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Article

Integrated Assessment of Hematological and Renal Biomarkers in Patients with β-Thalassemia Major: A Case–Control Study

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Abstract: Background: β-Thalassemia major causes chronic anemia, iron overload, and renal injury, requiring integrated biomarkers for early detection and improved clinical monitoring. Aims of the study: This study aimed to compare renal, metabolic, and iron-overload biomarkers between patients with β-thalassemia major and healthy controls. Methods: This analytical case–control study enrolled 80 participants aged 3–25 years, comprising 40 patients with transfusion-dependent β-thalassemia major and 40 healthy controls, from hospitals and laboratories in Al-Anbar during October–December 2023. Diagnosis was confirmed from clinical records, transfusion dependence, CBC, and hemoglobin analysis. After overnight fasting, venous blood was collected, processed, and analyzed for urea, creatinine, uric acid, magnesium, and ferritin using validated colorimetric and immunoassay methods. Demographic, anthropometric, transfusion, and chelation data were recorded, with standardized quality-control procedures applied throughout. Results: Patients with β-thalassemia major were younger than controls (12.13 ± 6.38 vs. 15.56 ± 5.71 years; P=0.013), while BMI did not differ significantly. Urea was numerically higher in patients (P=0.087), whereas creatinine was significantly lower (P<0.001). Ferritin was markedly elevated in patients (3974.42 ± 2554.74 vs. 71.57 ± 24.73 ng/mL; P<0.001), while magnesium was comparable (P=0.727). Uric acid was significantly higher in patients (4.80 ± 1.93 vs. 2.82 ± 1.40 mg/dL; P<0.001), indicating altered purine metabolism. Conclusions: Patients with β-thalassemia major demonstrated substantial iron overload, elevated uric acid, and reduced serum creatinine, while urea, magnesium, and BMI remained comparable to controls. Integrated biochemical and renal monitoring is recommended to identify early complications and improve long-term clinical management.

Keywords: β-thalassemia major; ferritin; renal biomarkers; uric acid; iron overload.

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1. Introduction

Transfusion-dependent β-thalassemia (TDT) or β-Thalassemia major is a very serious type of hemoglobinopathy in which the β-globin-chain production is significantly decreased or completely absent, due to a pathogenic variant. This imbalance between α- and β-globin chains causes excess α-globin to precipitate [1], oxidative damage to erythroid precursors, ineffective erythropoiesis, chronic hemolytic anemia and compensatory expansion of bone marrow [2]. Despite improvements in transfusion therapy, iron chelation and multi-disciplinary management, patients are at risk of multi-system complications [3] developing as a result of chronic anemia, iron overload, oxidative insult, and toxicity from treatment [4].

Regular red-cell transfusion is essential to inhibit ineffective erythropoiesis, to maintain adequate tissue oxygenation, for growth and to prevent extramedullary hematopoiesis and skeletal deformity [5]. However, there is a significant load of iron that is introduced into the body with every red-cell transfusion, and there is no known mechanism to remove excess iron from the body. Progressive iron accumulation then

occurs as a result of repeated transfusions [6] and of enhanced gastrointestinal iron uptake caused by reduced hepcidin levels [7]. Ferritin in the serum is readily available and is cost-effective in monitoring the iron burden but the interpretation may be affected by inflammatory conditions, liver damage, infection and short-term changes in iron distribution. Therefore it should be considered in conjunction with transfusion history, chelation use, liver iron concentration and magnetic-resonance measurement, if available [8].

The haematological picture of β-thalassemia major is a reflection of the globin-synthesis defect as well as the consequences of transfusion therapy. Hemoglobin concentration, erythrocyte count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, red-cell distribution width, leukocyte count and platelet count can offer complimentary information regarding the severity of anemia, suboptimal erythropoiesis, hypersplenism, transfusion need, and underlying inflammatory or nutritional abnormalities [9]. Anemia that persists and high erythrocyte heterogeneity may be related to insufficient transfusion support or shortened erythrocyte survival or to poor therapeutic control. The nutritional deficiencies, such as zinc, magnesium and vitamin D, and antioxidant nutrients, can further alter hematopoiesis, growth, immune regulation and oxidative balance [10].

The renal impairment phenomenon is becoming known as an important complication of β-thalassemia major, often overlooked. It is a multifactorial disease [11], with several of the above-listed mechanisms being possible factors for its pathogenesis; direct toxicity of the tubules caused by iron-chelation therapy is also a possible mechanism [12]. In susceptible patients, increased glomerular filtration can occur initially which is subsequently followed by progressive glomerular and tubular injury. Renal abnormalities have been shown to occur prior to the equivalent of any decrease in estimated glomerular filtration rate [13], as shown by using a variety of other markers such as cystatin C, urinary kidney injury molecule-1, N-acetyl-β-D-glucosaminidase, proteinuria and other conventional renal indices [14].

Both serum creatinine and urea are the most common renal markers used in the routine clinical setting; however, their limitations must be kept in mind in thalassemia. Age, sex, nutritional status, growth failure and skeletal-muscle mass affect the creatinine concentration, and a low creatinine value does not necessarily mean a better renal function in patients with low body mass [15]. The use of cystatin C can provide an alternative source of information, but may be less muscle mass-dependent and the assays are not as widely available or cheap as they are for creatinine [16]. Several other changes including erythroid turnover, oxidative stress, renal handling and chelation-induced changes can also influence the characteristics of uric acid. Thus, an integrated measure of renal biomarkers together with hematological and iron-overload biomarkers is more informative than using an individual laboratory measure [17].

Although there are increasing data on renal involvement in transfusion-dependent thalassemia, the linkage between routine hematological features, ferritin levels and classic renal markers are not well described in many resource limited populations. Population-specific biochemical patterns might be obtained because of differences in transfusion intensity, chelation regimen, nutrition, age distribution and access to specialist follow-up and to novel therapies such as gene therapy [18]. Thus, the present case–control study set to compare the various hematological, anthropometric, renal, metabolic and iron-overload markers between the β-thalassemia major patients and healthy controls.

2. Materials and Methods

2.1 Study design, participants and laboratory analysis

This analytical case–control study was carried out in the Thalassemia Centers of Fallujah Teaching Hospital and Ramadi Teaching Hospital and some private laboratories in Al-Anbar Governorate (Al-Anbar) in the period from October to December 2023. Eighty participants aged 3–25 years, 40 patients with confirmed TD β-thalassemia major and 40 apparently healthy controls were included in the study. Patients were recruited consecutively during routine clinical follow-up and controls were selected from

individuals without known hematological, renal, hepatic, inflammatory, or hereditary disorders, whose clinical records were available. β-Thalassemia major was confirmed from clinical records, transfusion dependence, complete blood count (CBC) results, and the available hemoglobin-electrophoresis or high-performance liquid-chromatography (HPLC) results. Acute infection, active inflammatory disease, CKD (not due to thalassemia), diabetes mellitus, malignancy, other hemoglobinopathies and incomplete lab data were excluded. A standardized data collection form was used to obtain demographic and clinical data such as age, sex, transfusion history, chelation treatment, relevant medical history. All measurements were taken on a calibrated digital scale (body weight), a stadiometer (height) and a body mass index (BMI) was calculated as mass in kg/m2. After 8–12 hours of fasting, about 5 mL of peripheral venous blood was drawn under aseptic conditions into a serum-separator tube, allowed to clot for about 30 minutes and centrifuged at 1,500–2,000 ×g for 10 minutes. The serum was divided into labeled aliquots and tested immediately or kept in the laboratory in proper conditions until testing. All the serum parameters (urea, creatinine, uric acid, magnesium) were measured by a validated colorimetric method with commercially available reagent kits following the manufacturers' instructions; serum ferritin was measured by a validated immunoassay method. In each analytical run, calibration materials and Internal Quality Control sera were used, and hemolyzed, very lipemic, inadequately collected or improperly stored specimens were excluded.

2.2 Statistical analysis

IBM SPSS Statistics version 25 was used for statistical analysis. Continuous variables were presented as mean ± SD where they were approximately normally distributed and median ± interquartile range (IQR) where they were skewed; categorical variables were presented as frequencies and percentages. The normality of the data was checked by Shapiro-Wilk test and graphical methods. Normally distributed continuous variables were analyzed using Independent-samples Student's t-test or Welch's t-test; the Mann–Whitney U test was used for non-normally distributed continuous variables. The chi-square test or Fisher's exact test was used for comparisons of categorical variables. All tests were two-sided, and $P<0.05$ was considered statistically significant.

2.3 Ethical approval

The study protocol was reviewed and approved by the responsible institutional research ethics committee prior to recruitment of participants and the study was carried out in line with the Declaration of Helsinki. All adult participants and all participants under 18 years of age (or age appropriate consent if applicable) gave written informed consent. Participant data was coded and treated confidentially and personal identifiers were not included in the analytical data.

3. Results

Comparative assessment of age and body mass index between the two study groups

Patients with β-thalassemia major were significantly younger than controls (12.13 ± 6.38 vs. 15.56 ± 5.71 years, P=0.013) as indicated in Table 1. Mean BMI was lower in patients than in controls (20.43 ± 4.86 vs. 22.69 ± 6.33 kg/m²), but the difference was not statistically significant (P=0.075). Thus, the groups differed in age but not in BMI.

Table 1. Sociodemographic and Anthropometric Characteristics of Patients with β-Thalassemia Major and Healthy Controls

Variable	Healthy Controls (n = 40)	β-Thalassemia Major (n = 40)	P-value
Age (years)	15.56 ± 5.71	12.13 ± 6.38	**0.013**
Body mass index (kg/m²)	22.69 ± 6.33	20.43 ± 4.86	0.075

Serum urea and creatinine concentrations in the patient and healthy-control groups

The mean value of serum urea was numerically higher in the β-thalassemia major patients when compared to the healthy control; 24.91 ± 8.64 vs. 21.86 ± 7.04 mg/dL,

respectively (P=0.087) (as presented in Table 2). On the other hand, patients had significantly lower serum creatinine levels compared to the controls (0.500 ± 0.187 vs. 0.683 ± 0.231 mg/dL, P<0.001). The lower creatinine level needs to be interpreted with caution because it could be attributed to age and/or muscle mass differences in patients rather than better renal function.

Table 2. Comparison of Renal Function Biomarkers Between Patients with β-Thalassemia Major and Healthy Controls

Variable	Healthy Controls	β-Thalassemia Major	P-value
Urea (mg/dL)	21.86 ± 7.04	24.91 ± 8.64	0.087
Creatinine (mg/dL)	0.683 ± 0.231	0.500 ± 0.187	**<0.001**

Assessment of iron-overload and mineral-status biomarkers across the two study groups

The level of serum ferritin is obviously elevated in the β-thalassemia major patients compared to healthy controls (3974.42 ± 2554.74 vs. 71.57 ± 24.73 ng/mL, P<0.001), and there is a considerable variability between patients. However, the concentrations of magnesium in the serum were similar in the patients and the controls (2.112 ± 0.249 vs. 2.143 ± 0.498 mg/dL) with no statistically significant difference (P=0.727). Because the ferritin distribution was markedly skewed, the mean ± SD values should be interpreted with caution.

Table 3. Comparison of Serum Ferritin and Magnesium Levels Between β-Thalassemia Major Patients and Healthy Controls

Variable	Healthy Controls	β-Thalassemia Major	P-value
Ferritin (ng/mL)	71.57 ± 24.73	3974.42 ± 2554.74	**<0.001**
Magnesium (mg/dL)	2.143 ± 0.498	2.112 ± 0.249	0.727

Evaluation of purine-metabolism differences between patients with β-thalassemia major and healthy individuals

The mean serum uric acid concentration was significantly higher in the patients with β-thalassemia major than in healthy controls (4.80 ± 1.93 vs. 2.82 ± 1.40 mg/dL, P<0.001) as demonstrated in Table 4. This discovery represents a significant difference between the groups in purine metabolism, which may be related to increased erythroid turnover and destruction of erythroid precursors. The cross-sectional comparison however, is insufficient to conclude that the increase in uric acid concentration is directly caused by the presence of β-thalassemia.

Table 4. Comparison of Serum Uric Acid Levels Between β-Thalassemia Major Patients and Healthy Controls

Variable	Healthy Controls	β-Thalassemia Major	P-value
Uric acid (mg/dL)	2.82 ± 1.40	4.80 ± 1.93	**<0.001**

4. Discussion

The present study found significant biochemical differences between patients with β-thalassemia major and healthy controls with special regards to the serum ferritin, uric acid, and creatinine levels. The age difference between the groups, however, needs to be carefully interpreted as it may influence BMI and serum creatinine due to age, growth, muscle mass, and pubertal development. Because no age- and sex-adjusted analysis was performed, and highly skewed biomarkers such as ferritin were summarised as means, the between-group comparisons should be interpreted with caution.

Patients were significantly younger than controls, and had a nonsignificant tendency to lower BMI. Impaired growth occurs in about half of the transfusion-dependent β-thalassemia patients [19] and may be due to chronic anemia, tissue hypoxia, iron-induced endocrine dysfunction, delayed puberty, nutritional deficiency, and chelator toxicity [20]. Recent research has reported growth retardation, decreased growth velocity, weight loss, and decreased bone development in affected children and adolescents, especially in the presence of iron overload or poor transfusion control [21]. However, the lack of a significant BMI difference in the present study was in accordance with the results of other studies which have reported that modern transfusion/chelation programs can maintain body mass while linear growth remains impaired [22]. Variability between studies might be caused by variations in age composition, frequency of transfusion, socioeconomic/nutritional factors, endocrine involvement, and chelation compliance. BMI is also not an ideal metric for children as it needs to be compared to age and sex specific percentile or z-scores, not adult values.

The serum urea level was higher, but not significant, in the patients. This suggests that the excretion of nitrogenous waste was not markedly impaired. In contrast, patients had significantly lower serum creatinine. The low concentration of creatinine should not be interpreted as an indication of improved renal function as skeletal muscle mass, nutritional status, age and growth are all important factors affecting the production of creatinine, as noted in the Introduction. This may be because the younger patients were smaller. Apparently normal or low levels of creatinine have been reported in studies of transfusion-dependent thalassemia with such findings as glomerular hyperfiltration, tubular injury, proteinuria, increase of cystatin C, and increase of urinary kidney injury molecule-1 [23]. These findings corroborate the hypothesis that the creatinine clearance is underestimated in early renal impairment in thalassemia.

However, some published reports have shown an elevation in creatinine or decrease in the estimated glomerular filtration rate in older individuals with older disease duration [24]. This discrepancy could be accounted for by the cumulative exposure to iron, chelator nephrotoxicity, diabetes, cardiac dysfunction, and renal reserve loss due to aging. Creatinine elevation and renal tubular abnormalities have been reported in susceptible patients treated with deferasirox, but these changes are reversible; younger patients with low muscle mass may have misleadingly low creatinine levels [25]. Thus, in the future, an evaluation should be based on the use of creatinine, cystatin C, urine albumin-to-creatinine ratio, β_2-microglobulin, KIM-1, and calculated filtration estimates. The current recommendations for kidney function also suggest that for the assessment of kidney function, the simultaneous estimation of creatinine and cystatin C is preferable, where creatinine is likely to be affected by reduced muscle mass [26].

The highest result was the mean ferritin approximately 55 fold higher among patients. This is biologically feasible as frequent transfusion provides large amounts of iron, and ineffective erythropoiesis leads to a decrease in hepcidin secretion and iron absorption in the gastrointestinal tract [27]. Other studies have found significantly higher ferritin levels in transfusion-dependent patients [28], with levels depending on the amount of transfusion history, chelation compliance, hepatic iron stores and endocrine or cardiac complications [29]. The very large standard deviation seen here suggests that there is a lot of variability in the amount of iron overload, which may be due to variable durations of transfusion, variable chelation treatments, variable compliance, inflammatory states, liver damage and the presence of splenectomy.

However, ferritin is also an acute-phase reactant and is not a good reflection of total body iron stores. In some cases, there is only a moderate correlation between serum ferritin and the liver or cardiac iron measured by MRI, especially if the liver is injured or infected or if there is inflammation [30]. These results appear contradictory due to the double role played by ferritin (iron storage and inflammatory activity) and to the direct estimation of tissue iron by MRI. Thus, the present ferritin levels are a good indicator of iron overload at the group level but cannot be used as a sole criterion to define the individual organ iron burden. Because the ferritin data were highly skewed, future analyses should report the median and interquartile range rather than the mean ± SD.

Groups did not differ significantly in their level of magnesium. This is in line with studies showing preserved serum magnesium levels with chronic transfusion, due to the fact that the magnesium in serum is tightly regulated, and only a small portion of total body magnesium stores [31]. Other studies, however, have found low levels of magnesium in β-thalassemia, which has been proposed to be due to renal tubular abnormalities, dietary deficiency, endocrine abnormalities, oxidative stress, or chelation-induced mineral depletion [32]. These discrepancies can be attributed to the different dietary intake, hemolysis, kidney function, type of chelators, and analytical method used. Intracellular or ionized magnesium and urinary magnesium excretion may show disturbances that would not be detected by the total serum magnesium.

The uric acid level of the patients was significantly elevated in serum. This discovery is consistent with enhanced purine production related to impaired erythropoiesis, increased erythroid activity and increased erythroid precursor destruction [33]. Increased urate production may result from oxidative stress, tissue hypoxia, tubular handling, and high cell turnover. However, normal uric acid reported by studies may be those who were younger, who had less transfusion exposure, more effective chelation, other diets, or maintained renal excretion. However, other factors, such as renal function, medications, hydration, and metabolic factors, can also contribute to the development of hyperuricemia, so it cannot be solely blamed on thalassemia [34].

5. Conclusion

Together, these findings suggest high iron loading and different levels of purine metabolism, with a low serum creatinine level which may reflect age and muscle loss, rather than better kidney function. The cross-sectional design, small sample and age imbalance between groups which make the findings difficult to interpret and to generalise. Longitudinal studies in the future should include additional parameters such as transfusion history, chelation history, inflammatory markers, liver magnetic resonance imaging with or without ferritin, cardiac magnetic resonance imaging, age adjusted anthropometric indices, tubular injury biomarkers, to further elucidate the relationship between iron overload, growth, and early renal injury.

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