

Renal tubular function in patients with β -thalassaemia major in Zahedan, southeast Iran

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ABSTRACT

Introduction: In patients with beta-thalassaemia major, impaired biosynthesis of the beta-globin leads to accumulation of unpaired alpha-globin chain. Shortened red cell lifespan and iron overload cause functional and physiological abnormalities in various organ systems. Thus, in patients with beta-thalassaemia major, the most important cause of mortality and morbidity is organ failure due to deposits of iron. The aim of this study is to investigate renal tubular and glomerular functions in patients with beta-thalassaemia major.

Methods: 166 subjects with beta-thalassaemia major (96 male, 70 female) were enrolled in the study. Fasting blood and 24-hour urine samples were obtained for haematological and biochemical analyses.

Results: Patients with beta-thalassaemia major showed significant signs of renal tubulopathy, such as hypercalciuria (12.9 percent), proteinuria (8.6 percent), phosphaturia (9.2 percent), magnesiumuria (8.6 percent), hyperuricosuria (38 percent) and excretion of beta-2 microglobulin (13.5 percent). We found that 95.1 percent of patients had iron overload (ferritin more than 1,000 ng/ml).

Conclusion: The determination of biochemical indices of renal function might help prevention of serious kidney damage before any clinical symptom is observed. Beta-thalassaemia patients present multiple renal abnormalities which may be due to iron overload. We suggest the appropriate chelation therapy and regular monitoring of the status of iron overload.

Keywords: β -thalassaemia, iron overload, renal function, renal tubular function, thalassaemia major

INTRODUCTION

Thalassaemia is a type of chronic, inherited, microcytic anaemia that is characterised by defective haemoglobin synthesis and ineffective erythropoiesis. In all thalassaemias, clinical features that result from anaemia, transfusional, and absorptive iron overload are similar but vary in severity.⁽¹⁾ β -thalassaemia is a group of heterogeneous autosomal recessive disorders due to the absence or reduced synthesis of the β -globin chain.⁽²⁾ Over 200 different mutations leading to β -thalassaemia have been characterised worldwide. β -globin is encoded by a structural gene found in a cluster with the other β -like genes spanning 70 Kb on the short arm of chromosome 11(11p15.4).⁽³⁾

Thalassaemia major (homozygous β -thalassaemia or Cooley's anaemia) is characterised by grossly defective synthesis of haemoglobin A, impaired red blood cell (RBC) production and increased haemolysis of the defective RBC. Affected individuals are dependent on repeated blood transfusions and most succumb before 20 years of age. Death is usually attributable to cardiac failure resulting from iron deposition in the myocardium. There are several reports indicating renal dysfunction in β -thalassaemia major.⁽⁴⁻¹⁰⁾ There are two main varieties of β -thalassaemia alleles: β^0 -thalassaemia in which no β -globin is produced, and β^+ -thalassaemia in which some β -globin is produced, but less than normal. Less severe forms are sometimes designated β^{++} to reflect the minimal deficit in the β -chain production.⁽³⁾ More than 200 β -thalassaemia alleles have been characterised; population studies indicate that about 40 of those account for 90% or more of the β -thalassaemias worldwide.⁽¹¹⁾ The aim of the present study was to evaluate the renal and tubular functions in patients with β -thalassaemia major in Zahedan, southeast Iran, where the disease is prevalent.

METHODS

A total of 166 patients (96 male, 70 female) suffering from major β -thalassaemia were enrolled in the study. Exclusion criteria were cardiac disease, liver disease, diabetes mellitus and diuretic therapy. Fasting blood was obtained for haematological and biochemical tests. A 24-hour urine

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Table I. The laboratory biochemical parameters in 24-hour urine of β -thalassaemia major patients.

Parameters	Minimum value	Maximum value	Mean \pm SD
Protein (mg/m ² .day)	0.1	16	1.70 \pm 1.89
Calcium (mg/m ² .day)	0.1	11.3	2.27 \pm 1.81
Phosphorus (mg/kg.day)	0.6	80	8.82 \pm 9.07
Uric acid (mg/kg.day)	0.9	70	12.18 \pm 8.72
Sodium (meq/day)	12.20	930	127.37 \pm 108.63
Potassium (meq/day)	4	528	37.16 \pm 50.46
Magnesium (mg/m ² .day)	1	427	83.73 \pm 72.76
Creatinine (mg/kg.day)	5	66	16.07 \pm 7.91
β_2 -microglobulin (mg/24 hr)	0	14.16	0.61 \pm 1.38

specimen was collected for the determination of creatinine, sodium, potassium, calcium, uric acid, magnesium, phosphorus, β_2 -microglobulin and protein. Sodium and potassium was assayed using flame photometer. Urine β_2 -microglobulin and serum ferritin were assayed by Immunometric Enzyme Immunoassay kit (ORGENTEC Diagnostika GmbH, Mainz, Germany). Other biochemical tests were assayed by spectrophotometric methods using commercial kits. Statistical analysis was performed using the Statistical Package for Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA). Pearson correlation test was performed between biochemical parameters and a *p*-value of less than 0.05 was considered to be significant.

RESULTS

166 patients (96 male, 70 female) with β -thalassaemia major were included in this study. The mean (\pm standard deviation) age and weight were 13.34 \pm 5.13 (range 5–30) years, and 31.78 \pm 10.25 (range 13–71) kg, respectively. Table I summarises the biochemical parameters of the 24-hour urine sample of patients. The level of serum ferritin was 3,258 \pm 1,700 (minimum 365, maximum 9,960) ng/ml, and 95.1% patients had ferritin more than 1,000 ng/ml. There was no correlation found between the age of patients and urine biochemical parameters (protein, calcium, phosphorus, uric acid, sodium, potassium, magnesium, β_2 -microglobulin) (*p* > 0.05).

There was also no correlation between the levels of serum ferritin and urine biochemical parameters (*p* > 0.05). Patients with β -thalassaemia major showed significant signs of renal tubulopathy, such as hypercalciuria (12.9%), proteinuria (8.6%), phosphaturia (9.2%), magnesiumuria (8.6%), hyperaciduricuria (38%) and excretion of β_2 -microglobulin (13.5%). Using the two-tailed Pearson test, significant correlation (*p* < 0.05) was found between urinary protein and creatinine, calcium and creatinine, phosphorus and acid uric, phosphorus and creatinine, magnesium and uric acid, sodium and potassium. There was no correlation between β_2 -microglobulin and biochemical parameters (*p* > 0.05).

DISCUSSION

The results showed significant signs of renal tubulopathy, such as hypercalciuria (12.9%), proteinuria (8.6%), phosphaturia (9.2%), magnesiumuria (8.6%), hyperaciduricuria (38%) and excretion of β_2 -microglobulin (13.5%) in β -thalassaemia major patients. We found that 95.1% patients had iron overload (ferritin more than 1,000 ng/ml). In patients with β -thalassaemia major, the most important cause of mortality and morbidity is organ failure due to deposits of iron. Aldudak et al reported that the mean values of blood urea nitrogen, serum creatinine, creatinine clearance, serum sodium, urine osmolality, and fractional excretion of sodium, potassium and uric acid, were not statistically different between healthy controls and patients with thalassaemia major. They found that serum levels of potassium, phosphorus and uric acid, the urine volume, high urinary protein to creatinine (UP/Cr) levels, urinary N-acetyl- β -D-glucosaminidase to creatinine (UNAG/Cr) levels, urinary malondialdehyde to creatinine (UMDA/Cr) levels, and the tubular reabsorption of phosphate (TRP) values were higher in β -thalassaemia major patients than in normal subjects. Proximal renal tubular damage may be secondary to oxidative lipid peroxidation mediated by the iron overload.⁽¹²⁾

Shortened red cell lifespan and excess iron cause functional and physiological abnormalities in various organ systems in thalassaemia patients. β -thalassaemia patients have a high prevalence of renal tubular abnormalities. The severity correlated with the degree of anaemia, being least severe in patients on hypertransfusion and iron chelation therapy, suggesting that the damage might be caused by the anaemia and increased oxidation induced by excess iron deposits.⁽¹³⁾ In β -thalassaemia major, impaired biosynthesis of β -globin leads to accumulation of unpaired α -globin chain. Iron overload, usually observed, generates oxygen-free radicals and peroxidative tissue injury.⁽¹⁴⁾ β_2 -microglobulin is a small protein of about 100 amino acids found in association with HLA-1 molecules on all nucleated cells. The endogenous production is relatively constant, and the protein is filtered and fully catabolised

by the kidney.⁽¹⁵⁾ Renal tubular disease does not lead to reappearance of the protein in the plasma.

Cetin et al reported that 14.6% of patients with β -thalassaemia minor showed significant signs of renal tubulopathy, such as hypercalciuria, decreased tubular reabsorption of phosphorus with hypophosphataemia, hypomagnesaemia with renal magnesium wasting, hypouricaemia with renal uric acid wasting, and tubular proteinuria. Proximal renal tubular dysfunction is not rare in patients with β -thalassaemia minor.⁽⁷⁾ Lapatsanis et al reported phosphaturia in patients with β -thalassaemia major.⁽¹⁶⁾

We found proximal tubular abnormalities in β -thalassaemia major patients. Increased oxidative stress, possibly iron induced, may play an important role. Early identification of patients at high risk of developing renal failure is of great importance, as it may allow specific measures to delay the progression of renal damage and thus reduce the incidence of end-stage renal failure and mortality. Our study clearly showed that patients with β -thalassaemia major presented with multiple renal abnormalities which may be due to iron overload. We suggest the appropriate chelation therapy and regular monitoring of the status of iron overload in these patients.

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