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Original Article

Hematological and Biochemical Parameters of β-Thalassemia Major Patients in Bushehr City: A Comparative Analysis

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ABSTRACT

Background and Aims: β-thalassemia is the most common genetic disorder worldwide. β-thalassemia major results in severe anemia and serious complications. So, this study aims to evaluate the hematological and biochemical markers in β-thalassemia major patients in Bushehr city.

Materials and Methods: Our study included 94 transfusion-dependent β-thalassemia major were compared with 94 normal healthy subjects as controls. Hematological assessments included complete blood count indices. The biochemical evaluations included liver, kidney, and thyroid function tests, lipid profile, sodium, potassium, calcium, phosphorus, fasting blood sugar, and serum ferritin.

Results: All hematological parameters in patients, such as hemoglobin ($p < 0.01$), hematocrit ($p < 0.01$), mean corpuscular volume ($p < 0.05$), and mean corpuscular hemoglobin ($p < 0.05$), were significantly reduced compared to the control group except mean corpuscular hemoglobin concentration which was insignificant ($p > 0.05$). Higher levels of triglyceride, phosphorus, fasting blood sugar, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, uric acid, total and direct bilirubin, and lower levels of cholesterol, high-density lipoprotein, and low-density lipoprotein were observed in patients in comparison to the control group ($p < 0.05$). Serum sodium, potassium, calcium, and albumin was not significantly different from the control group ($p > 0.05$). The prevalence of primary hypothyroidism (thyroid stimulating hormone > 4.5 mIU/l and T4 < 5.6 µg/dl) was reported at 5.31%.

Conclusions: This study emphasized the necessity for regular follow-up and evaluation of β-thalassemia, which could be used to improve treatment protocols.

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Introduction

β-thalassemia is an inherited autosomal recessive disorder related to the deficiency of the production of beta-globin chains. The homozygous form of β-thalassemia may lead to either thalassemia major or thalassemia intermedia [1]. Thalassemia major is the most common genetic disorder worldwide, resulting in severe anemia requiring regular red blood cell transfusions [2, 3]. β-thalassemia is so highly prevalent in Iran that it has been shown that there are more than three million beta-thalassemia carriers (4-8%) and approximately 20,000 patients [4]. The disease is prevalent along the margins of the Caspian Sea, the Persian Gulf, and coastal cities in general [5]. These patients have been managed based on systematic blood transfusions to retain a hemoglobin level above 9 mg/dl [6]. Due to a long time necessity of repeated transfusion, excess iron gets accumulates in different organs of the body, namely, the liver, kidney, pancreas, and heart, implicating in excessive generation of free radicals which are capable of inducing damage to cellular membranes, protein, and DNA that consequently leads to wide-ranging impairment in cellular function. The manifestations include cirrhosis, cardiomyo-pathies, diabetes mellitus, secondary hypogo-nadism, and primary hypothyroidism [7-9]. Also, previous studies have reported a high outbreak of endocrine disorders in major thalassemia patients. That deficiency of trace minerals may be suggested as a causative agent in endocrinopathies. Besides, the estimation of trace minerals such as calcium, sodium, and potassium is valuable in these patients [10]. Due to the high prevalence of thalassemia in Bushehr and the lack of a comprehensive study on this disease, the present study has been designed to evaluate biochemical and hematological aspects of β-thalassemia major patients hoping to improve or modify the management and treatment protocols.

Materials and Methods

This study was performed on patients referred to the thalassemia center of Bushehr province from March 2018 to November 2018. The statistical population included 94 β-thalassemia major patients (female: 54 and male: 40) aged 12-46. In contrast, the control group included 94 healthy persons in the same age range. Demographic data of the patients, including age, gender, and medical history, was collected through their medical and laboratory records. The diagnosis of β-thalassemia major in early life has been accomplished via peripheral blood smear and electrophoresis of hemoglobin. Patients of thalassemia intermedia and minor and patients with acute illness were excluded from the study. The Human Ethics Committee of Bushehr University of medical sciences approved the study protocol.

Sample collecting and evaluation

About 5 mL of every patient's blood was collected, aliquoted 2.0 ml into the K2 Ethylenediaminetetraacetic acid (EDTA) tube, and mixed completely. Hematological assays such as hemoglobin, hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular

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hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) were evaluated by a blood cell counter (Sysmex XP-300, Germany) before 2 hours. The remaining samples (3 mL) were transferred to the clotting tube and centrifuged for 10 min at 3,000 rpm. Plasma samples were used for assessing biochemical factors such as fasting blood sugar (FBS), blood urea nitrogen (Bun), creatinine (Cr), uric acid (UA), triglyceride (TG), cholesterol (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), calcium (Ca), phosphor (Ph), aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), albumin, total and direct Bilirubin by using DIRUI CS-400 auto analyzer and commercial kits according to the manufacturer's instruction (Pars Azmoon, Iran). Ferritin and thyroid function tests such as thyroxin (T4) and thyroid stimulating hormone (TSH) were assessed by Enzyme-linked immunosorbent assay (ELISA) kits (Monobind INC, USA). Sodium (Na) and potassium (K) levels were determined according to the manufacturer's instruction (Pars Azmoon, Iran) by the JOKOH EX-D electrolyte analyzer (JOKOH, Japan).

Statistical analysis

Statistical analysis was conducted using SPSS 16.0, and a p-value < 0.05 was considered significant. Data are presented as Mean ± standard deviation (SD). The results were analyzed using analysis of variance (ANOVA) followed by the independent t-test. Correlations were calculated by Pearson's correlation coefficients.

Results

The average ages of β-thalassemia major cases and the control group were 27.2 and 29.8 years, respectively. Most patients were taken iron chelation with deferoxamine. In this section, the age and gender of β-thalassemia major patients versus the corresponding control group are represented (Table 1). No significant difference was found between the patients and the control regarding age or sex ($p > 0.05$). The highest percentage of patients was observed in the age range of 21 to 30 (Fig. 1). On average, blood transfusions were prescribed for patients from the age of 2.9 years. The overall mean transfusion interval was 20.90 days, but it was 20.61 days for males and 21.20 days for females. The mean height and weight were 158 ± 10.34 cm and 49.24 ± 9.49 Kg, respectively. Pre-transfusion hemoglobin in males and females was 8.7 ± 0.9 (g/dL) and 8.1 ± 1.0 (g/dL), respectively.

According to one-way ANOVA and two-tailed Dunnet's test, as shown in Table 2, all hematological parameters in patients such as Hb ($p < 0.01$), HCT ($p < 0.01$), MCV ($p < 0.05$) and MCH ($p < 0.05$) were significantly reduced compared to the control group except MCHC which was insignificant ($p > 0.05$).

As shown in Table 3, the average of T4 and TSH was close to normal range values. All thyroid function tests in β-thalassemia major patients were not significantly different from controls ($p > 0.05$). According to the Pearson correlation test, there was a significant correlation between age and T4 value ($R = -.44$; $p < 0.05$).

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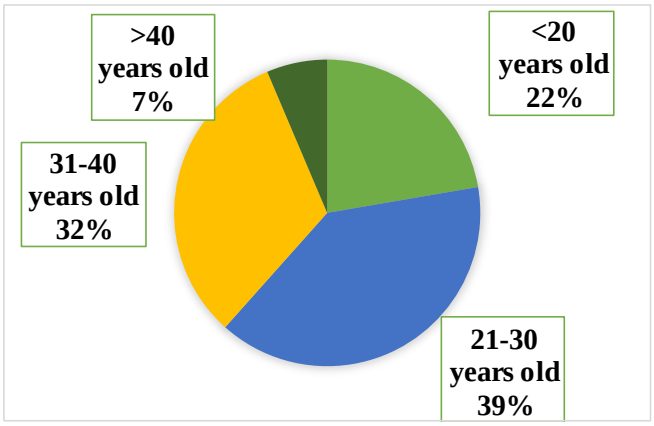

Fig. 1. Percentage of four age groups in studied thalassemia patients

Table 1. Age and sex of β-thalassemia major patients and control group (n=94)

Indices (Unit)	Sex	β-thalassemia	Control
Sex	Female	54	54
	Male	40	40
Age (yr)	Female	12-45	12-46
	Male	13-46	12-46

Table 2. Hematological characteristics in β-thalassemia major patients and controls (n=94)

Indices (Unit)	Case Mean ± SD		Control Mean ± SD		P-value
	Female	Male	Female	Male	
Hemoglobin (g/dL)	8.1 ± 1.0	8.7 ± 0.9	12.8 ± 1.2	13.4 ± 1.6	P< 0.01
Hematocrit (%)	27.0 ± 2.6	27.1 ± 2.6	38.1 ± 7.9	43.1 ± 8.4	P < 0.01
Mean corpuscular volume (µm^3)	73.9 ± 6.0	75.9 ± 5.5	83.6 ± 11.1	84.5 ± 12.0	P < 0.05
Mean corpuscular hemoglobin (pg)	25.9 ± 2.4	25.8 ± 1.0	29.1 ± 2.5	31.9 ± 2.0	P < 0.05
Mean corpuscular hemoglobin concentration (g/dL)	31.8 ± 1.3	31.9 ± 1.5	32.8 ± 1.4	33.1 ± 2.3	P > 0.05
Ferritin (µg/L)	3407 ± 2553	3674 ± 2730	38 ± 19	52 ± 21	P < 0.01

P-value < 0.05: Significant

Table 3. Thyroid function tests in β-thalassemia major patients and controls (n=94)

Indices (Unit)	Sex	Case Mean ± SD	Control Mean ± SD	P value
T4 (µg/dl)	Female	7.8± 2.2	8.2 ± 1.5	P > 0.05
	Male	6.8 ± 1.7	7.5 ± 2.2	P > 0.05
Thyroid stimulating hormone (mIU/l)	Female	2.9 ± 1.7	2.3 ± 1.2	P > 0.05
	Male	3.3 ± 2.3	2.6 ± 1.1	P > 0.05

P-value < 0.05: Significant

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Table 4. Sugar, lipid, and kidney function test in β-thalassemia major male and female patients as compared to control

Parameters (Unit)	Sex	Case (Mean ± SD)	Control (Mean ± SD)	P value
Sugar and lipid (mg/dL)				
Fasting blood sugar	F	121± 70	95± 12	P<0.05
	M	128 ± 65	98 ± 9	
Triglyceride	F	151 ± 70	98 ± 17	P < 0.05
	M	132 ± 72	93 ± 13	
Cholesterol	F	127 ± 31	151 ± 28	P < 0.05
	M	108 ± 31	162 ± 20	
High-density lipoprotein	F	30.3 ± 10.3	69.1 ± 9.8	P < 0.05
	M	26.5 ± 9.2	70.6 ± 11	
Low-density lipoprotein	F	61.4 ± 19.6	86.8 ± 10.4	P < 0.05
	M	54.1 ± 22.0	90.4 ± 13.0	
Kidney Function Test (mg/dL)				
Blood urea nitrogen	F	15.3± 7.9	14.9± 8.4	P>0.05
	M	17.1± 7.2	16.4± 6.7	
Creatinine	F	0.81± 0.33	0.80± 0.31	P>0.05
	M	0.82± 0.17	0.79 ± 0.2	
Uric acid	F	4.8± 1.1	3.4± 0.6	P<0.05
	M	5.3± 1.2	3.2± 0.7	
Electrolytes				
Sodium (mEq/L)	F	135.5± 1.6	136± 2.4	P>0.05
	M	135.2± 2.0	137± 2.7	
Potassium (mEq/L)	F	4.2± 0.15	4.0± 0.1	P>0.05
	M	4.2± 0.2	4.0± 0.3	
Calcium (mg/dL)	F	9.9± 0.6	9.6± 1.2	P>0.05
	M	9.9± 0.68	9.7± 1.6	
Phosphorus (mg/dL)	F	5.5± 0.75	4.2± 0.5	P<0.05
	M	5.3± 0.9	3.99± 0.6	

M= Male, F= Female, pvalue< 0.05: Significant

Table 5. Liver function tests and vitamin D_3 in β-thalassemia major male and female patients as compared to control

Parameters (Unit)	Sex	Case (Mean± SD)	Control (Mean± SD)	P value
Aspartate aminotransferase	F	41.4± 18.8	21.3± 6.7	P<0.05
	M	45.8± 20.7	20.2± 8.9	
Alanine transaminase (U/L)	F	44.2± 21.4	19.1± 7.4	P<0.05
	M	47.4± 23.1	21.2± 5.9	
Alkaline phosphatase (U/L)	F	305± 165	186± 122	P<0.05
	M	338± 116	201± 117	
Total bilirubin (mg/dL)	F	1.7± 0.9	0.4± 0.2	P<0.05
	M	2.9± 1.1	0.5± 0.2	
Direct bilirubin (mg/dL)	F	0.61± 0.21	0.2± 0.1	P<0.05
	M	0.57± 0.21	0.2± 0.1	
Albumin(g/dL)	F	3.9± 0.3	3.7± 0.2	P>0.05
	M	4.1± 0.4	3.8± 0.3	

M= Male; F= Female, pvalue< 0.05: Significant

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As shown in Table 4, the patients have shown significantly high serum FBS levels compared to the control group ($p < 0.05$). Also, the FBS level was more than 105 mg/dL in 35 patients (37.2%). The lipid profile in patients was significantly different from the control group ($p < 0.05$). Eighteen patients (19.1%) had over 200 mg/dL serum TG. Serum HDL was less than 30 mg/dL in 68 patients (72.3%). Moreover, cholesterol was reported to be less than 200 mg/dL in all patients and below 110 mg/dL in 48 patients (51%). A significant difference between patients and the control group was observed for uric acid ($p <0.05$), whereas serum creatinine and Bun were not significantly different from the control group ($p > 0.05$) . In Table 4, the examination of some biochemical indices levels in β-thalassemia major patients and controls has been presented. Serum Na, K, and Ca were not significantly different from the control group ($p > 0.05$), while high serum PH was observed in 82.9% of the patients.

According to one-way ANOVA and two-tailed Dunnet's test, as shown in Table 5, AST, ALT, Alkp, Direct, and total bilirubin levels in patients were significantly higher than the control group ($p < 0.05$). High serum total and direct bilirubin levels were observed in 63.8% and 80.8% of the patients, respectively. In 96% of patients, Albumin level was observed in the normal range, and there was no significant difference between the study and control groups ($p > 0.05$).

Discussion

β-Thalassemia, as a genetic disorder, is characterized by ineffective erythropoiesis, leading to chronic anemia and abnormal iron metabolism [11]. In order to prevent complications like chronic anemia and bone changes, these patients need regular blood transfusions, which leads to iron overload in their bodies [12]. In recent years, chelation therapy has progressed to diminish iron overload, but endocrinopathies still threaten the quality of patients' lives [13]. Moreover, various biochemical and hematological abnormalities are other symptoms among these patients [14]. In the present study, the biochemical and hematological factors were investigated among β-thalassemia major patients in Bushehr.

In this study, all hematological parameters such as Hb, HCT, MCV, and MCH have been significantly decreased in patients compared to the control group. However, there was no significant difference in MCHC compared to the control group. Similarly, Fazlul Karim et al. reported that Hematological parameters such as Hb, HCT, MCV, and MCH have been significantly reduced in patients except for MCHC [10]. In the present study, the mean ferritin level in patients was 3540 µg/L, and compared with the control group, serum ferritin was raised significantly ($p < 0.01$). This is due to the iron overload caused by regular blood transfusion. The findings are consistent with several similar studies. For example, Surchi et al. reported a mean serum ferritin level of 2803.4 µg/L [15], and Eghbali et al. reported a mean serum ferritin level of 1927.1 µg/L. [16]. Many studies have assessed the toxic effect of excess iron and peroxidative injuries on liver cells, leading to an increase in liver

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enzymes[17, 18]. In these patients, the mean ALT, AST, and ALP were 43.6 U/L, 45.8 U/L, and 321.5 U/L, respectively, substantially high due to the developed abnormal liver function. Hashemizadeh et al., in the Sarvar clinic of Mashhad, found that the mean ALT and AST were 70 U/L and 95 U/L, respectively [2]. In a study in Qatar, Kanbour et al. reported that the mean ALT, AST, and ALP were 61.9 U/L, 52 U/L, and 145.46 U/L, respectively [19]. The serum AST and ALT positively correlated with serum ferritin with correlation coefficients r = +0.45 and r = +0.42, respectively ($P<0.05$). The study's results correlate well with previous studies [10, 17].

In the present study, the average level of total and direct serum bilirubin in the study group was significantly higher than the control group ($P < 0.05$), which can be due to the excessive destruction of red blood cell. Sultana et al. reported similar results: mean serum bilirubin of 2.04 ± 0.70 mg/dL in Patients [20]. Moreover, this study showed that most β-thalassemia major patients had lower total cholesterol, LDL-C, and HDL-C levels than the control group. Though, a high level of triglycerides has been observed. These fluctuations may be due to iron overload, liver injury, hormonal disturbances, and aging [21]. Our findings align with the outcome of Shams et al. and Ragab et al. [22, 23]. However, Haghpanah et al. showed that the triglyceride level was not significantly different from the control group [24]. In this study, 14.8% of patients had FBS>126 mg/dl, which agrees with similar studies, such as Chahkandi et al.'s study. In Birjand city, eastern Iran, who reported the mean serum FBS levels in patients were 124.19 mg/dl, and 14.3% of patients had FBS ≥ 126 mg/dl [13]. In studies conducted in Pakistan, research on 124 β-thalassemia major patients showed that 29.4% of patients had FBS ≥ 126 mg/dl [25].

In our study, the mean serum creatinine and Bun were within the normal range and not significantly different from the control group. However, the uric acid level was significantly higher than the control group. Our findings align with the outcome of Aldudak et al. and Sen et al. [26, 27], while in contrast, Ahmadzadeh et al., in their study, found normal range serum uric acid level [28]. Renal damage in patients with β-thalassemia major can be due to long-lasting anemia, iron overload, and deferoxamine toxicity [29]. There was also a slight difference in Na and K in the patients compared to the control group. Similar findings were reported by previous studies [27, 30]. However, in a study carried out in Bangladesh, higher levels of Na and K were found in patients compared to healthy individuals [10].

In this study, the Ph levels in female and male patients were 5.5 ± 0.75 mg/dL, and 5.3 ± 0.9 mg/dL, respectively. In general, 67.8% of phosphorus was above 4.5 mg /dL. Similar results have been observed in other studies [31-33]. Also, the mean serum calcium of patients was not significantly different from the control group. Our outcomes agree with the result obtained by Surchi et al. [15]. However, Ayyash et al., in their study, showed that the level of Ca in patients was significantly lower than in the control group [17]. One of the main causes of hypothyroidism in β-thalassemia

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major patients is mentioned poisoning of the thyroid gland with iron overload. The prevalence of hypothyroidism varied in different studies. For example, the highest and lowest prevalence of hypothyroidism was reported (26.7% and 0%) in Najafipour and Mostafavi et al.'s studies, respectively [34, 35] . In this study, the prevalence of primary hypothyroidism (TSH>4.5 mIU/l and T4< 5.6 µg/dl) was reported at 5.31%. The incidence of hypothyroidism varies widely, depending on age, region, and type of remedy, including the number of red-packed cell transfusions per month, chelation therapy, and follow-up intervals of cases. This fact answers why the prevalence of hypothyroidism is so different in different studies [5].

Conclusion

In conclusion, the difference in hematological and biochemical parameters between β-thalassemia major patients and controls has been demonstrated. In this study, the serum ferritin is increased in most patients because of the breakdown of red blood cell and chronic blood transfusion, leading to iron accumulation in the body. Also, it has been indicated that increasing ferritin levels led to a subsequent increase in the serum levels of liver enzymes (ALT, AST, and Alkp). The present study revealed that 52% and 19.1% of patients had hypocholesterolemia and hypertriglyceridemia, respectively, and 5.31% had hypothyroidism. Consequently, due to iron overload in patients with thalassemia major that resulted in permanent tissue damage, this is necessary to evaluate iron toxicity and follow up on the β-thalassemia major patients regularly. We are hopeful that current findings will contribute to developing a guideline concerning the early diagnosis and mode of treatment among β-thalassemia major patients.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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