SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 8.
Issue: 11
Page N. 188-193
Year: 2024

Original Article www.wjahr.com

RENAL COMPLICATIONS IN THALASSEMIC PATIENTS

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Article Received date: 23 September 2024 **Article Revised date:** 14 October 2024 **Article Accepted date:** 02 November 2024

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ABSTRACT

Background: Thalassemia is a genetic disorder causing erythrocyte hemolysis, ineffective erythropoiesis, and iron overload. Renal disease in thalassemia is a multifactorial process involving iron overload, urinary iron loss, ineffective erythropoiesis, and chronic hepatitis C infection. Early detection of renal dysfunction is crucial for both patients and their caregivers. **Aim:** To compare the serum and urinary renal function parameters between the thalassemic patients and normal health individuals. **Patients and Methods:** The study involved 194 individuals with β-thalassemia, with 97 admitted to Al-Hadbaa Hospital in Nineveh province, Iraq, and 97 healthy controls. Data collection included age, sex, blood transfusion frequency, urinary symptoms, and iron-chelating agent treatment. The study followed ethical principles and was approved by the Nineveh DOH's Ethical Committee of Research. Venous blood was collected, and biochemical variables like blood urea nitrogen, creatinine, uric acid, phosphorus, magnesium, and calcium levels were measured. Renal USG was performed for all patients. **Results:** The study involved 97 patients with thalassemia, with 85.6% being thalassemia major and 14.4% being thalassemia inter. Urinary parameters showed significant differences between cases and controls, with lower creatinine, higher calcium, and higher urinary protein. Serum parameters showed higher ferritin levels and Hb levels among cases, but no significant differences were found between thalassemia major and inter. **Conclusion:** The study found significant changes in urinary and serum parameters in thalassemic patients, affecting creatinine, calcium, protein, ferritin, and hemoglobin levels, but no significant differences were observed between thalassemia types.

KEYWORDS: Renal Complications, Thalassemia Inter, Thalassemia Major.

INTRODUCTION

Thalassemia is one of the most common genetic disorders in the world. The underlying mechanisms of thalassemia are a mutation or deletion of the human globin genes. The thalassemia forms are alpha-thalassemia and beta-thalassemia. There are certain consequences of these technical abnormalities.[1] Hemolysis of the erythrocytes, ineffective erythropoiesis, and imbalance of the globin chain production leading to tissue hypoxia and the accumulation of inert iron in the body are some of these. Additionally, secondary hemochromatosis developing as a result of increased non-transferrin bound iron content in the body is observed in the severe forms of thalassemia. In recent years, developing tissue iron overload and related complications have been prevented by iron chelation therapy. The management and prevention of thalassemia complications significantly impact the patient's quality of life.[2, 3]

Renal complications are important reasons for the morbidity and mortality seen in thalassemic patients. Although glomerular, tubular, and endocrine problems are associated with renal complications developing secondary to iron overload, the base mechanism has not been clarified precisely.[4,5] The most important mechanism is cytotoxicity and the production of inflammatory cytokines released when tissue toxic free oxygen radicals increase as a result of iron overload. Another important parameter causing renal complications is iron toxicity. The way thalassemia is developing and especially the improvement in prognosis in recent years makes specialists encounter long-term organ complications more frequently. Therefore, renal complications developing in secondary hemochromatosis seem to be an important health problem. In this chapter, we will examine the renal complications in beta-thalassemic patients. We decided to develop this study because of the increased risk of these complications in contemporary times. The most important step for both

beta-thalassemia patients and their caretakers is watchfulness.[4]

Renal disease in thalassemia is a multifactorial process involving iron overload on the kidney, urinary iron loss, ineffective erythropoiesis, and chronic hepatitis C infection. Renal dysfunction is common in thalassemia, and it becomes overt or can be detected early based on the thalassemia type and other laboratory results. Elevated serum creatinine and urea and/or reduced renal function tests were the main findings.[6, 7] There are some techniques that can help in the detection of the functional and/or structural abnormalities. The recommended diagnostic strategy for chronic kidney disease in thalassemic patients included at the very least the analysis of serum markers and blood concentration of various iron-related molecules, together with urinary retinol binding protein, microalbumin, and beta-2 microglobulin, and complete blood count.[4]

Aim of the study

To compare the serum and urinary renal function parameters between the thalassemic patients and normal health individuals.

Patients and Methods

A total of 194 people participated in the current case-control research, 97 of them were patients admitted to Al-Hadbaa Hospital in the Iraqi province of Nineveh. A total of 97 healthy individuals who were matched for age and sex made up the control group. The sample size was determined by taking into account prior research that was detailed in a meta-analysis.[8]

Ethical Considerations. This study was performed based on to the World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. This study was approved by the Ethical Committee of Research of Nineveh DOH (number:; date:). Before enrollment, the participants and their guardians were fully informed of the research purpose and written consent was obtained. They were assured that their personal information would be confidential.

Data collection: Patients with β-thalassemia were asked to provide all of their clinical information, including their age at diagnosis, age at presentation, sex, number and frequency of blood transfusions, urinary symptoms, and iron-chelating drug therapy. Additionally, each patient's diagnosis of thalassemia type—that is, thalassemia major (TM) or thalassemia (TI)—was documented. Those with β-thalassemia who were on diuretic therapy, had a history of renal pathology, such as nephrotic syndrome, systemic illnesses (cardiac complications, thyroid diseases, hepatic diseases, or diabetes mellitus), or had taken nephrotoxic medications, such as corticosteroids, trimethrim, or cephalosporin, within the previous week were not allowed to participate in this study.

Methods: Under controlled circumstances, venous blood was drawn from both patients and controls. For hemoglobin (Hb) analysis, a portion of each blood sample was placed in ethylenediamine tetraacetic acid (EDTA) tubes; the remaining fraction was moved to plain tubes for the remaining biochemical studies. Following sera separation, specimens were either frozen until analysis within two days or subjected to rapid analysis. The Sysmex™ Automated Hematology Analyzer KX-21N (Sysmex Corporation, Kobe, Japan) was used to measure the Hb level.

The Automated Clinical Chemistry Analyzer, Cobas INTEGRA 400 plus (Roche, Germany), was used to assess the biochemical variables: blood urea nitrogen (BUN), serum creatinine (Cr), serum uric acid (UA), serum phosphorus (Ph), serum magnesium (Mg), and serum calcium (Ca). Flame photometry was used to determine the amounts of potassium (K) and sodium (Na) in the blood. Additionally, using bioMérieux kits (France), the serum ferritin (mg/l) level was measured using a MINI VIDAS system.

Both the patients and the controls were afebrile when urine samples were taken from first-morning urination specimens. First, the RBC and WBC in the urine were measured using a urine dipstick or under a microscope. The urine samples were then kept at -4°C until they were analyzed to determine the urinary parameters. The same techniques used to estimate the serum levels were also used to estimate the urine Ca, Mg, Ph, UA, and Cr levels. In comparison, the Automated Clinical Chemistry Analyzer ARCHITECT plus c4000 (Abbott Laboratories, USA) was used to analyze the amounts of albumin, Cr, Na, and K in the urine.

Every step was carried out exactly as the manufacturer had instructed. Each urinary variable was then divided by its urine Cr value to get the urinary Na/Cr, K/Cr, Ca/Cr, Mg/Cr, Ph/Cr, UA/Cr, and urinary albumin/Cr ratios for each participant (patients and controls). A 24-hour urine collection from these people was challenging, hence these urinary variables were calculated as ratios. To determine the size of the kidneys and the existence of renal stones, renal USG was done on every patient who was recruited in the trial.

Statistical analysis

The t-test for independent two means was used to compare the parameters between the studied groups through SPSS-26.

RESULTS

The study sample included 97 patients with thalassemia; 85.6% of them was thalassemia major and only 14.4% was thalassemia inter as shown in figure (1).

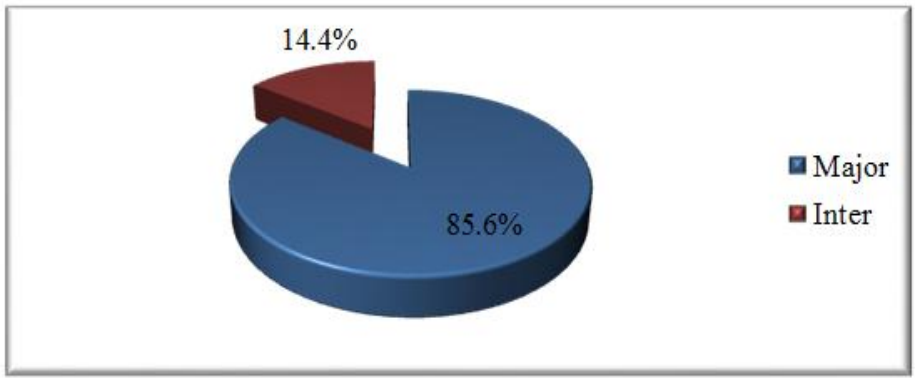

Figure (1): Types of thalassemia among the patients under the study.

The distribution of the studied patients according to the clinical features and predisposing factors was demonstrated in figure (2). This figure showed that splenectomy was found among 14 patients, dysuria found in 17 patients, loin pain in 13 patients. No one of the patients used drugs or chronic disease.

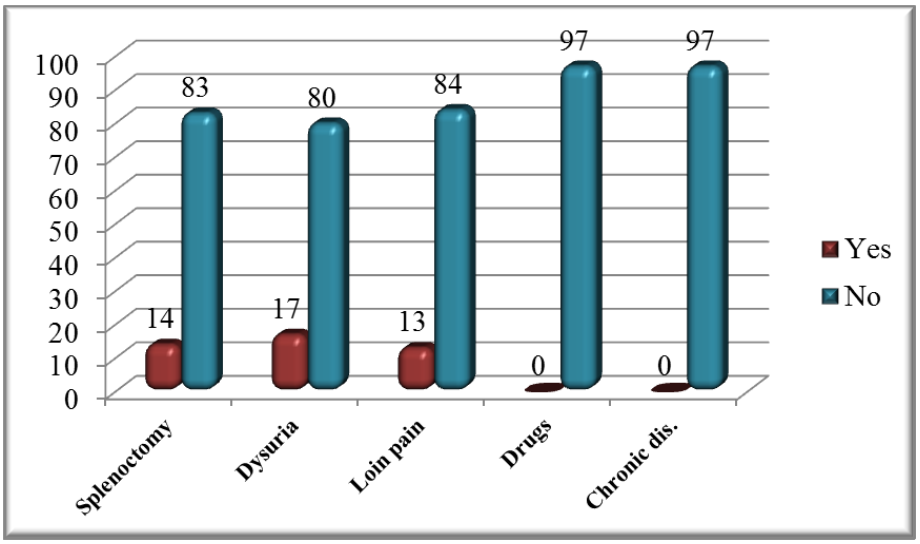

Figure (2): Distribution of the patients according to clinical features and predisposing factors.

The comparison of the urinary parameters between cases and controls was demonstrated in table (1) and revealed that urinary creatinine among the cases (63.01±25.360) was lower than that among the control (73.34±24.277) in a statistically significant way (p=0.004). The urinary calcium was significantly (p=0.033) higher among cases (3.22±2.176) than among the control (2.63±1.618). Concerning the urinary protein, among the cases it was (25.65±7.838) while among the control, it was (19.16±6.212); the difference was statistically significant (p=0.000). The other parameters showed no significant differences.

Table (1): Comparison of the urinary parameters between cases and controls.

Urinary parameters	Cases (n=97)	Control (n=97)	p-value*
	Mean± SD	Mean± SD	
U. Creatinine	63.01±25.360	73.34±24.277	**0.004**
U. Urea	31.45±8.168	30.58±6.899	0.426
U. Na	91.73±32.327	93.72±28.920	0.652
U. K	38.46±11.347	35.75±10.036	0.080
U. Ca	3.22±2.176	2.63±1.618	**0.033**
Ur. Phosph	3.10±0.566	2.96±0.523	0.076
U. Mg	2.55±0.286	2.52±0.270	0.476
Uric acid	47.67±12.190	47.07±8.981	0.698
Urinary Protein	25.65±7.838	19.16±6.212	**0.000**
**Independent t- test for two means*			

Table (2) showed the differences between cases and controls concerning the serum parameters, and depicted that the ferritin level among the cases was significantly higher than that among the controls (p=0.000), while the Hb level was 8.72±1.199 and 12.07±1.845 among the cases and control respectively; this difference was statistically significant (p=0.000). No significant differences were found regarding the other parameters.

Table (2): Comparison of the serum parameters between cases and controls.

Serum Parameters	Cases	Control	p-value*
	Mean± SD	Mean± SD	
S. Creatinine	0.43±0.162	0.40±0.134	0.213
Bl. Urea	25.06±5.924	23.94±4.977	0.158
S. Na	142.23±2.617	142.31±2.686	0.829
S. K	4.11±0.340	4.99±5.996	0.152
S. Ca	2.38±0.122	2.40±0.109	0.210
S. Phosph	1.23±0.145	1.24±0.145	0.871
S. Mg	1.97±0.093	1.94±0.142	0.120
S. Uric acid	3.99±1.090	3.77±0.822	0.105
Ferritin	3594.45±2616.335	71.18±175.026	**0.000**
Hb	8.72±1.199	12.07±1.845	**0.000**
**Independent t- test for two means*			

Comparison of the urinary parameters between the types of thalassemia was demonstrated in table (3) and showed no significant statistical differences.

Table (3): Comparison of the urinary parameters between the types of thalassemia.

Urinary parameters	TI (n=14)	TM (n=84)	p-value*
	Mean± SD	Mean± SD	
U. Creatinine	63.64±26.473	62.90±25.333	0.920
U. Urea	31.35±8.025	31.46±8.240	0.962
U. Na	87.50±28.413	92.44±33.044	0.599
U. K	42.07±11.425	37.85±11.290	0.200
U. Ca	3.66±1.896	3.14±2.221	0.417
Ur. Phosph	3.26±0.518	3.08±0.572	0.263
U. Mg	2.56±0.322	2.54±0.281	0.847
Uric acid	51.07±8.999	47.09±12.603	0.261
Urinary Protein	26.85±8.690	25.45±7.724	0.539
**Independent t- test for two means*			

No significant statistical differences were found between thalassemia major and thalassemia inter concerning the serum parameters as shown in table (4).

Table (4): Comparison of the serum parameters between the types of thalassemia.

Serum parameters	TI (n=14)	TM (n=84)	p-value*
	Mean± SD	Mean± SD	
S. Creatinine	0.47±0.174	0.42±0.160	0.288
Bl. Urea	24.92±6.094	25.08±5.932	0.928
S. Na	143.00±2.287	142.10±2.659	0.240
S. K	4.27±0.380	4.09±0.327	0.059
S. Ca	2.34±0.137	2.39±0.118	0.110
S. Phosph	1.19±0.148	1.24±0.145	0.254
S. Mg	3.95±0.713	4.00±1.145	0.887
S. Uric acid	1.94±0.148	1.97±0.080	0.193
Ferritin	3388.28±2131.31	3629.22±2699.12	0.752
Hb	8.65±0.993	8.73±1.235	0.821
**Independent t- test for two means*			

DISCUSSION

Scientific study has already focused on beta-thalassemia, one of the most prevalent genetic illnesses in Asia[9], as well as most other countries of the world. The homozygous status of one of the hemoglobin Lepore or thalassemia genes during infancy or childhood causes a range of severe and inherited illnesses known as thalassemia syndromes).[10]

Of the 97 thalassemia patients in the research sample, 85.6% had thalassemia major and only 14.4% had thalassemia inter. In the current study, the patients' urine creatinine levels were lower than the control group's. Cases had a noticeably greater urine calcium level than the control group. In terms of urine protein, the cases had greater levels than the control group. The Hb level was lower in the cases than in the controls, while the ferritin level was noticeably greater in the cases than in the controls. Clinical and laboratory results were utilized to evaluate renal impairment in patients with TM and TI in the case-control research by Shaalan *et al.*,.[11] Higher urine Na/Cr, K/Cr, Ca/Cr, Mg/Cr, Ph/Cr, UA/Cr, and albumin/Cr ratios in patients compared to controls showed irregular renal tubular and glomerular function in children and adolescents with β-thalassemia, according to the research. Nonetheless, there was no discernible difference between individuals with TM and TI in terms of serum and urine renal indicators. Conflicting findings have been reported by several researchers. For instance, Mahmoud *et al.*[12] found no significant change in serum Na and Ca between the two groups, but a substantial rise in blood urea, Cr, and K in β-TM patients as compared to the controls. Additionally, they discovered that β-TM patients had significantly higher urine UA/Cr, U Ca/Cr, U albumin/Cr, and UK/Cr than the controls. Aside from a greater urine protein/Cr ratio in thalassemia patients, Şen *et al.*[13] also found no significant difference in serum urea, Cr, or serum and urine electrolyte (Na, K, Ca, and Ph) values between patients and controls. Simultaneously, Hamed *et al.*,[14] found that the β-thalassemia patients had substantially higher urine albumin/Cr, Ca/Cr, UA/Cr, and Ph/Cr ratios as well as serum Cr, serum phosphate, and serum UA levels than the controls.

In investigations by Aleem *et al.*[15], Abdalla *et al.*[16], and Karimi *et al.*[17], patients with beta-thalassemia had substantially lower serum calcium levels ($P<0.05$) than the controls. This study found a low amount of magnesium, and hypomagnesemia can be explained by reduced thyroid hormones brought on by iron excess.[18]

Measurements of potassium and sodium levels have shown that beta-thalassemia patients had slightly greater potassium and slightly higher sodium levels than controls. These variations in potassium and sodium levels in the serum are not statistically significant ($P>0.05$). These results are comparable to those of previous scientific investigations.[19, 20]

Patients with red blood cell hemolysis have elevated potassium levels, which can happen in stored blood that is transfused to the patient because potassium tends to seep out of the RBC in stored blood.[19] Iron overload-induced renal injury may be the cause of elevated sodium levels in beta-thalassemia patients.[20] Abdalla *et al.*[16] discovered that a high creatinine level signifies a very low kidney functional capability; nevertheless, more research is required to support them. The concurrent iron excess in individuals with β thalassemia has also been linked to renal problems.[21] Clinical studies demonstrated relationships between serum ferritin and markers of tubular injury.[22] Surprisingly, many studies attributed renal dysfunction in β thalassemia to the use of iron chelation therapy, demonstrating their deleterious effect on tubular function and increases in serum creatinine.[23]

CONCLUSION

The thalassemic patients had changes in their urinary and serum parameters. In this study, the changes were significant concerning the urinary creatinine, urinary calcium, urinary protein, serum ferritin, and Hb. There were no significant differences between the types of thalassemia regarding the urinary and serum parameters.

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