J, Hughes J, Péault B. Pericytes in the renal vasculature: roles in health and disease. *Nat Rev Nephrol*. 2018; 14(8):521-34. doi:10.1038/s41581-018-0032-4

[32] Wang B, Li ZL, Zhang YL, Wen Y, Gao YM, Liu BC. Hypoxia and chronic kidney disease. *EBioMedicine*. 2022;77:103942. doi:10.1016/ j.ebiom.2022.103942

[33] Shah FT, Sayani F, Trompeter S, Drasar E, Piga A. Challenges of blood transfusions in β-thalassemia. *Blood Rev*. 2019;37:100588. doi:10.1016/j.blre.2019.100588

[34] Sleiman J, Tarhini A, Taher AT. Renal complications in thalassemia. *Thalassemia Reports*.2018;8(1):7481. doi:10.4081/thal. 2018. 7481

[35] Safaeiasi A, Maleknejad S, Heidarzadeh A, Ghandi Y. Urine B2 microglobulin and other biochemical indices in beta-thalassemia major. *Acta Med Iranica*. 2009;47:443-60.

[36] Demosthenous C, Eleftheriou P, Apostolou C, Sarafidis P, Perifanis V, Vlachaki E. β-Thalassemia and renal complications: A narrative review of pathophysiologic mechanisms. *Integr Mol Med*.2018;5(4):1-7. doi:10.15761/IMM.1000340

[37] Shaalan MG, Hassan MK, Al-Shanoof HJ, Al Naama LM. Renal dysfunction in pediatric patients in Iraq with β-thalassemia major and intermedia. *Cureus*. 2022;14(9):e29183. doi: 10.7759/cureus.29183

[38] Liu Q, Zong R, Li H, et al. Distribution of urinary N-acetyl-beta-D-glucosaminidase and the establishment of reference intervals in healthy adults. *J Clin Lab Anal*. 2021; 35(5):e23748. doi:10.1002/jcla.23748

[39] Lou W, Cheng Q, Liang Y, Xia D. Urinary N-acetyl-β-D-glucosaminidase (NAG) levels and risk of cardiovascular events in diabetic patients. *Int J Gen Med*. 2021;14:10495-505. doi:10.2147/IJGM.S337874

[40] Omozee EB, Okaka EI, Edo AE, Obika LF. Urinary N-acetyl-beta-D-glucosaminidase levels in diabetic adults. *J Lab Physicians*. 2019;11(1):1-4. doi:10.4103/JLP.JLP_164_17

[41] Vibulcharoenkitja P, Suginta W, Schulte A. Electrochemical N-Acetyl-β-D-glucosaminidase urinalysis: Toward sensor chip-based diagnostics of kidney malfunction. *Biomolecules*. 2021;11(10):1433. doi: 10.3390/biom11101433

[42] Tantawy AA, El Bablawy N, Adly AA, Ebeid FS. Early predictors of renal dysfunction in Egyptian patients with β-thalassemia major and intermedia. Mediterr J Hematol Infect Dis. 2014;6(1):e2014057. doi:10.4084/MJH ID.2014.057

[43] Musallam KM, Taher AT. Mechanisms of renal disease in β-thalassemia. J Am Soc Nephro. 2012;23(8):1299-302.

[44] Bakr A, Al-Tonbary Y, Osman G, El-Ashry R. Renal complications of beta-thalassemia major in children. Am J Blood Res. 2014;4(1):1-6.

[45] Li CK. New trend in the epidemiology of thalassemia. Best Pract Res Clin Obstet Gynaecol. 2017;39:16-26. doi:10.1016/j.bpo bgyn.2016.10.013

[46] Motta I, Mancarella M, Marcon A, Vicenzi M, Cappellini MD. Management of age-associated medical complications in patients with β-thalassemia. *Expert Rev Hematol.* 2020;13(1):85-94. doi:10.1080/17474086.20 20.1686354

[47] Romadhon PZ, Ashariati A, Bintoro SUY, et al. Markers of renal complications in beta thalassemia patients with iron overload receiving chelation agent therapy: A systematic review. J Blood Med. 2022; 13:725-38. doi:10.2147/JBM.S387416

[48] Demosthenous C, Vlachaki E, Apostolou C, et al. Beta-thalassemia: Renal complications and mechanisms: A narrative review. *Hematology*. 2019;24(1):426-38. doi: 10.1 080/16078454.2019.1599096

[49] Jalali A, Khalilian H, Ahmadzadeh A, et al. Renal function in transfusion-dependent pediatric beta-thalassemia major patients. *Hematology*. 2011;16(4):249-54. doi:10.1179/102453311X129530 15767662

[50] Mallat NS, Mallat SG, Musallam KM, Taher AT. Potential mechanisms for renal damage in beta-thalassemia. *J Nephrol*. 2013; 26(5): 821-28. doi:10.5301/jn.5000253

[51] Abd El-Khalik SR, Sharaby RM, Nasif E, Hamza MB, Ibrahim RR. Netrin-1 and clusterin: Innovative potential diagnostic biomarkers for early renal damage in β-thalassemia major children. *IUBMB Life*. 2021;73(5):800-10. doi:10.1002/iub.2464

[52] Şen V, Ece A, Uluca Ü, et al. Urinary early kidney injury molecules in children with beta-thalassemia major. *Ren Fail*. 2015;37(4):607-13. doi:10.3109/0886022X.2015.1007871

[53] Mahmoud AA, Elian DM, Abd El Hady NM, et al. Assessment of subclinical renal glomerular and tubular dysfunction in children with beta-thalassemia major. *Children (Basel)*. 2021;8(2):100. doi: 10.3390/children8020100

[54] Youssry I, Makar S, Abdelkhalek K, Hisham D, Sawires H. Comparing different markers of tubular dysfunction in transfusion-dependent thalassemia patients. *Int Urol Nephrol.* 2022;54(2):421-28. doi:10.1007/ s11255-021-02914-7

[55] Hashemieh M, Radfar M, Azarkeivan A, et al. Renal hemosiderosis among Iranian transfusion-dependent β-thalassemia major patients. Int J Hematol Oncol Stem Cell Res. 2017;11(2):133-38.

[56] Bekhit OEL, El Dash HH, Ahmed MS. Early detection of kidney dysfunction in Egyptian patients with beta-thalassemia major. *Gaz Egypt Paediatr Assoc*. 2017;65(3):85-89. doi:10.1016/j.epag.2017.02.002

[57] Andreucci M, Faga T, Pisani A, Perticone M, Michael A. The ischemic/nephrotoxic acute kidney injury and the use of renal biomarkers in clinical practice. *Eur J Intern Med*. 2017;39:1-8. doi:10.1016/j.ejim.2016.12.001

[58] Kim SR, Lee YH, Lee SG, et al. Urinary N-acetyl-β-D-glucosaminidase, an early marker of diabetic kidney disease, might reflect glucose excursion in patients with type 2 diabetes. *Medicine (Baltimore)*. 2016; 95(27):e4114. doi:10.1097/MD.0000000000 004114

[59] Chaloemwong J, Tantiworawit A, Rattanathammethee T, et al. Hyperuricemia, urine uric excretion, and associated complications in thalassemia patients.Ann Hematol. 2019;98(5):1101-10. doi:10.1007/ s00277-019-03630-0

[60] Al Tameemi WF, Altawry ZMJ. Earlier detection of glomerular dysfunction in β-thalassemia major patients. Thalassemia Reports. 2020;10(1):9007. doi:10.4081/ thal.2020.9007

[61] Mohkam M, Shamsian BS, Gharib A, Nariman S, Arzanian MT. Early markers of renal dysfunction in patients with beta-thalassemia major. Pediatr Nephrol. 2008; 23(6):971-76.doi:10.1007/s00467-008-0753.

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