Urine β2 Microglobulin and other Biochemical Indices in β Thalassemia Major

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Abstract- To find if some indices have predictive value for renal complications. We conducted a cross sectional and included 80 patients with the age ranged 5-17 years, all with the proven diagnosis of β-thalassemia major. A urine and 5 ml of blood sample were obtained from all of the cases. Biochemical indices such as serum levels of creatinine, Na, Mg, Hb, and ferritin and also urine levels of Na, Mg, creatinine and β2 microglobulin was measured. All data analysis was performed using SPSS 14.0. P-Spearman test was applied to assess correlation between urine beta-2-microglobulin and other variables. Patients GFR was in normal range. Abnormal level of urine β2 microglobulin was reported in 44 patients (55%). P Spearman test proved correlation only between urine β2 microglobulin and FE-Mg. We concluded that renal proximal tubular dysfunction may oocur in children with β thalassemia major without clinical manifestations of renal dysfunction or decrease in GFR. We warn not to rely only on GFR as a early indicator for renal complications among children with β thalassemia major.

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Key words: β thalassemia, β2 microglobulin, FE-Mg, proximal tubular

Introduction

In 1925, Cooley et al reported a series of 4 children with anemia, hepatosplenomegaly, jaundice, and cranial and facial Hyperostosis (1). More than a decade later, Whipple and Bradford found that diseases such as Von Jakesch Anemia, Cooley's Anemia and Mediterranean Anemia are different description of the same disease, thalassemia . Nowadays, thalassemic syndromes are the most common genetic disorder worldwide (2,3).

They include congenital disorder of hemoglobin due to defect in synthesis of one or more α or β chains of globin. Patients with β-thalassemia major have severe anemia because of rapid hemoglobin destruction. Treatments for thalassemia have improved greatly in the past few years. People who have moderate and severe thalassemia are now living longer and have better quality of life than before. However, complications from thalassemia and their treatments are frequent. Koliakos G et al reviewed 91 patients with β-thalassemia major to find the incidence of renal complications. They introduced iron overload as the main reason responsible for renal malfunctioning (4).

Similarly, Aldudak et al indicated significant changes in renal biochemical indices of thalassemic patients with respect to the normals which proved proximal tubular damage secondary to oxidative peroxidation of lipids due to iron overload (5). Thus, renal complications were the field of interest in our study. We prepared it to find if some indices have predictive value for renal complications.

Patients and Methods

We conducted a cross sectional and included 80 patients with the age ranged 5-17 years, all with the proven diagnosis of β-thalassemia major based on clinical manifestations and electrophoresis. The patients with renal disease, history of splenectomy, current treatment with diuretics or familial history of renal disease were excluded.

A urine and 5 ml of blood sample were obtained from all of the cases. Biochemical indices such as serum levels of creatinine, Na, Mg, Hb, and ferritin and also urine levels of Na, Mg, creatinine and β2 microglobulin was measured by a single laboratory technician under direct observation of a pathologist. Glomerular filtration rate (GFR), fraction of excretion Na and Mg (FE-Na and FE-Mg, respectively) were calculated using standard formulas.

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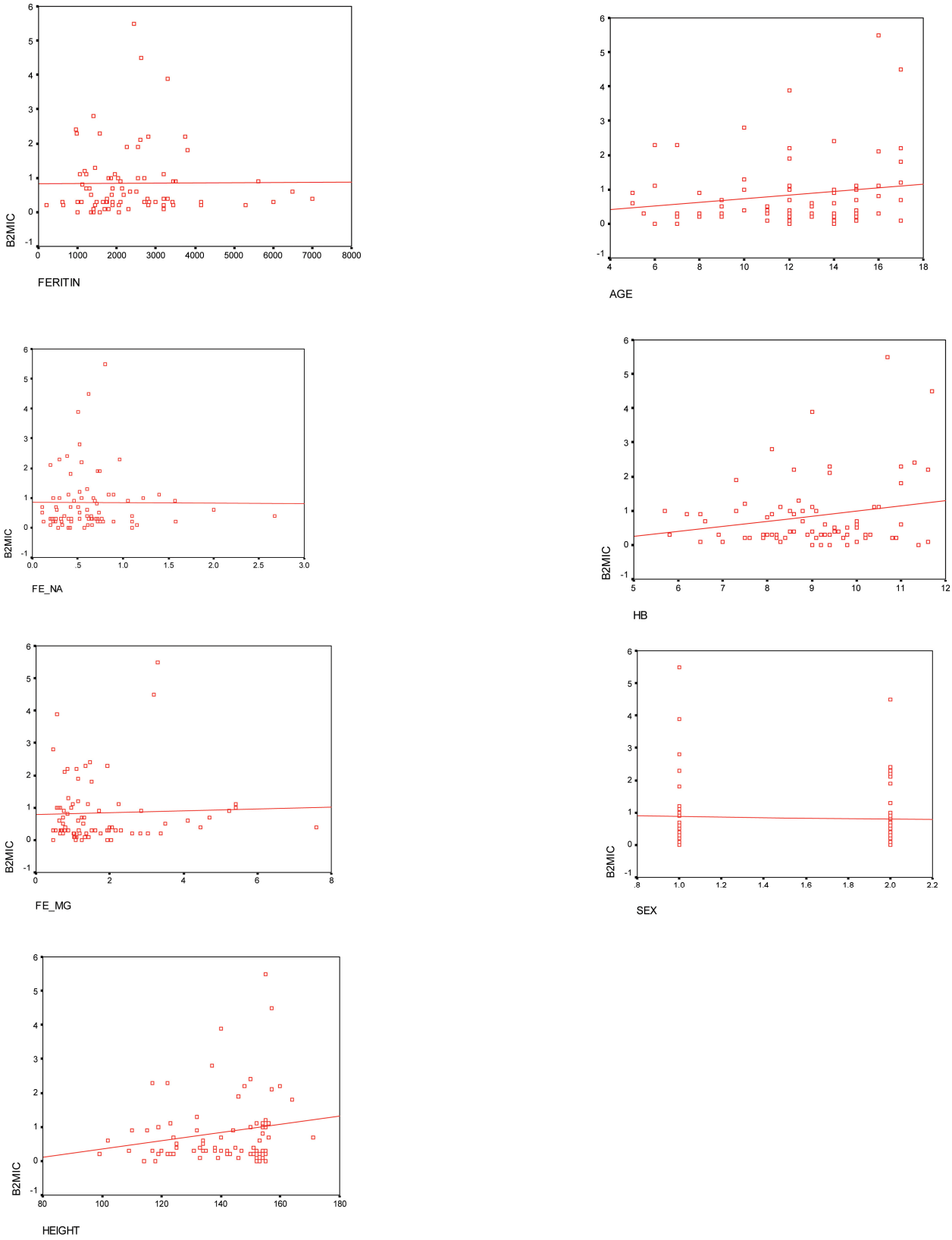

Figure 1. Scattergram of beta-2-microglobulin according to the patients' Ferritin (a) ,Age(b),FE-Na (c), hemoglobin (d) FE-Mg (e), sex (f) and Height (g).

Informed consent was obtained from all of included patients. Demographic data in addition to the above were registered in a predesigned data sheet. All data analysis was performed using SPSS 14.0. P Spearman test was applied to assess correlation between urine beta-2-microglobulin and other variables.

Results

Each sex constituted half of studied population. Patients GFR was in normal range. Other demographics and lab data were abstracted in table 1. Abnormal level of urine β2 microglobulin was reported in 44 patients (55%). Table 2 demonstrated it according to the other variables. P Spearman test proved correlation only between urine β2 microglobulin and FE-Mg.

Figure 1-a to 1-f indicated urine β2 microglobulin scattergram with respect to some other variables.
The mean GFR was 155.3 mL/min with 42.3 mL/min as standard deviation.

Table 1. Demographics and lab data

Age Group	
< 10 years	21 (26.3%)
11-15 years	48 (60%)
> 16 years	11 (13.8%)
Sex	
Female	40 (50%)
Male	40 (50%)
Height	
< 100 Cm	1 (1.3%)
100-120 Cm	11 (13.7%)
120-150 Cm	38 (47.5%)
> 150 Cm	30 (37.5%)
Hemoglobin	
Normal	21 (26.3%)
Abnormal	59 (73.7%)
Ferritin	
Normal	5 (6.3%)
Abnormal	75 (93.7%)
FE-Na	
Normal	69 (86.2%)
Abnormal	11 (13.8%)
FE-Mg	
Normal	73 (91.3%)
Abnormal	7 (8.7%)
β2-Microglobulin	
Normal	36 (45%)
Abnormal	44 (55%)

The normal value of the mentioned indices were as follow: Hb ≥ 10 mg/dL, Ferritin < 1000, FE-Na ≤ 1, FE-Mg ≤% 4, and β2-Microglobulin ≤ 0.3.

Table 2. β2 microglobulin level according to other Variables

Variable	β2-Microglobulin Normal/Abnormal	P
Age	11.59±3.17/12.31±3.47	0.34
Height	138.3±15.78/141.4±15.84	0.38
Hb	8.9±1.36/9.0±1.44	0.68
Ferritin	2264 ±1277/2481±1334	0.46
GFR	152.7±44.48/157.4±41.01	0.62
FE-Na	0.56±0.32/0.68±0.48	0.18
FE-Mg	1.44±0.75/1.97±1.67	0.06

Discussion

There are many studies which indicated renal proximal tubular damage in patients with β thalassemia major. β 2 microglobulin is a low molecular weight protein that can be detected in urine sample after proximal tubular damage; therefore, it can be used as a indicator of proximal tubular damage. Nowadays, measurement of this protein is applicable using a special kit in almost every laboratory. Cianciulli et al in 1994 reported 13 patients with renal tubular damage out of 19 studied patients with major thalassemia. Among these 13 patients with tubular damage, 11 cases (85%) demonstrated β2 microgolobulin level more than normal range (6). In our study, we found 44 patients with abnormal levels of urine β2 microglobulin (55%). The difference may be due to the improvements of thalassemic patients' care which probably lead to decreased rate of proximal tubular damage. Although these results emphasize on the significancy of the renal complications in the patients with thalassemia one more time. There was no case of diminished GFR in our population. It indicated that according to GFR index and Schwartz formula.renal function had not been affected by the disease among studied children with thalassemia which was similar to the report b Koliakos G and aldudak B et al (4,5). Conversely, Tabatabaei SMT et al reported 19/0 % of thalassemic children with decreased creatinine clearance. However, they could not indicate any clinical evidence of disturbance in renal function (7). Of noteworthy GFR in Aldudak B et al was 164.4±45.3 mL/min(5). It should be concern that the mean height of children with thalassemia was lower than normal age-matched children.
However, there is no specific height chart to monitor the height of these patients. Generally, it is believed that with regular blood transfusion and improvement of chronic anemia, their physical configuration especially of face and total height will be in normal range. It is known that growth and development disorder among

patients with major thalassemia caused by several factors including nutrition, hormonal problems, and Zinc deficiency which can be prevented by regular and sufficient blood transfusion and Desferal prescription (8,9). In thalassemic population, chronic anemia affects total height in prepuberty period whereas in puberty, endocrine disorders and growth hormone deficiency leads more disturbance in growing up (8). Our results showed a higher average of height among children with abnormal levels of urine β2 microglobulin in comparision with those with normal levels which may be due to the appropriate follow up protocol. Also we hypothesized that proximal tubular damage could not affect total height independently. In our study, abnormal level of FE-Mg was observed in 7 patients, all with abnormal level of urine β2 microglobulin. FE-Mg is an important index to evaluate loop of Henle and its ascending limb. The relation between FE-Mg and β2 microglobulin, which was found in our study may exhibit that these portion of renal tubules is damaged earlier than others. Thus, we concluded that FE-Mg can be used to evaluate renal tubular function especially of the loop of Henle. In the other hand, increase in FE-Mg may be an indicator of tubulointerestitial damage of kidneys due to endothelial microvascular damaged caused by chronic anemia (10). Kalman et al conducted a study on patients with β thalassemia minor. They indicated abnormal level of FE-Mg among children with anemia (11). FE-Na with respect to urine β2 microglobulin has assessed in several studies including Mohkam et al (12) Aldudak B et al (5), and Koren G et al (13). Renal tubular damage, specially in proximal portion, has a determinant effect on FE-Na. Thus, it seems that urine β2 microglobulin is more sensitive than FE-Na in evaluation of renal tubular function. The priority of changes in urine β2 microglobulin level before the onset of disturbance in FE-5a overemphasizes this issue. We did not find any relationship between patients' sex or age and urine β2 micro globulin similar to Aldudak B et al (5) and Koliakos et al4, respectively. Thus, we concluded that both gender with any age should be undergone monitoring test for proximal tubular function. However, we found that children older than 15 years of age exhibited abnormal level of urine β2 microglobulin approximately two times more frequent than those under the age of 10 years.

The levels of β2 microglobulin in urine were relevant neither to the patients' serum hemoglobin nor to the ferritin. Conversely, Koliakos et al found a statistically significant relationship. They concluded that increasing level of ferritin was associated with glomerular rather than tubular damage (4).

In conclusion, we concluded that renal proximal tubular dysfunction may occur in children with β thalassemia major without clinical manifestations of renal dysfunction or decrease in GFR. We warn not to rely only on GFR as an early indicator for renal complications among children with β thalassemia major.

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