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RESEARCH PAPER

Hematological and biochemical status of βeta-thalassemia major patients in Koya city.

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A B S T R A C T:

Thalassemia major is a severe anemia that requires blood transfusions. In this study, we searched into the hematological and biochemical status of βeta-thalassemia major patients in Koya. Hematological analysis revealed severe anemia in βeta-thalassemia patients when compared to controls. The hemoglobin levels in patients were less than 30% of that of controls. Furthermore, patients had a significant leukocytosis compared to the controls. Red blood cell incidences are decreased except RDW, which were Hct includes (23.8±2.9 % vs. 34.6±2.3 %), MCV (71.8±7.1 fl vs. 77.5±4.1 fl), MCH (20.2±2.4 pg vs. 23.5 ± 2.2 pg) and MCHC (30.8±0.7 g/dl vs. 30.1±1.2 g/dl), while RDW % (20.5±9.7 % vs. 14.2±2.5 %). The linear regression analysis showed non-correlation between iron overload with RBC, WBC, and red blood cell incidences (hemoglobin (Hb), hematocrit (Hct), mean corpuscle hemoglobin (MCH), and mean corpuscle hemoglobin concentration (MCHC), while PLT count, mean corpuscular volume (MCV) and red cell distribution width (RDW) showed a significant positive correlation with iron overload. The biochemical characteristics of the patients showed a significant increase in the levels of liver enzymatic parameters, ALP, ALT, and AST as compared to controls.

KEY WORDS: Anemia, βeta-thalassemia major, Hematological change, Biochemical change.
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1. INTRODUCTION:

Thalassemia is a term referring to a class of genetic disorders caused by inadequate hemoglobin development, with a deficiency in hemoglobin synthesis. It is sometimes referred to as Mediterranean anemia. Thalassemia impacts European, African, and Asian people [1, 2].

Thalassemia is one of the world's most severe genetic disorders. It is the most common cause middle east persistent hemolytic anemia [3, 4]. In some nations, the distribution of beta thalassemia major appears dependent on ethnics and community relationships [5]. In order to understand how thalassemia influences the human body, we first need to understand how blood lais created. If the body does not generate enough globin alpha and beta chains, the red blood cells will not shape correctly and will not be able to carry enough oxygen. The effect is anemia that begins in early childhood and persists for life. Genes involved are those regulating the development of hemoglobin-containing alpha and

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beta-globin [6]. Thalassemia may be identified by signs or by the impaired genes. The two major forms of thalassemia, alpha, and beta, are named for the two normal adult hemoglobin protein chains [7]. Beta thalassemia major is an inherited defect hemolytic state in the synthesis of the beta-globin chain, individuals with beta-thalassemia major usually present with severe anemia in the first two years of life, requiring regular transfusions of red blood cells (RBCs) to survive in life [8]. Impaired beta-globin biosynthesis contributes to an aggregation of unpaired alpha-globin string, the shorter life span of red cells, and iron deficiency triggering functional and physiological defects in many organ systems such as the pancreas, which lead to diabetic in some of the patients [9, 10]. The purpose of this study was to compare the liver function parameters, kidney function parameters, and hematological features of beta-thalassemia patients to a control group of children from Koya City.

2. MATERIALS AND METHODS

2.1. Study design:

The present investigation consists of 86 subjects divided equally between two groups as shown in (Figure 1), the first group consists of 43 β-thalassemia major children currently being transfused and managed for the clinical symptoms and manifestations of the disease at the Shaheed Dr. Khalid Teaching Hospital, and the second group consists of healthy control study design. No significant differences appear in the ages between patients and control groups The controls were patient age and sex-matched, the mean patient age (9.1±2.2 years) and the controls (8.8±1.9 years) of this study. Six 6 Milliliters of venous blood samples were collected from each patient with a disposable syringe prior to the planned blood transfusion. This was then used to predict checks on hematological and biochemical parameters.

2.2. Collection of data:

The analysis included 43 transfusion-dependent β-thalassemia majors of different ages and communities from different regions and villages in Koya. Both patients receive a daily transfusion of blood. Several patients underwent splenectomy and had additional iron deficiency surgical problems.

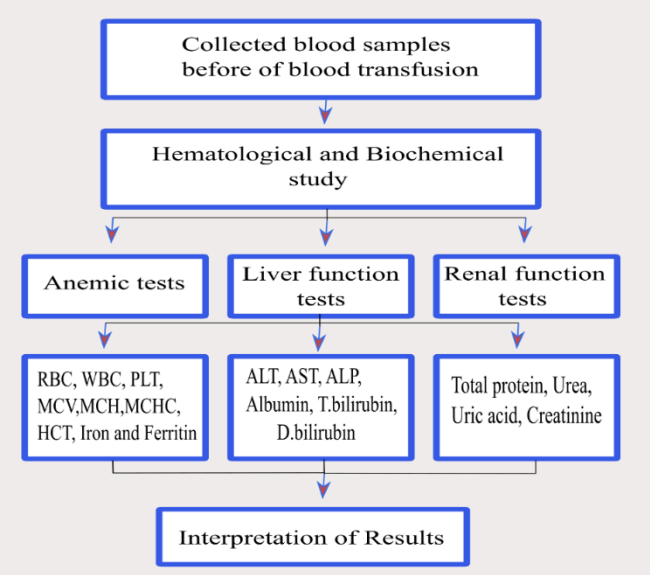

Figure 1. general design of the research.

In addition, the research data collected for the type of causative mutation, biochemical and hematological parameters of the β-thalassemic minor by questionnaire and blood test examination. Before blood transfusion, the consultation with the patients and their caregivers and relatives was held in Shaheed Dr. Khalid's general hospital. Specific information is taken from each person at the point of thalassemia diagnosis, including name, sex, race, residency, and education, in general, whether it was before or after one year of age. A detailed and thorough record of the disease provided then asked questions about the family history, which included consanguinity between parents (Figure 2), number of infected and unaffected children, number of dead siblings of any thalassemic kin.

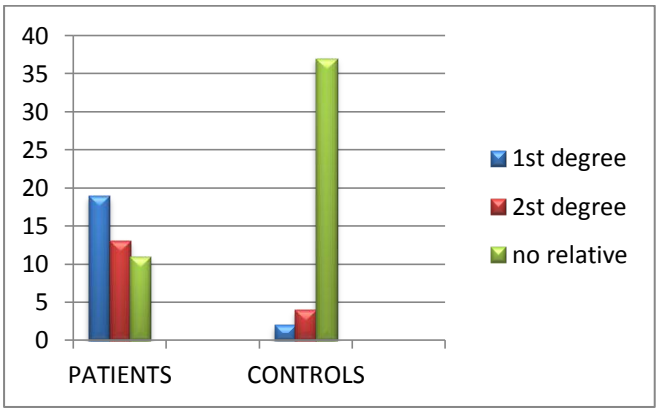

Figure 2. Degree of consanguinity among patients.

In general, data relating to blood transfusion (the total number and rate of blood transfusion and any transfusion-related complications) and chelation

therapy (chelation sort and regularity) were analyzed. Splenectomy was specifically asked about it and its pacing. Anemia, physical improvements, and skin pigmentation were then investigated by each person. In their visiting hours, they asked to fill out a survey application of medical review and before blood transfusion. Forty-three of the healthy people from various Koya groups (without Hemoglobin disorders) are spontaneously aged and paired with the patient populations used as a control group.

2.3. Biochemical analysis:

Fully automatic chemical analyzer used to evaluate biochemical parameters (Human Star-180), hematological parameters: blood samples are analyzed for blood parameters using a fully automated hematological analyzer in accordance with the protocol of the manufacturer. On the day the blood samples were taken, the hematological parameters (WBC, RBC, Hb, Plt, Hct, and MCV, MCH, and MCHC) are evaluated.

2.3. Statistical analysis:

The current study data were expressed as mean, a standard mean deviation (Mean ± S.D.M) and statistical software (SPSS) (Version 20) was used to analyze the data. Two T-test samples (independent student t-test between healthy and thalassemia patients and paired sample t-test between male thalassemia and female thalassemia) and correlation coefficient were used to analyze differences in mean values between 2 groups. The level of significance of P-value ($P<0.05$) was probably considered statistically significant.

3. RESULTS

Approximately 44% of the major children's parents with β-thalassemia are first-degree cousins compared to the control group with a percentage of less than 5%. In fact, the percentage of 2nd degree consanguineous marriages in the patient groups is significantly higher than that of the control group, 30.2 %, and 9.3 % respectively. The general characteristics of the study groups mentioned in (Table 1A).

3.1. Clinical characteristics of thalassemia

The general and clinical characteristics of the patients are summarized in (Table 1B) which revealed that the majority (67.4%) of the patients are receiving a blood transfusion every 2-3 weeks and 29.9 % every 4 -5 weeks. While only two patients (4.6%) require transfusion at longer intervals, more than 5 weeks.

Table 1A. General characteristics of the studied population.

Variables	Patients group (n=43)		
Age / year	Male	Female	Total
	8.9±2.3	8.8±1.4	9.1±2.2
Number	23	20	43
Percentage	53.48	46.51	100
Parents consanguinity	**Patients group (n=43)**		
Degree of consanguinity	1st degree	2nd degree	No relative
Number	19	13	11
Percentage	44.1	30.2	25.5
Results expressed as Mean ±SD			

Table 1B. General characteristics of the studied population.

Variables	**Controls group (n=43)**		
Age / year	Male	Female	Total
	9±2.3	8.7±3.1	8.8±1.9
Number	23	20	43
Percentage	53.48	46.51	100
Parents consanguinity	**Patients group (n=43)**		
Degree of consanguinity	1st degree	2nd degree	No relative
Number	2	4	37
Percentage	4.6	9.3	86.0
Results expressed as Mean ±SD			

Splenectomies thalassemic patients represented only 20.9% of the cases. Regarding iron chelation of the patients withdraw the overloaded iron through the subcutaneous pumps (deferral pumps) used by 46.5%, of the patients, through intramuscular infusion about 34.8%, while intravenous infusion about 11.6% and oral chelation (X-Jade) of iron is used by 6.9% of the patients. The presence of other thalassemic patients within the same family (brothers or sisters) is obvious and 67.3% of the current patients have other thalassemic brothers and /or sisters **(**Table 2).

Table 2. Clinical characteristics of thalassemia.

Period of transfusion	**Number**	**% Percentage**
2-3 weeks	29	67.4
4-5 weeks	12	27.9
More than 5 weeks	2	4.6
Iron chelation	**Number**	**% Percentage**
Desferal pump	20	46.5
Intramuscular infusion	15	34.8
Intravenous infusion	5	11.6
Oral (x-Jade)	3	6.9
Splenectomy	**Number**	**% Percentage**
Yes	9	20.9
No	34	79.0
Thalassemic brothers/sisters	Number	% Percentage
0	14	32.5
1	17	39.5
4	3	6.9
2	9	20.9

3.2. Incidence of the thalassemia

3.2.1. Distribution of age and sex:

Age ranged among the patient populations (1-19 years), 8 patients between the ages (1-4 years), 18 patients between the ages (5-9 years), 11 patients between the ages (10-14 years) and 6 patients between the ages (15-19 years), 53.4% male and 46.5% female.

3.2.2. Family history of thalassemia:

Twenty-one (48.8%) recruited patients had another sibling (either alive or deceased) or thalassemia relative and 22 (51.1%) patients had no sibling or thalassemia relative affected (either alive or deceased).

3.2.3. Age at first diagnosis:

Twenty-six (60.4 percent) of the recruited patients were diagnosed before two years of age, while the diagnosis was rendered after two years of age in the remaining patients.

3.2.4. Skeletal changes:

All patients assessed for skeletal changes and such changes were noted in 17 cases (39.53%) and included facial bone expansion characteristics, large skull, frontal bone bossing. Such bone modifications in the remaining 26 (60.46 percent) patients have been of varying degrees, ranging from mild to severe degrees, with no apparent or major structural shifts.

3.2.5. Skin pigmentation:

Skin pigmentation was observed in 19 patients (44.18%) which varied from a slight increase in skin pigmentation to very dark-colored skin, especially in the face and hands, and 23 remaining patients (53.48%) retained normal skin pigmentation.

3.2.6. Viral hepatitis assessment:

Most thalassemia patients checked for hepatitis B and C specifically for whole blood using a hepatitis B and C strip of the 43 patients surveyed, 27 patients tested positive for hepatitis C were nearly (62.7 percent), while none of our patients tested positive for hepatitis B.

3.3. Pre-transfusion levels of hemoglobin:

Pre-transfusion levels of hemoglobin were available in 36 (83.7%) of patients enrolled. The pre-transfusion distribution of hemoglobin levels in these patients and indicates that it was below 9 gm / L in 20 patients (66.6%) and below 16 gm / L in 12 patients (33.3%).

3.3.1. Hematological features of thalassemia:

Both complete blood counts parameters and red blood cell indexes in patients with beta-thalassemia assessed in this analysis have identified important issues. Compared to healthy controls, a severe anemic presentation was seen in patients. The rate of hemoglobin in patients decreased to about 30 percent of the amount reported in healthy controls,8.0±1.0 g / dL vs. 11.4±0.8 g / dL, while the incidence of red blood cells decreased with the exception of RDW, which included Hct (23.8±2.9 vs. 34.6±2.3), MCV (71.8±7.1fl vs. 77.5±4.1fl), MCH (20.2±2.4 vs. 23.5 ± 2.2), MCHC (30.8±0.7 vs. 30.1±1.2), and RDW percent (20.5±9.7 vs. 14.2±2. In contrast, severe leukocytosis was also found in patients relative to healthy controls 11.8 ± 4.6 vs.7.1±2.2 X 109/L, and linear regression testing was used in the current study to assess the association between blood cell rates (RBC, WBC, and PLT) and incidences of red blood cells (Hb, Hct, MCV, MCH, and MCHC) of iron excess concentrations

in thalassemia. no correlation was found between RBC and iron (r = - 0.036, P = 0.410), also for WBC no correlation was found with iron (r =0.069, P =0.030), while for PLT significant (r = 0.292, P = 0.029) positive correlation was found with iron, whereas for red blood cell incidences there is no correlation between blood cell incidences (Hb, Hct, MCH , MCHC and RDW) and iron, except MCV and RDW blood cell incidence, which have a significant positive correlation with iron overload (Table 3), (Table 4), and (Figure 3).

Table 3. Correlation between RBC incidences and iron overload.

	Iron overload	
parameters	Pearson correlation (r)	P-value (p)
Hb	r= - 0.036	P = 0.410
Hct	r= - 0.069	P =0.330
MCV	r= 0.232	P = 0.029
MCH	r= - 0.036	P = 0.410
MCHC	r= 0.069	P = 0.330
RDW	r= 0.292	P = 0.029

Table 4. Correlation between blood cell and iron overload.

	Iron overload	
parameters	Pearson correlation (r)	P-value (p)
RBC	r= - 0.036	P = 0.410
WBC	r= 0.069	P = 0.330
PLT	r= 0.292	P = 0.029

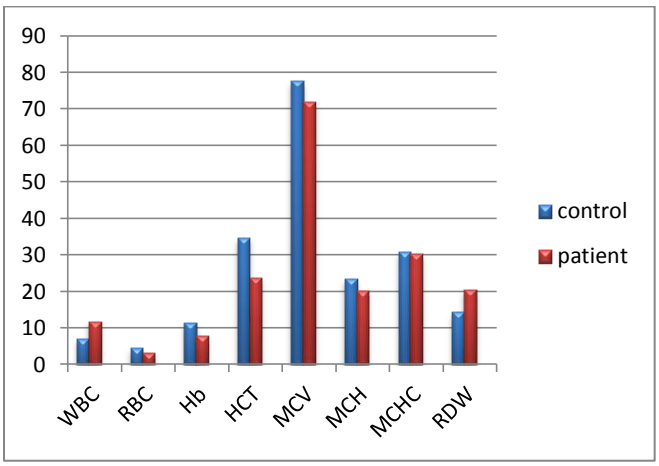

Figure 3. Hematological changes in thalassemia.

3.4. Biochemical characteristics of thalassemia

3.4.1. Renal function test parameters:

The results of the current study showed a significant decrease in serum total protein and serum creatinine levels in beta-thalassemia patients (6.1±0.6g / dl, 0.43±0.07mg / dl) compared to healthy controls of the same age and sex (6.9±0.4 g / dl, 0.51±0.9mg / dl), while thalassemia patients showed a significant increase in serum uric acid levels (4.4 ±0.4 g / dl, 0.51 ±0.9mg / dl), as it clear in the (Figure 4). In addition of it in the correlation relation between all renal parameters have no significant correlations as shown in the Table (5).

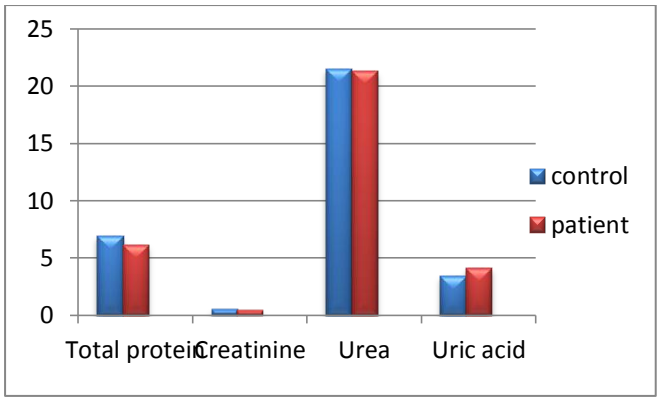

Figure 4. Changes in the renal function of thalassemia.

Table 5. Correlation between renal parameters and iron overload.

	Iron overload	
parameters	**Pearson correlation (r)**	**P-value (p)**
Creatinine	r= 0.097	P = 0.268
Uric acid	r= 0.190	P = 0.111
Urea	r= - 0.028	P = 0.430
Total protein	r= 0.096	P = 0.269

3.4.2. Liver function test parameters

3.4.2.1. Enzymatic liver parameters:

The findings of the current study show a significant increase in the level of liver enzymatic parameters ALP, ALT and AST (187.1 ± 51.3 UI / L, 47.5 ± 23.1UI / L and 56.3 ± 31.3UI / L) compared to healthy controls (83.2 ± 29.1UI / L, 16.3 ± 13.4UI / L and 25.9 ± 5.1UI / L) respectively (Figure 5) show a positive significant correlation between ALT and iron overload, while for ALP and AST shows no correlation with iron overload.

3.4.2.2. Non-enzymatic parameters of the liver:

The findings of the current study showed a significant improvement in the rate of non-enzymatic parameters of the liver, serum total bilirubin, serum direct bilirubin and serum indirect bilirubin (1.1±0.7mg / dl, 0.43 ± 0.39mg / dl and0.67±0.43mg / dl) compared to healthy controls of the same age and sex (0.6 ± 0.1mg / dl, 0.22 ± 0.08mg / dl and0.38±0.11mg / dl). Nonetheless, the findings of serum albumin rate liver-related non-enzymatic parameters showed a

significant decrease in stable regulation relative to its point (4.1 ±0.3 g / dl, 4.6 ±0.3g / dl). (Figure 6) comparisons of all non-enzymatic liver parameters with iron values in iron overload patients indicate poor non-significant correlations, full bilirubin, and indirect bilirubin parameters display low positive iron overload correlations, while specific bilirubin and albumin parameters show weak negative iron overload correlations.

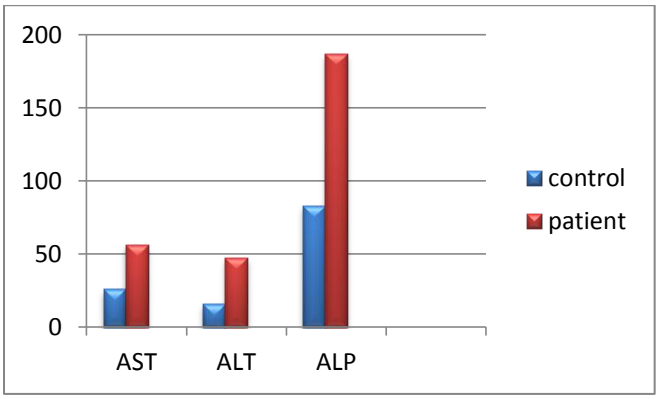

Figure 5. Changes in the enzymatic liver functions of thalassemia.

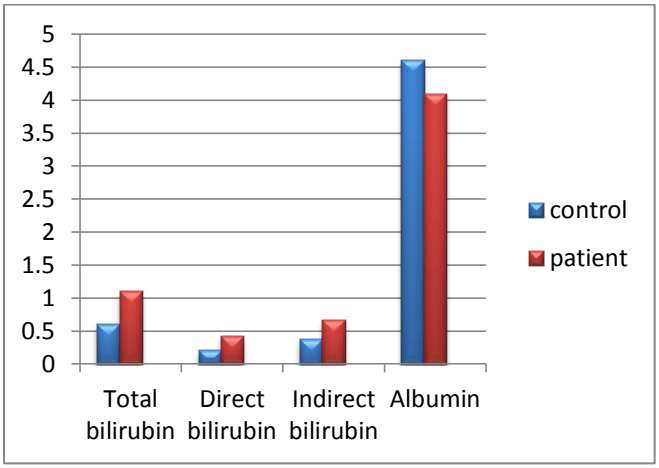

Figure 6. Changes in the non-enzymatic liver function parameters.

3.4.2.3. Iron profile:

The study findings showed significant changes in serum ferritin and iron (3132.0 ± 1012.1 ug / dl, 167.1 ±0.423 ng / ml) vs. (44.3 ± 22.3 ug / dl, 112.3 ± 0.68 ng / ml) relative to control point respectively. Furthermore, in the sample populations, association evaluation of iron profile (iron and ferritin) with iron overload in thalassemic patients shows high positive associations with iron values (r= 0.368, p=0.008).

4. DISCUSSION

4.1. Incidence of the thalassemia distribution

4.1.1. Beta-thalassemia major age distribution:

The information gathered in the context of a questionnaire. Patients involved in the actual research suggested the age and gender distribution of thalassemia patients. The age range was between (1-19 years) of the registered thalassemia patients. These include eight patients aged 1-4 years, 18 patients aged 5-9 years, 11 patients aged 10-14 years, and 6 patients aged 15-19 years. The patient's gender allocation proportions were male (53.4 percent) and woman (46.5 percent). Significant differences are observed in the consanguinity of parents of thalassemic patients and healthy controls, suggesting that consanguinity is correlated with the incidence of β-thalassemia in boys, this was clarified by the parents ' low health education and knowledge of the disorder, the findings of an earlier study designed to evaluate the consanguinity of parents with contrast, the proportions of 2nd degree consanguineous marriages in client populations are significantly higher than those of the control group, respectively 30%, and 9.3%. This result is consistent with the results published in preliminary studies [1, 11] in the current study, approximately twenty-one enrolled patients (48.8%) had another sibling either thalassemia relative (either alive or deceased) and (51.1%) had no sibling or thalassemia relative affected (either alive or deceased). Early reviews also found in another study showing that clinicians with thalassemia have another parent or family with thalassemia [2].

4.1.2. Viral hepatitis thalassemia:

Hepatitis is liver inflammation. For instance, medications, alcohol, chemicals, and autoimmune diseases may cause inflammation of the liver, but some viruses cause around half of all hepatitis in humans. Viruses that target liver specifically are referred to as hepatitis viruses. There are several varieties of hepatitis viruses; including types A, B, C, D, E. Varieties A, B, and C are the most prevalent and all hepatitis viruses that cause acute hepatitis, although persistent hepatitis may be triggered by viral types B and C. Thus, as a consequence of blood transfusion, most thalassemia patients had untreated hepatitis, of 43 patients surveyed around 27 patients (62.7%) tested positive for hepatitis C. None of our doctors, on the other side, tested positive for hepatitis B. It is also linked to the viral transmission pathway, the most common blood and needle transmission of HCV; hence it’s more

frequent in patients with thalassemia. Severe anemic occurs as a consequence of thalassemia and involves healthy red blood cells each month. Otherwise, HBV is the most common route of spread among thalassemia patients in the studied population [7].

4.1.3. Association of thalassemia with other diseases:

All patients evaluated for skeletal changes in this investigation, and such changes were noted in 39.53 percent of patients including characteristic facial bone expansion, large skull, and frontal bone bossing. Such shifts in the bone were of varying degrees, ranging from mild to severe degrees, the same skeletal feature as the previous study showed [12]. Bone defects present as rickets, scoliosis, extreme bone pain, spinal deformity, osteopenia, serious osteoporosis or multiple fractures, excess iron accumulation in the bones may affect the number and function of osteoblasts and interfere with mineralization, contributing to osteoporosis [13, 14]. No significant changes in the skeleton are found in the remaining 26 patients (60.46 percent). Skin pigmentation was observed in 19 patients (44.18%) which ranged from a slight increase in skin pigmentation to a very dark-colored skin, especially in the face and hands, while the other 23 patients (53.48%) retained normal skin color. Past [15] research affirms and aligns with these findings. Therefore, indicated that the majority of patients (67.4%) undergo blood transfusion every 2-3 weeks and 29.9% 4-5 weeks, whereas only two patients (4.6%) need a transfusion at longer intervals, more than 5 weeks, as stated by [16] agreement. Blood transfusions are the most common treatment for all major thalassemia types. Such transfusions are necessary in order to provide the person with hemoglobin capable of providing the oxygen needed by the body of the patient Splenectomy is clarified as it prevents the extra corpuscular process responsible for the increased degradation of healthy donor red cells in the bloodstream of the person. In respect to iron chelation, nearly half of clinicians extract the excessive iron through subcutaneous pumps (deferral pumps), 46.5% through intramuscular infusion, while 34.8% by intravenous infusion. 6.9% of clinicians used oral chelation (X-Jade) for titanium. Chelation therapy's key goal is to reduce tissue iron to a level where there is no iron-mediated toxicity. Therefore, chelate should have a high iron specificity [17].

4.2. Biochemical characteristics of thalassemia

4.2.1. Renal thalassemia parameters:

Results from this study showed that thalassemia patients renal function parameters changed significantly with the exception of serum urea. The findings showed a significant rise in the amount of serum uric acid relative to healthy volunteers, a significant reduction in the rate of serum creatinine according to its level of healthy controls. Such results confirm [18]. Total plasma protein concentrations were dramatically reduced in patients relative to healthy controls Similar results have been reported by [19] verifying our observations. Uric acid in red blood cells is considered to be the metabolically inactive end product of purine metabolism [20]. Rapid erythrocyte turnover in conjunction with reduced reabsorption of diluted uric acid from possible weakened renal tubules may explain the reported rise in serum uric acid concentrations in thalassemia patients [21]. Creatinine is a waste product usually processed out of the blood and excreted with the urine. High creatinine levels may be correlated with kidney function dysfunction or/and decreased muscle mass in thalassemic patients. The possible cause for reduced serum total protein, kidney disease, and liver disease [22], and there is no association of urea, creatinine, and albumin in the statistical analysis of the relationship between the renal parameters in thalassemic patients.

4.2.2. Liver parameters of thalassemia

4.2.2.1. Enzymatic liver parameters:

There was a substantial increase in thalassemic patients' liver enzymatic parameters compared to control samples in our studies. For adolescents with β-thalassemia, elevated liver enzymatic are suggestive of liver failure and liver enzyme leak into the plasma [1, 15]. Liver cell trauma allows the enzymes to escape into the bloodstream, in turn, enzyme parameter elevations are primarily used to assess whether the liver has been compromised and its activity is weakened liver disease, often correlated with frequent blood transfusions of thalassaemic patients and the effects of liver enzyme association testing. It is also correlated with the damage caused by iron overloading of liver cells during blood transfusion and contributes to leakage of enzymes into the blood circulation [23].

4.2.2.2. Non-enzymatic liver parameters:

Non-enzymatic liver variables such as overall bilirubin levels have increased dramatically in contrast to healthy control and specific bilirubin levels have significantly increased relative to healthy control. However, this observation is compatible with the findings of [24]. The increase and specific rates of bilirubin in thalassemic patients were consistent with the hemolytic cycle and reinforce the existing damage to the liver. The iron overload found in β-thalassemic patients could theoretically produce hepatic toxicity and, therefore, elevated overall and specific bilirubin levels, while the rate of albumin showed a significant decrease relative to normal regulation, the possible cause of decreased serum albumin is the secondary reduction of protein synthesis by the liver, its consent to findings were obtained [6, 10].

4.3. Iron profile:

The study findings showed a substantial increase in serum ferritin and iron compared to a healthy control group. This observation was compatible with the findings of [25]. This is a reasonable result where both transfusion iron deficiency and insufficient gastrointestinal absorption are observed in thalassemic patients. This observation was backed by several reports, such as [18] and [21]. From a biochemical point of view, it seems obvious that high iron concentrations have detrimental effects on the body organs and disrupt certain organs to conduct their own normal functions Lack of physiological process in beta-thalassemia major to remove excessive iron triggers their tissue deposition. Serum ferritin represents the state of the body's iron stores. Iron tissue overloaded is the most critical complication of β-thalassemia and is a major topic of management [26] and explanation of association study between iron overload and ferritin suggests a highly significant connection between iron overload and ferritin values in the body in positive states, indicating that as iron values rise in the body, ferritin values often increase in positive states.

4.4. Gender-related hematological and biochemical characteristics of patients:

The hematological and biochemical features of thalassemia males and females showed no significant gender differences. This demonstrated in population studies by the age of thalassemic patients as most of the thalassemic patients in population studies were under 16 years of age. This indicates that under the age of puberty, a thalassemic disorder often plays a major role in children's lag in puberty and development. Such results have been supported by previous [1, 26] studies.

CONCLUSIONS

In the present study, concluded that in patients with beta -thalassemia major, higher incidence of hematological and biochemical changes occurs in addition to iron overload in all patients. There is no any gender-related hematological and biochemical significantly changes.

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Declaration of conflicting interests

Authors also confirmed that there are no potential conflicts of interest with regard to the study, authorship and/or publishing of this paper.

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