Taylor & Francis
Taylor & Francis Group

Check for updates

ORIGINAL ARTICLE

β2-Microglobulin, Neutrophil Gelatinase-Associated Lipocalin, and Endocan Values in Evaluating Renal Functions in Patients with β-Thalassemia Major

Petek Uzay Cetinkaya[a] (ID), Fatih Mehmet Azik[b] (ID), Volkan Karakus[c] (ID), Bulent Huddam[d] (ID) and Nigar Yilmaz[e] (ID)

[a]Department of Child Health and Diseases, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey; [b]Department of Child Health and Diseases, Hematology Oncology, Mugla Sitki Kocman University, Faculty of Medicine, Mugla, Turkey; [c]Department of Hematology, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey; [d]Department of Nephrology, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey; [e]Department of Biochemistry, Faculty of Medicine, Mugla Sitki Kocman University, Mugla, Turkey

ABSTRACT

Chronic anemia, transfusion-associated iron deposition, and chelating agents lead to renal impairment in β-thalassemia (β-thal) patients. The present study aimed to determine the most reliable and practical method in assessing and predicting renal injury in β-thal major (β-TM) patients. Therefore, we assessed the predictive values of urine β2-microglobulin (β2-MG) and neutrophil gelatinase-associated lipocalin (NGAL) levels, their ratios to urine creatinine, and serum endocan level. Sixty β-TM patients and 30 healthy controls were included. Renal functions of the patients and controls were evaluated by means of urine protein/creatinine ratio, urine β2-MG, urine NGAL, and serum endocan level. The β-TM and control groups were comparable in terms of the demographic characteristics. Of the β-TM patients, 26.7% had glomerular hyperfiltration and 41.7% had proteinuria. Compared with the control group, the β-TM group had significantly higher levels of urine protein/creatinine, urine β2-MG, urine β2-MG/creatinine, urine NGAL, urine NGAL/creatinine, and serum endocan. These parameters did not differ between the chelating agent subgroups in the patient group. Urine β2-MG/creatinine and NGAL/creatinine ratios were the parameters with high specificity in predicting proteinuria. There were significant correlations of urine β2-MG, urine NGAL, and serum endocan levels with serum ferritin concentration. Urine β2-MG/creatinine, NGAL/creatinine, and protein/creatinine ratios were correlated with each other in the patient group. Positive correlations of urine β2-MG, urine NGAL, and serum endocan levels with serum ferritin concentration indicated that iron deposition was associated with endothelial damage and renal injury.

Introduction

β-Thalassemia (β-thal) is the most common form of hemoglobinopathy worldwide. β-Thalassemia major (β-TM) develops as a result of mutations of the β-globin gene on chromosome 11 [1]. Erythrocyte transfusion and iron chelation therapy are the basis of treatment of β-TM. In patients with inadequate chelation therapy, iron deposition in the tissues leads to tissue injury and organ failure. Iron deposition occurs in all body systems, primarily in the heart, liver and endocrine organs [2,3].

Abnormalities of glomerular filtration rate (GFR) and tubular dysfunction resulting from chronic anemia, hypoxia, iron load and nephrotoxic effects of chelators are seen in β-thal patients [4,5]. Glomerular filtration rate, urea, creatinine, creatinine clearance and serum cystatin C are frequently used to assess glomerular functions; whereas, urine density, pH, and presence of bicarbonate, phosphate, glucose and amino acids in the urine are frequently used to assess tubular functions [6]. Moreover, diagnostic and predictive values of various biomarkers have also been investigated. Among these biomarkers, β2-microglobulin (β2-MG) is a low molecular weight protein used to assess renal tubular

functions. β2-Microglobulin is filtered by the glomeruli of normal kidneys, 99.9% of the β2-MG is reabsorbed, and it is excreted in negligible amounts in the urine. Elevated β2-MG level in the urine is the early indicator of proximal tubular damage [7]. Neutrophil gelatinase-associated lipocalin (NGAL) is a small protein and is minimally expressed in many tissues. Its expression increases in situations that lead to epithelial injury. Neutrophil gelatinase-associated lipocalin has a critical role as an indicator of acute renal injury [8]. Endocan is a proteoglycan secreted from the vascular endothelial cells and a marker of endothelial activation. Thus, increased endocan expression is in question in the presence of inflammatory diseases, endothelial pathologies and tumor progression [9].

Patients with multiple disorders such as glomerular damage, tubular damage, and endothelial damage need to be followed-up regularly using reliable methods. Therefore, evaluation of new biomarkers is required. From this point of view, the present study aimed to determine the most reliable and practical parameter in detecting renal injury in β-TM patients, and thus, to assess the predictive values of urine

β2-MG and NGAL levels, their ratios to urine creatinine and serum endocan level.

Materials and methods

A total of 60 pediatric and adult β-TM patients who were followed-up at our center and regularly attending their transfusion programs were enrolled. Patients with renal or endocrine problems, those having acute infection during the study, those receiving drugs other than iron chelating agents that might cause renal injury or tubulopathy, and those with a change in their chelation therapies within the last 6 months were excluded. Furthermore, 30 healthy pediatric and adult subjects who visited outpatient clinics and had similar demographic characteristics as the patients but no anemia and infections, were included as a control group. Informed consent was obtained from the participants (or the parents). The study was approved by the Clinical Researches Ethics Committee of Mugla Sitki Kocman University Faculty of Medicine, Mugla, Turkey.

Demographic information, medical history, routine complete blood count, and blood and urine biochemistry analyses of the patient and control groups were recorded, and urine β2-MG, urine NGAL, and serum endocan levels were measured. The results were analyzed by dividing the patient group into two subgroups according to the chelating agents they were receiving [those using deferasirox (DFX) and combinations and those using other chelating agents].

Glomerular filtration rate values of the patients and controls were calculated using the Schwartz formula for those <18 years old [10] and using the Chronic Kidney Disease Epidemiology Collaboration formula for those >18 years old [11]. Values higher than the normal by 2SD according to age were considered as glomerular hyperfiltration, and the values lower than the normal by 2SD according to age were considered as low GFR. Tubular phosphate reabsorption (TPR) was calculated using the following formula depending on urine (U), plasma phosphate (P_{PO4}),and creatinine values: TPR (%) = $(1 - [(U_{PO4}/P_{PO4})/(U_{creatinine}/P_{creatinine})] \times 100$. A TPR value of <75.0% was considered significant. Presence of proteinuria was determined according to the normal urine protein/creatinine values by age. β2-Microglobulin (mg/L) and NGAL (ng/mL) levels in spot urine were studied by the enzyme linked immunosorbent assay (ELISA) method and the results were evaluated by proportioning to the urine creatinine level. Serum endocan level (ng/mL) was also studied by the ELISA method.

Statistical analyses

Data were analyzed using the Statistical Package for Social Science (SPSS) version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were expressed as numbers and percentages for categorical variables and as median [minimum-maximum (min-max)] for numerical variables. In comparing two independent groups, the Student's t-test was used for normally distributed numerical variables and the Mann-Whitney U test was used for non normally distributed numerical variables. Pearson's χ^2 test statistics was used for the comparison of the qualitative data. Relationship between the variables was assessed by the Spearman's correlation analysis. Logistic regression analysis was used for predicting the risk factors of proteinuria. The receiver operating characteristic (ROC) curve analysis was used to predict the cutoff values of the predictors of proteinuria. A p value of <0.05 was considered to be statistically significant.

Results

There were 60 patients aged between 2 and 52 years in the β-TM group and 30 healthy subjects aged between 2 and 36 years in the control group. No difference was observed between the groups in terms of demographic characteristics. However, hemoglobin (Hb) and ferritin concentrations and renal functions were significantly different between the groups (Table 1). In comparison with the control group, the β-TM group had significantly higher urine β2-MG and NGAL levels and serum endocan levels, as well as β2-MG/creatinine and NGAL/creatinine ratios (Table 1). The results of correlation analysis of the parameters in the β-TM group are demonstrated in Table 2.

All patients in the β-TM group were receiving iron chelation therapy. Accordingly, 42 (70.0%) patients were receiving DFX, six (10.0%) patients were receiving deferiprone (DFP), three (5.0%) patients were receiving the combination of DFX and desferoxamine (DFO), two (3.3%) patients were receiving the combination of DFX and DFP, and seven (11.7%) patients were receiving the combination of DFP and DFO. There were no significant differences between the patients receiving DFX and the other combinations ($n = 47$) and the patients receiving other chelators and combinations ($n = 13$) in terms of urine protein/creatinine, urine β2-MG, β2-MG/creatinine, urine NGAL, NGAL/creatinine, and serum endocan (data not shown).

When β-TM patients were evaluated regarding the presence of proteinuria, GFR ($p = 0.001$), urine β2-MG level ($p = 0.001$), urine β2-MG/creatinine ratio ($p = 0.001$), urine NGAL level ($p = 0.001$) and urine NGAL/creatinine ratio ($p = 0.001$) were found to be significantly higher in the patients with proteinuria ($n = 25$) than those without ($n = 35$). The groups were not significantly different in terms of TPR ($p = 0.855$) and serum endocan levels ($p = 0.121$).

The GFR, urine β2-MG/creatinine, and urine NGAL/creatinine measurements were evaluated using the backward stepwise logistic regression analysis to identify the risk factors associated with proteinuria in the β-TM patients. A significant model including urine β2-MG/creatinine and GFR was obtained at the fourth step. Accordingly, the risk of proteinuria increased by 3.395-fold for every one unit increase in urine β2-MG/creatinine [95% confidence interval (95% CI): 1.463–7.876] and elevated GFR increased the risk of proteinuria by 17.294-fold (95% CI: 2.390–125.110). Urine β2-MG/creatinine and GFR were found to be the independent risk factors for proteinuria.

Table 1. Demographic characteristics and laboratory findings of the β-thalassemia major patients and control group. (Bold *p* values are significant).

Parameters	β-TM group (*n* = 60)	Control group (*n* = 30)	*p* Value
Gender:			
Females [*n* (%)]	24 (40.0)	12 (40.0)	1.000
Males [*n* (%)]	36 (60.0)	18 (60.0)	
Age [median (min–max)]:	21 (2–52)	22 (2–36)	0.970
<18 Years [*n* (%)]	22 (36.7)	11 (36.7)	
>18 Years [*n* (%)]	38 (63.3)	19 (63.3)	
Body weight [(kg; median (min–max)]	56.0 (10.0–85.0)	61.5 (14.0–90.0)	0.061
Height [cm; median (min–max)]	160 (84–187)	165 (89–183)	0.420
Age at diagnosis [months; median (min–max)]	6 (2–84)	–	
Age at starting chelator use (months; median (min–max)]	32 (20–116)	–	
Presence of splenectomy [*n* (%)]	20 (33.3%)	–	
Quantity of transfusion in the last year:			
>35 kg or >18 years [unit/year; (min–max)]	32 (24–40)	–	
<35 kg or <18 years [mL/kg/year; median (min–max)]	130 (120–130)	–	
Hb [g/dL; median (min–max)]	9.3 (6.0–13.8)	13.8 (11.8–17.0)	**0.001**
Serum ferritin [ng/mL; median (min–max)]	921.5 (287.0–8689.0)	46.4 (20.4–156.7)	**0.001**
Serum urea [mg/dL; median (min–max)]	28.4 (13.0–46.0)	27.4 (13.8–43.2)	0.216
Serum creatinine [mg/dL; median (min–max)]	0.5 (0.2–1.0)	0.7 (0.3–1.2)	**0.001**
Urine protein/creatinine [mg/mg; median (min–max)]	0.20 (0.06–1.00)	0.1 (0.03–0.30)	**0.001**
Urine creatinine [mg/dL; median (min–max]	61.3 (19.0–471.0)	134.4 (0.8–524.9)	**0.001**
Urine phosphate [mg/dL; median (min–max)]	52.1 (4.1–215.1)	51.6 (14.9–118.6)	0.959
TPR [% (min–max)]	90.0 (73.0–99.0)	93.5 (83.0–98.0)	**0.006**
GFR [mL/min./1.73 m²; median (min–max)]	114.2 (103.1–300.0)	125.6 (99.8–198.6)	**0.001**
Presence of proteinuria [*n* (%)]	25 (41.7)	0 (0.0)	**0.001**
Urine β2-MG [ng/mL; median (min–max)]	0.9 (0.5–4.0)	0.3 (0.1–0.7)	**0.001**
Urine β2-MG/creatinine [mg/g; median (min–max)]	1.70 (0.20–15.40)	0.20 (0.02–1.00)	**0.001**
Urine NGAL [ng/mL; median (min–max)]	9.5 (8.0–23.1)	6.2 (1.3–8.8)	**0.001**
Urine NGAL/creatinine [ng/mg; median (min–max)]	15.3 (2.1–76.0)	3.8 (0.4–11.9)	**0.001**
Serum endocan [ng/mL; median (min–max)]	84.9 (53.8–170.9)	37.2 (18.8–50.0)	**0.001**

n: number; β-TM: β-thalassemia major; TPR: tubular phosphate reabsorption; GFR: glomerular filtration rate; β2-MG: β2-microglobulin; NGAL: neutrophil gelatinase-associated lipocalin.

Table 2. Correlation analysis of the parameters in the β-thalassemia major group. (Bold *p* values are significant).

	Protein/creatinine		β2-MG		β2-MG creatinine		NGAL		NGAL/creatinine		Endocan	
	p Value	*r*	*p* Value	*r*	*p* Value	*r*	*p* Value	*r*	*p* Value	*r*	*p* Value	*r*
Hemoglobin	0.558	−0.077	0.970	−0.04	0.975	−0.004	0.525	−0.080	0.730	−0.045	0.460	0.097
Serum ferritin	0.331	0.128	0.008	0.335	0.008	0.341	0.007	0.307	0.374	0.117	**0.001**	0.963
GFR	0.041	0.265	0.58	0.246	0.327	0.129	0.128	0.199	0.968	−0.005	0.526	0.083
TPR	0.537	−0.081	0.708	0.049	0.708	0.049	0.746	−0.043	0.746	−0.043	0.005	0.355
β2-MG	0.001	0.489	–	–	–	–	–	–	–	–	–	–
β2-MG/creatinine	**0.001**	0.629	**0.001**	0.589	–	–	–	–	–	–	–	–
NGAL	**0.001**	**0.449**	**0.001**	**0.746**	**0.001**	**0.563**	–	–	–	–	–	–
NGAL/creatinine	**0.001**	0.465	**0.037**	0.270	0.001	0.820	**0.042**	0.264	–	–	–	–
Endocan	0.104	0.212	**0.001**	0.834	0.003	0.383	0.001	0.861	0.293	0.138	–	–

GFR: glomerular filtration rate; TPR: tubular phosphate reabsorption; β2-MG: β2-microglobulin; NGAL: neutrophil gelatinase-associated lipocalin.

The ROC analysis was performed to determine the cutoff values for urine β2-MG/creatinine ratio and for urine NGAL/creatinine ratio in predicting proteinuria. For urine β2-MG/creatinine ratio, the area under the curve was 84.9% with the standard error of 5.3% and the cutoff value was 2.82 (sensitivity 60.00%, specificity 97.14%, positive predictive value 93.75% and negative predictive value 77.27%) [Figure 1(a)]. For urine NGAL/creatinine ratio, the area under the curve was 75.4% with the standard error of 6.5% and the cutoff value was 23.05 (sensitivity 52.00%, specificity 91.43%, positive predictive value 81.25% and negative predictive value 72.73%) [Figure 1(b)].

Discussion

There is limited information about the epidemiology of renal complications in β-thal patients. Nevertheless, renal problems have been reported to be the fourth most common cause of morbidity (4.0%) in β-thal patients after endocrine, cardiovascular and hepatic disorders [12]. Renal injury develops due to the progression of glomerular and tubular damage. Early detection of glomerular and tubular dysfunctions is of critical importance to prevent renal disorders or to reverse the renal functions.

Development of acute renal failure and Fanconi syndrome due to the use of chelating agents has been reported in β-thal patients [13–15]. Deferasirox is the most frequently preferred chelating agent. The present study failed to demonstrate any effect of DFX on glomerular functions. However, besides affecting the GFR, renal tubular abnormalities have been reported, particularly in pediatric patients [16]. Some studies have shown that DFX causes hemodynamic changes that consequently decrease GFR and serum creatinine clearance. This opinion is supported by the fact that these changes arise early in the treatment period but do not get worse with continuation of treatment. In fact,
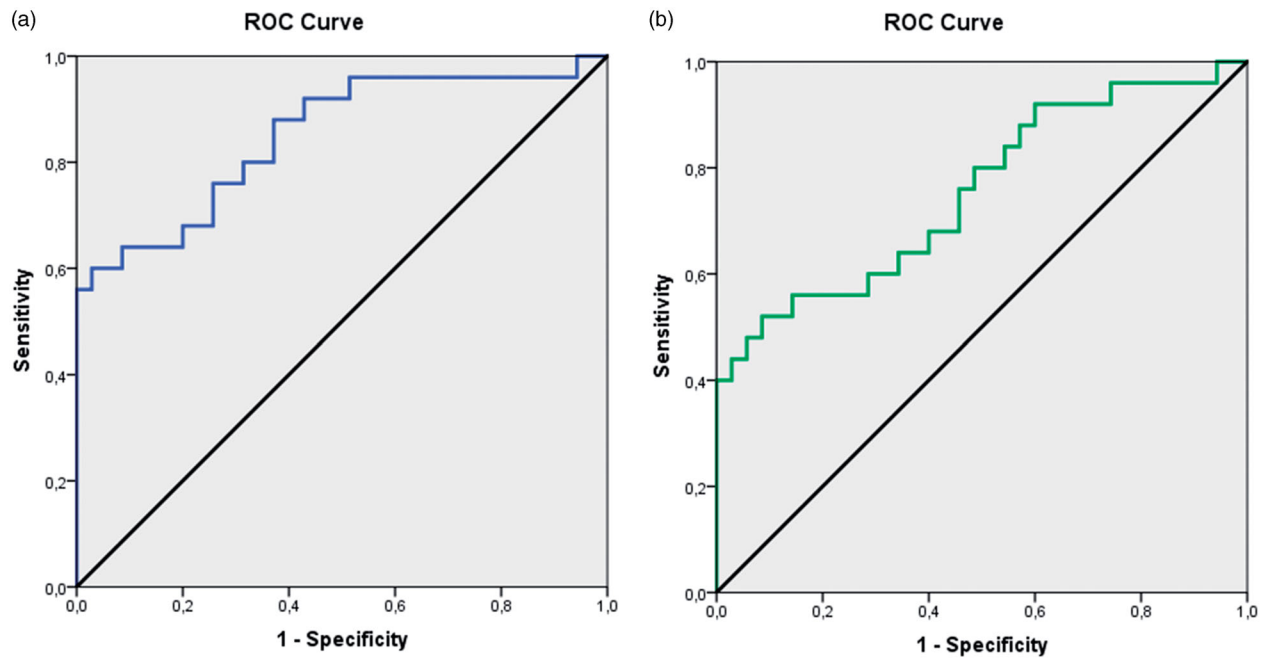
(a)

ROC Curve

(b)

ROC Curve

Figure 1. In the patients with β-TM: (a) ROC curve of the urine β2-MG/creatinine ratio in predicting proteinuria, and (b) ROC curve of the urine NGAL/creatinine ratio in predicting proteinuria.

long-term observational studies showed that the increase in serum creatinine is plateaued after the initial treatment period but indicating that renal adverse events occurring during the registration studies did not provoke irreversible or progressive long-term effects on renal function [17,18]. Moreover, this effect can be controlled by dose adjustment or by drug switch [18]. In the light of this information, the absence of difference between the drug subgroups might have resulted from the regulation of DFX therapy in our β-TM patients. However, our study revealed that glomerular dysfunction accompanied β-TM independent from the patients' treatment even though drug selection and dose adjustment were performed.

Serum urea level, which is used to assess glomerular functions, is elevated in case of renal injury. Level of urea can also be influenced by extra-renal factors such as dehydration, diet, fever, shock, pregnancy, *etc.* Therefore, urea clearance may be a guide for GFR; however, it is a weak indicator. Serum creatinine level also gives rough information about GFR. Elevation of serum creatinine level indicates decreased creatinine clearance and thereby decreased GFR. Nevertheless, serum creatinine level can also be influenced by various extra-renal factors such as muscle mass, activity, diet, anemia, hyperthyroidism, *etc.* [19]. Studies have determined no significant difference between β-TM patients and healthy controls in terms of blood urea nitrogen and serum creatinine levels [20–22]. In the present study, there was no statistically significant difference between serum urea levels of the β-TM and control groups; however, creatinine level was significantly lower in the control group. It should be kept in mind that creatinine level is also influenced by many extra-renal factors and is not an exact indicator of glomerular functions.

Urine protein/creatinine ratio is increased in case of glomerular and tubular pathologies. Clinical studies have demonstrated that urine protein/creatinine ratio is significantly increased in β-thal patients and is high in pediatric β-TM patients [20,21,23]. In a study in which 37 β-thal patients were followed-up at monthly intervals regarding protein/creatinine ratio for 44 months, significant elevation was determined in protein/creatinine ratio (>0.8) in seven (18.9%) patients and proteinuria was detected in 12 (0.8%) of 1490 measurements. The risk of proteinuria was reported to be higher in the patients younger than 23 years old and at DFX doses below 29 mg/kg/day [24]. Estimation of tubular damage using GFR parameters alone is difficult in β-thal patients because of already existing hyperfiltration. For this reason, in the present study, with the use of biomarkers indicating renal injury, such as urine β2-MG and NGAL levels, the β-TM patients with proteinuria were demonstrated to have significantly higher urine β2-MG level, β2-MG/creatinine ratio, urine NGAL level, and NGAL/creatinine ratio than those without. There were also positive correlations of protein/creatinine ratios with urine β2-MG level, β2-MG/creatinine ratios, NGAL level, and NGAL/creatinine ratios. This suggests that using protein/creatinine ratio together with urine β2-MG and urine NGAL biomarkers would be a more reliable method in assessing renal injury.

Phosphate reabsorption in proximal tubule is used to assess tubular functions. Proximal tubular damage may cause an increase in the urinary excretion of phosphorus that is normally found in the cell. However, hypoparathyroidism, which is one of the complications of the disease, can also reduce phosphorus absorption in the kidneys [25]. Economou *et al.* [26] determined no difference in terms of TPR values in β-TM patients. Aldudak *et al.* [20] reported

lower TPR levels in β-TM patients as compared to healthy controls. Uzun *et al.* [23] evaluated different forms of pediatric β-thal and found TPR values not to be different from those of the control group. In the present study, TPR value was lower in the β-TM patients than in the control group. However, no correlation was determined between TPR and other parameters associated with renal functions. This finding and different results in the literature suggest that TPR cannot be a reliable marker of tubular function in β-TM.

One of the markers of tubular function is urine β2-MG level [19]. β2-Microglobulin is freely filtered at the glomerulus and almost completely reabsorbed through the proximal tubules. Therefore, it is found in negligible amounts in the urine. Increased urine concentration of β2-MG is one of the early markers of proximal tubular damage. Hamed *et al.* [27] evaluated β-TM patients as two groups, one receiving chelation therapy and the other not, and found urine β2-MG/creatinine ratio to be higher in both groups as compared to the healthy controls. Earlier studies investigating different forms of β-thal have reported that β2-MG level is higher only in β-TM cases compared with the controls and that β-thal minor and β-thal intermedia (β-TI) groups have similar β2-MG levels to that of controls [23,26,28]. Quinn *et al.* [22] determined increased β2-MG levels in the β-thal patients, but found no significant correlation between β2-MG increment and transfusion status. Koliakos *et al.* [29] reported tubular dysfunction in the β-TM patients. They determined an increase in β2-MG level in the urine and demonstrated a significantly positive correlation between this increment and ferritin. They concluded that this finding pointed out iron deposition as the major factor leading to tubular dysfunction. In our study, urine β2-MG level and β2-MG/creatinine ratio were significantly higher in the β-TM patients as compared to the control group. Significant correlations between these values and serum ferritin concentration suggest that β2-MG level is a marker in monitoring renal injury caused by iron deposition. In addition, positive correlations between these values and protein/creatinine ratio, NGAL level, and NGAL/creatinine indicate that β2-MG level can be a reliable parameter in detecting renal injury. In the logistic regression analysis, β2-MG/creatinine was found to be an independent risk factor of proteinuria. In the ROC analysis, β2-MG/creatinine showed high specificity with a cutoff value of 2.82. These findings demonstrated the reliability and availability of β2-MG/creatinine in predicting proteinuria. Positive correlations of β2-MG and β2-MG/creatinine with serum endocan level, a new marker of endothelial injury, also suggest that β2-MG and β2-MG/creatinine are alarming parameters for endothelial injury. Based on all these findings, β2-MG is considered as a significant and valuable parameter indicating tubular damage.

Kattamis *et al.* [30] reported increased plasma NGAL level in the β-TM patients. In the same study, it was stated that plasma NGAL level correlated with cystatin C level, which indicated that renal impairment was related to tubular damage. In the present study, urine NGAL level and NGAL/creatinine ratio were higher in the β-TM group than in the control group. The significant correlation of urine NGAL level with serum ferritin suggests that iron leads to renal injury and that urine NGAL level is a marker for monitoring iron-related renal injury. Moreover, the urine NGAL/creatinine ratio was also positively correlated with urine protein/creatinine, urine β2-MG, urine β2-MG/creatinine, and serum endocan level. The NGAL/creatinine level showed high specificity in predicting proteinuria with a cutoff value of 23.05. Based on these findings, we can suggest that urine NGAL level and NGAL/creatinine ratios are valuable early biomarkers of renal injury.

Endocan has been reported to be a prognostic value in hypertension, renal transplant rejection, and chronic renal failure and endocan level has been found to show a negative correlation with GFR [31]. However, to the best of our knowledge, there is no study in the literature investigating endocan level in β-thal patients. In the present study, endocan level was significantly higher in the β-TM group as compared to the control group. A significant positive correlation was determined between endocan level and serum ferritin concentration. This verifies the fact that increased ferritin concentration leads to endothelial damage. On the other hand, we determined no correlation between serum endocan level and urine protein/creatinine ratio and GFR. Proteinuria is a finding that occurs due to endothelial damage. Therefore, a relationship between the presence of proteinuria and endocan level was expected.

In our clinic, we closely monitor our patients for proteinuria and in case proteinuria occurs, we immediately initiate treatment and evaluate patients at frequent intervals. As a result of this, we found the urine protein/creatinine ratio as median 0.2 mg/mg (min-max: 0.06–1 mg/mg). In other words, urine protein/creatinine ratio was not very high even in the patients with proteinuria. Absence of a relationship between proteinuria and endocan level might have resulted from the limited number of patients with severe proteinuria. Nevertheless, there were positive correlations of endocan level with urine β2-MG, β2-MG/creatinine and NGAL values. Therefore, absence of a relationship between proteinuria and endocan level, which we considered gave information about renal injury, was noticeable. This might have resulted from the limited number of patients in the β-TM group, the limited number of patients with remarkable increase in protein/creatinine ratio, and wide age range of the patients. Therefore, further studies are needed on this issue.

Finally, we concluded that urine β2-MG/creatinine, NGAL/creatinine, and protein/creatinine ratios are the markers of renal injury. Regarding the relationship of urine β2-MG, urine NGAL, and serum endocan with ferritin concentration, all of the three parameters increased as ferritin increased. This reveals that iron is associated with endothelial damage and renal injury and attracts our attention once more to the importance of ferritin monitoring. Absence of the relationship of protein/creatinine ratio with Hb and ferritin concentrations suggested that protein/creatinine ratios could be used for monitoring renal problems without being influenced by anemia and iron deposition. Urine β2-MG/creatinine and urine NGAL/creatinine were found to be the parameters with high reliability in predicting proteinuria.

Considering the relationships of urine β2-MG and NGAL values with serum endocan level, these three parameters were found to be the indicators of endothelial damage. However, to the best of our knowledge, there is no study investigating endocan level in β-thal patients and thus, further studies evaluating the relationship between endocan level and renal injury are needed. It would be possible to protect patients against renal complications by early detection of renal injury and by taking necessary measures.

Disclosure statement

Funding

ORCID

Petek Uzay Cetinkaya http://orcid.org/0000-0002-0236-8330
Fatih Mehmet Azik http://orcid.org/0000-0001-5715-4244
Volkan Karakus http://orcid.org/0000-0001-9178-2850
Bulent Huddam http://orcid.org/0000-0002-8412-1584
Nigar Yilmaz http://orcid.org/0000-0001-7108-9135

Data availability statement

The data that support the findings of this study are available from the corresponding author (PUC), upon reasonable request.

References

[1] Taher AT, Weatherall DJ, Cappellini MD. Thalassaemia. Lancet. 2018;391(10116):155–167.
[2] Rund D, Rachmilewitz E. β-Thalassemia. N Engl J Med. 2005; 353(11):1135–1146.
[3] Ware HM, Kwiatkowski JL. Evaluation and treatment of transfusional iron overload in children. Pediatr Clin North Am. 2013;60(6):1393–1406.
[4] Ponticelli C, Musallam KM, Cianciulli P, et al. Renal complications in transfusion-dependent β thalassemia. Blood Rev. 2010; 24(6):239–244.
[5] Mallat NS, Mallat SG, Musallam KM, et al. Potential mechanisms for renal damage in β-thalassemia. J Nephrol. 2013;26(5): 821–828.
[6] Mouton R, Holder K. Laboratory tests of renal function. Anaesth Intensive Care Med. 2006;7(7):240–243.
[7] Schardijn GH, Statius van Eps LW. β2-Microglobulin: its significance in the evaluation of renal function. Kidney Int. 1987; 32(5):635–641.
[8] Devarajan P. Review: neutrophil gelatinase-associated lipocalin: a troponin-like biomarker for human acute kidney injury. Nephrology (Carlton). 2010;15(4):419–428.
[9] Kali A, Shetty KS. Endocan: a novel circulating proteoglycan. Indian J Pharmacol. 2014;46(6):579–583.
[10] Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, adolescents. Pediatr Clin North Am. 1987; 34(3):571–590.
[11] Levey AS, Stevens LA, Schmid CH, Zhang Y(L). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612.
[12] Demosthenous C, Vlachaki E, Apostolou C, et al. β-Thalassemia: renal complications and mechanisms: a narrative review. Hematology. 2019;24(1):426–438.
[13] Prasannan L, Flynn JT, Levine JE. Acute renal failure following deferoxamine overdose. Pediatr Nephrol. 2003;18(3):283–285.
[14] Rafat C, Fakhouri F, Ribeil JA, et al. Fanconi syndrome due to deferasirox. Am J Kidney Dis. 2009;54(5):931–934.
[15] Grangé S, Bertrand DM, Guerrot D, et al. Acute renal failure and Fanconi syndrome due to deferasirox. Nephrol Dial Transplant. 2010;25(7):2376–2378.
[16] Dee CM, Cheuk DK, Ha SY, et al. Incidence of deferasirox-associated renal tubular dysfunction in children and young adults with β-thalassaemia. Br J Haematol. 2014;167(3):434–436.
[17] Origa R, Piga A, Tartaglione I, et al. Renal safety under long-course deferasirox therapy in iron overloaded transfusion-dependent β-thalassemia and other anemias. Am J Hematol. 2018;93(7):E172–175.
[18] Kattamis A. Renal function and abnormalities and deferasirox. Lancet Child Adolesc Health. 2019;3(1):2–3.
[19] Gowda S, Desai PB, Kulkarni SS, et al. Markers of renal function tests. N Am J Med Sci. 2010;2(4):170–173.
[20] Aldudak B, Bayazit AK, Noyan A, et al. Renal function in pediatric patients with β-thalassemia major. Pediatr Nephrol. 2000; 15(1–2):109–112.
[21] Şen V, Ece A, Uluca Ü, et al. Urinary early kidney injury molecules in children with β-thalassemia major. Ren Fail. 2015; 37(4):607–613.
[22] Quinn CT, Johnson VL, Kim HY, et al. Renal dysfunction in patients with thalassaemia. Br J Haematol. 2011;153(1):111–117.
[23] Uzun E, Balcı YI, Yüksel S, et al. Glomerular and tubular functions in children with different forms of β thalassemia. Ren Fail. 2015;37(9):1414–1418.
[24] Bayhan T, Ünal Ş, Ünlü O, et al. The questioning for routine monthly monitoring of proteinuria in patients with β-thalassemia on deferasirox chelation. Hematology. 2017;22(4):248–251.
[25] Kavukçu S. Bobrek fonksiyon testleri ve KlinikYorumu. Turkey Klinikleri J Pediatr Sci. 2008;4(1):1–12.
[26] Economou M, Printza N, Teli A, et al. Renal dysfunction in patients with β-thalassemia major receiving iron chelation therapy either with deferoxamine and deferiprone or with deferasirox. Acta Haematol. 2010;123(3):148–152.
[27] Hamed EA, ElMelegy NT. Renal functions in pediatric patients with β-thalassemia major: relation to chelation therapy: original prospective study. Ital J Pediatr. 2010;36:39
[28] Annayev A, Karakaş Z, Karaman S, et al. Glomerular and tubular functions in children and adults with transfusion-dependent thalassemia. Turk J Haematol. 2018;35(1):66–70.
[29] Koliakos G, Papachristou F, Koussi A, et al. Urine biochemical markers of early renal dysfunction are associated with iron overload in β thalassemia. Clin Lab Haematol. 2003;25(2): 105–109.
[30] Kattamis A, Margeli A, Hantzi E, et al. Assessment of renal function in transfused β-thalassemia patients based on cystatin C measurements and equations. Blood. 2007;110(11):2769–2769.
[31] Afsar B, Takir M, Kostek O, et al. Endocan: a new molecule playing a role in the development of hypertension and chronic kidney disease? J Clin Hypertens (Greenwich). 2014;16(12): 914–916.