Urinary Kidney Injury Molecule-1 and Heart-Type Fatty Acid Binding Protein as Novel Early Markers of proximal and Distal Renal Tubular Dysfunction in Children with B-Thalassemia Major

Youssef DM, Sherief LM, El-Safy UR, Zidan A and Moawed ME
MD Department of Pediatrics Faculty of Medicine, Zagazig University, Egypt

Introduction:

Several authors **(1, 2, 3)** found renal tubular dysfunction in patients with thalassemia. Chronic anemia, iron overload as well as the use of specific iron chelators are believed to lie behind these abnormalities**(4).**Detection of the progressive renal damage using conventional parameters, such as serum creatinine levels (Cr) or creatinine clearance (Ccr) is often misleading**(5)**. The early development of glomerular hypertrophy enhances creatinine excretion and gives false normal results of both Cr and Ccr**(6).** Therefore, the renal dysfunction becomes evident rather late. For that reason, the identification of markers that detect early renal dysfunction as well as further progression to end stage renal disease is of great importance**(5).**

Recently, several novel early biomarkers for detection of renal damage to specific region of the nephron have been studied in a rat injury model in a large prospective study by the Predictive Safety Testing Consortium, a collaborative consortium between European EMEA and academia, industry, the US Food and drug administration**(7,8,9,10)**.The most promising of these biomarkers include urine KIM-1, fatty acid binding protein and N-acetyl-b-D-glucosaminidase(NAG)**(11)**

Aim:

Was to investigate urinary kidney injury molecule-1(KIM-1) and urinary heart type fatty acid binding protein (H-FABP) as novel early markers of renal tubular dysfunction in children with β-thalassemia major.

Patients and methods:

This cross-sectional, case control study was performed on a total of **124 children**: **62** children with **β-TM** selected by a systemic random sample method and followed up regularly at Outpatient Clinic of Pediatric Hematology, Faculty of Medicine, Zagazig University Hospitals and **62** healthy children as **control** group. (The diagnosis of β-thalassemia was based on clinical presentation, haematological indices and haemoglobin electrophoresis). We included Children with β-thalassemia without renal symptoms, both sexes and age more than 5 years and less than 18 years old. Children with systemic hypertension, kidney or heart failure, diabetes mellitus, acute or chronic infection or any inflammatory disease were excluded from the study.

The control group consisted of children without any potential diseases affecting the kidney function, which were undergoing pre-surgical examination for minor surgery or routine checkups. The study protocol was approved by the research and ethical committee of our hospital (IRP) and informed consent was taken from parents or guardian of each participant.

All eligible children (patients and controls) were subjected to; history taking with special emphasis on demographic characteristics, disease duration, frequency of transfusions, iron chelation regimen including type, dose, duration and compliance. Thorough clinical examination including anthropometric measures and all system evaluation were performed. Routine laboratory investigations for follow up thalassemia patients that included; complete blood count, liver function tests, renal function tests, serum ferritin, hepatitis markers and complete urine examination were taken.

Estimated glomerular filtration rate (eGFR) was calculated according to modified Schwartz formula for children: eGFR(mL/min/1.73m2= height(cm) x 0.423/ serumCr(mg/dl) **(12).** The mean GFR level for the patients between 2 years and adolescence was accepted as 127 mL/min/1.73 m2 whereas the levels above 165 mL/min/1.73 m2 were thought as hyperfiltration. Renal dysfunction was defined as eGFR less than < 90ml/min/1.73 m2 **(13).**

Morning urine samples were obtained and centrifuged at 1500 rpm for 10 min at 4 c. The supernatant were separated and stored at -80 for estimation of kidney injury molecule-1 and fatty acid -binding protein. Both kidney injury molecule-1 and fatty acid- binding protein were determined by ELISA assay using a commercial available ELISA kit.

Results

Table(1):Demographic, anthropometric and laboratory characteristics of thalassemic patients and control

Variable	Cases (n=62)	Control (n=62)	P value
Age (years)	10.80 3.189	10.2 3.49	0.136
Weight (kg)	31.29 8.03	33.62 12.317	0.123
Height (cm)	131.95 15.25	133.16 12.84	0.141
BMI (kg/m^2)	18.474 4.41	17.55 1.03	0.08
Hemoglobin(Hb) (g/dl)	7.56 1.25	12.5 0.6	< 0.001
Bilirubin total (mg/dl)	1.71 0.382	0.81 0.19	< 0.001
ALT (U/l)	17.97 5.01	6.45 22.98	0.006
AST (U/l)	29.13 20.01	16.49 4.96	< 0.001
Urea (mg/dl)	22.60 3.13	21.96 3.65	0.105
Creatinine (mg/dl)	0.69 0.12	0.61 0.16	0.133
Serum ferritin (ng/ml)	3120.8 1244.1	65.213 20.6	< 0.001
eGFR	77.52 8.668	108.91 5.58	< 0.001
H-FABP (ng/ml)	565.74 351.96	102.55 27.88	< 0.001
KIM-1(ng/ml)	112.20 52.97	28.55 11.15	< 0.001

Table (2): Correlation of B-TM patients urinary KIM-1, H-FABP and other parameters

		r	P
KIM-1	Age (year)	0.575	< 0.001
	Hemoglobin (Hb) (g/dl)	0.121	0.349
	Serum ferritin (ng/ml)	0.507	< 0.001
	Urea (mg/dl)	0.302	0.017
	Creatinine (mg/dl)`	0.379	0.002
	Duration of transfusion	0.623	< 0.001
	Proteinuria	0.312	0.004
H-FABP	Age (year)	0.443	< 0.001
	Hemoglobin (Hb) (g/dl)	0.016	0.902
	Serum ferritin (ng/ml)	0.532	< 0.001
	Urea (mg/dl)	0.318	0.012
	Creatinine (mg/dl)	0.395	0.001
	Duration of transfusion	0.321	0.001
	Proteinuria	0.296	0.001

The main limitation of our study was that it was a cross-sectional analysis. We did not follow β -TM patients over time. We recommend longitudinal analysis of KIM-1 and H-FAB for their potential as screening tools for proximal and distal tubular function in β -TM patients

Conclusion:

We concluded that renal dysfunction is not rare in children with beta thalassemia major and that renal tubular dysfunction may not be detected by routine tests so the use of early markers KIM -1 and H-FABP is recommended in children with beta thalassemia.

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Conflict of interest
Authors declare no conflicts of interest.