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THE EFFECT OF MINOR THALASSEMIA ON THE LIVER FUNCTION AND LIPID PROFILE COMPARED WITH MAJOR THALASSEMIA

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ABSTRACT

It is thought that only patients with major thalassemia need to be under healthy control compared to minor. Thus, the aim of this work is to investigate the minor thalassemia complications in the liver status and compare them with the major thalassemia. So, 84 patients with thalassemia were randomly selected; 56 with major and 28 with minor. The Blood Samples were collected and used to determine the levels of ferritin, liver enzymes and lipid profiles. The results were showed that while there were no significantly differences in the ALP levels, ALT and AST levels were significantly higher in the major thalassemia compared to minor. All the patients with major and minor had abnormal higher ALP, 45% of major had abnormal higher AST and 30% of the major had abnormal ALT than normal range. Bild, BilT, cholesterol and trig levels were significantly higher while LDH and UHDL levels were significantly lower in the major compared to minor. The Bild levels in 90% of the major compared to 40% of the minor were abnormal higher than normal range. As conclusion, there were abnormality in the ALP and some lipid profile of minor thalassemia. So, the patients with minor thalassemia could be under risk of liver disorder so they need to be under control and to find the exact reason of this disorder need more researches.

KEYWORDS: Thalassemia, Ferritin, liver enzymes, lipid profiles.

INTRODUCTION

Thalassemia is an inherited blood disorder. Thalassemia is a combination of two Greek words: Thalassa, which means Mediterranean Sea, and anemia [1]. There are two types: α -thalassemia and β -thalassemia, in which the globin chain of the hemoglobin molecule is not synthesized adequately. The most clinically dangerous cases are homozygous β-thalassemia, while α-thalassemia homozygotes are frequently deadly in utero [2].

Beta-thalassemia is defined by decreased beta globin chain synthesis, which results in lower haemoglobin (Hb) levels in red blood cells (RBC), decreased RBC production, and anaemia [3]. The three forms of beta-thalassemia are major, intermedia, and minor [4]. Thalassemia major manifests clinically between the ages of 6 and 24 months. Infants who are affected do not flourish and develop pallor. Feeding difficulties, diarrhea, and irritability may occur, as may recurrently spells of fever and increased expansion of the abdomen due to spleen and liver enlargement. Growth and development are normally normal for 10 to 12 years if a regular blood transfusion program is established that maintains a minimum Hb concentration

of 9.5 to 10.5 g/dL. Patients who have been transfused may exhibit iron overload symptoms such as failure or delay in sexual development and growth retardation [5]. Individuals with thalassemia intermedia are asymptomatic until adulthood, with mild anaemia causing several difficulties. Beta-thalassemia Minors are normally asymptomatic; however, they might have mild anaemia [6].

The liver is an important organ in the human body that is in charge of many activities including metabolism, immunity, digestion, detoxification, and vitamin storage, all of which are regulated by liver enzymes. The liver enzymes alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) that help to speed up chemical reactions in the body. These chemical activities include the creation of bile and chemicals that aid in blood coagulation, the breakdown of food and toxins, and infection resistance [7]. When the liver is harmed, it releases enzymes into the circulation (most often ALT, AST, or ALK) in unusually high amounts [8].

The liver contains approximately one-third of the body's stored iron (ferritin and hemosiderin) [8]. Hepatic iron reserves are closely related to cumulative trans fusional iron load and have been used to predict chelation treatment success and prognosis [9]. Many researchers investigated the influence of iron overload in major thalassemia on liver status and discovered that it produces fibrosis, cirrhosis, and liver dysfunction, implying a relationship between hepatic iron levels and the development of iron-induced hepatotoxicity [8]. On the other hand, as our knowledge, there is no research about the minor complications especially on the liver. Thus, this work aimed to investigate the minor thalassemia complications in the liver status and compare them with the major thalassemia.

MATERIALS AND METHODS

This study was conducted on 84 patients with thalassemia that were randomly selected from visitor of Ibn Al-Balady Hospital (Hereditary Blood Disorder Center) in Bagdad, Iraq; 56 with major thalassemia and 28 with minor thalassemia. The age of participates was about 10-32 years. The biochemical analysis was conducted in Imam Ali Hospital. The Blood Samples (about 5ml) were collected from all participates by the vinous puncture in a gel tube. These tubes were centrifugated for 5 mints in 3000 r.p.m to separate serum.

The serum samples were collected in simple tubes and stored in a freezer at -20°C until they were utilized to detect the levels of:

1. Ferritin by Fluorescence immunochromatographic method using FinecareTM Kit and instrument from Wondfo Company/ China country
2. Liver enzymes including; alkaline phosphatase (ALP) using p-nitrophenyl phosphate (pNPP) as a phosphatase substrate according to Abnova Company kit/Taiwan, Alanine aminotransferase (ALT) by using Activity Assay according to Gen Way Biotech company kit/USA and Aspartate aminotransferase (AST) using p-nitrophenyl phosphate (pNPP) as a phosphatase substrate according to Abnova Company kit/Taiwan.
3. Lipid profiles by enzymatic colorimetric method including; total cholesterol (TC) using biolab company kit/France, Triglycerides (TG) and High-Density Lipoprotein (HDL) using linear chemical company kit / Spain.

Results were given as mean± SD or percentage for the case frequency. For multiple comparison using Stat view version 5.0, data were analysed using one-way analysis of variance (ANOVA) followed by Fisher's test or t-test. Regressions were analysed by CANOVA using Stat view version 5.0 too. When $p<0.05$, differences were deemed significant.

RESULTS

Table (1) summarizes the patients with minor and major thalassemia characteristic features. The mean age of major thalassemia was significantly higher than the minor (20.5±1.4 and 14.0±0.89 years, respectively). Moreover, the percentage of the major thalassemia removed their spleen was significantly higher than the minor (23% and 14%, respectively). In addition, the men percentage was significantly higher than the women in the major thalassemia (69% and 23%, respectively) which is opposite in the minor where the women percentage was significantly higher than the men (71% and 29%, respectively).

The features		Major Th.	Minor Th.	P-Value
Age (Years) (mean±SE)		20.5±1.4	14.0±0.89	0.0006
Spleen removal %		23%	14%	<0.0001
Gender %	Male	69%	29%	<0.0001
	Female	23%	71%	<0.0001
	P-Value	<0.0001	<0.0001	

Table (1): *(the characterized features of major and minor thalassemia)*

Figure (1) shows the value of ferritin in the patients. It was significantly increase in the major thalassemia compared to minor which is abnormal higher in the major but within the normal value (24-336 ng/ml) in the minor.

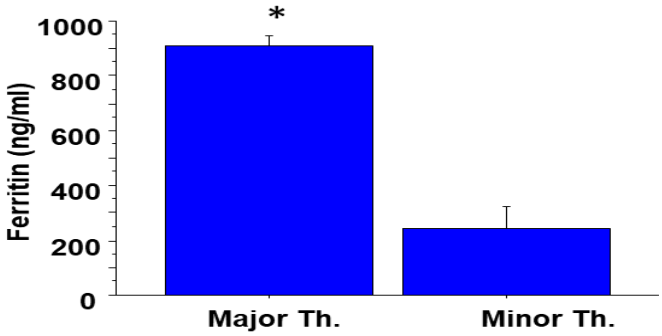

Figure (1): *(Ferritin level in major and minor thalassemia.)*

In table (2) determined liver enzymes in the patients. ALT and AST levels were significantly higher in the major thalassemia (29.23±0.74 and 32.85±2.60 U/L, respectively) compared to minor (6.43±0.26 and

25.67±1.13 U/L, respectively) while there were no significant variations in ALP levels between major and minor thalassemia. Although both means of ALT and AST were within the normal range, about 45% of the major thalassemia patients have abnormal higher level of the AST and 30% have abnormal higher ALT level compared to minor thalassemia who have only normal levels of ALT and AST. On the other hand, ALP levels in both major and minor thalassemia were abnormal higher according to the normal range.

Groups	ALT (U/L)	AST (U/L)	ALP (U/L)
Major Th.	29.23±0.74*	32.85±2.60*	163.15±12.21
Minor Th.	6.43±0.26	25.67±1.13	172.43±12.18
P-Value	<0.0001	0.024	0.598
Normal Value	4-36	8-33	44-147

Table (2): *(Liver enzymes levels in the major and minor thalassemia)*

In table (3) determined lipid profile in the patients. BilD, BilT, cholesterol and trig levels were significantly higher in the major thalassemia (0.64±0.04, 1.97±0.16, 110.5±3.2 and 133.6±12.8 mg/dl, respectively) compared to minor (0.26±0.03, 0.66±0.08, 148.3±8.02 and 92.57±9.31 mg/dl, respectively) while LDH and UHDL levels were significantly higher in the minor thalassemia (180.4±14.6 U/L and 44.57±2.3 mg/dl, respectively) compared to major thalassemia (112.7±14.2 U/L and 22.39±1.31 mg/dl, respectively). Chol, LDH and UHDL levels were within the normal range in both major and minor thalassemia while the BilD levels in 90% of the major thalassemia compared to 40% of the minor thalassemia were abnormal higher than the normal value. Although both means of BilT and Trig were abnormal higher than the normal range in the major, only 80% of them have abnormal higher level of the BilT and 70% have abnormal higher Trig.

Groups	BilD (mg/dl)	BilT (mg/dl)	Chol (mg/dl)	LDH (U/L)	Trig (mg/dl)	UHDL(mg/dl)
Major Th.	0.64±0.04*	1.97±0.16*	110.5±3.2	112.7±14.2	133.6±12.8*	22.39±1.31
Minor Th.	0.26±0.03	0.66±0.08	148.3±8.0*	180.4±14.6*	92.57±9.31	44.57±2.3*
P-Value	<0.0001	<0.0001	<0.0001	0.002	0.017	<0.0001
Normal V.	0-0.3	1-1.2	<200	105-333	<150	35-65

Table (3): *(Lipid profile levels in the major and minor thalassemia.)*

Table (4) shows the correlation of all studied biochemical parameters with the spleen removal, age and gender. The patient whose him spleen was removed represented by the number 2 and whose was not represented by the number 1. As well as, the woman represented by number 2 and the man represented by number 1. Only BilD, Trig and Ferritin have significant positive correlation with spleen removal while with age, there was significant positive correlation with the BilD, BilT, Trig and ferritin and negative correlation with ALP and UHDL. As well as, there was significant positive correlation of Chol, LDH and UHDL and negative correlation of BilD with the gender.

	Spleen removal	Age (age)	Gender
ALP (U/L)	P = 0.34, R = 0.14	↓P = 0.009, R = 0.37	P = 0.61, R = 0.07
ALT (U/L)	P = 0.63, R = 0.07	P = 0.23, R = 0.17	P =0.076, R = 0.26
AST (U/L)	P = 0.86, R = 0.03	P = 0.26, R = 0.17	P = 0.17, R = 0.2
BilD (mg/dl)	↑P = 0.03, R = 0.32	↑P<0.0001, R = 0.58	↓P =0.012, R = 0.37
BilT (mg/dl)	P = 0.42, R = 0.12	↑P = 0.0001, R= 0.52	P= 0.14, R= 0.22
Chol (mg/dl)	P = 0.51, R = 0.1	P = 0.32, R = 0.15	↑P<0.0001, R= 0.54
Trig (mg/dl)	↑P = 0.002, R = 0.44	↑P<0.0001, R = 0.7	P = 0.56, R = 0.09
LDH (U/L)	P = 0.38, R = 0.13	P = 0.29, R = 0.17	↑P= 0.0002, R = 0.52
UHDL (mg/dl)	P = 0.34, R = 0.14	↓P = 0.0003, R = 0.51	↑P = 0.003, R = 0.42
Ferritin (ng/ml)	↑ P = 0.006, R= 0.4	↑ P = 0.0004, R = 0.5	P = 0.24, R = 0.17

Table (4): *(Correlation of spleen removal, age and gender with the Ferritin, liver enzymes and lipid profile.)*

Table (5) shows the correlation of all liver enzymes with the lipid profile and ferritin with the liver enzymes and lipid profile. ALT has a significant positive correlation with BilT, Trig, and ferritin and a negative correlation with UHDL, but AST has a significant positive correlation with just trig and UHDL and a significant negative correlation with UHDL. However, ALP has only significant negative correlation with trig. On the other hand, ferritin has significant positive correlation with ALT, AST, BilD, BilT and Trig and negative correlation with Chol and UHDL.

	ALP (U/L)	ALT (U/L)	AST (U/L)	Ferritin (ng/ml)
BilD (mg/dl)	P = 0.82 R = 0.032	P = 0.12 R = 0.23	P = 0.49 R = 0.10	↑P<0.0001 R= 0.6
BilT (mg/dl)	P = 0.41 R = 0.12	↑P = 0.0008 R = 0.4	P = 0.58 R = 0.08	↑P<0.0001 R= 0.6
Chol (mg/dl)	P = 0.22	P = 0.19	P = 0.76	↓P<0.0001

	R = 0.18	R = 0.19	R = 0.045	R = 0.5
Trig (mg/dl)	↓P = 0.0002 R = 0.52	↑P = 0.005 R = 0.41	↑P = 0.014 R = 0.36	↑P= 0.0005 R = 0.4
LDH (U/L)	P = 0.14 R = 0.22	P = 0.93 R = 0.03	P = 0.57 R = 0.26	P = 0.27 R = 0.16
UHDL (mg/dl)	P = 0.49 R = 0.1	↓P = 0.015 R = 0.36	↓P = 0.009 R = 0.37	↓P<0.0001 R = 0.7
Ferritin (ng/ml)	P = 0.42 R = 0.12	↑P = 0.0004 R = 0.4	↑P= 0.023 R= 0.33	

Table (5): *(Correlations of liver enzymes with lipid profile and ferritin with liver enzymes and lipid profile.)*

DISCUSSION

Our results found that in the major thalassemia, age range was 20.5±1.4 years, which is agreed with the Prakash, 2012 [10], was significantly higher than it in the minor which was 14.0±0.89 years. The results of minor thalassemia couldn't compare it to the reference since we did not find research studied it. Thalassemia major is usually suspected in infants under the age of two who have severe microcytic anaemia, mild jaundice, and hepatosplenomegaly. Thalassemia minor appears later in life and causes lesser clinical signs [11]. So, the different between the age of major and minor could be because the patients with major thalassemia need to still under controlled by the doctors because its complications but the minor does not need it.

However, in the major, 69% from the patients were males compared to 29% females which were totally different than the minor where was only 23% males compared to 71% female. These findings corresponded with those of Nigam et al., 2020 [12], who discovered the same changes but considered them to be insignificant.

When hypersplenism raises blood transfusion requirements and hinders proper management of body iron with chelating treatment, splenectomy and ferritin raising levels are advised in the transfusion-dependent patient [13]. People with thalassemia minor or trait typically do not require blood transfusions since they either do not have anaemia or have only minor anaemia, as opposed to people with thalassemia major, who do [14]. These evidences could explain the increasing of the major thalassemia undergo splenectomy and the ferritin levels compared to minor and the positive correlation of ferritin with age and case frequency of splenectomy.

The liver is the only organ that produces transferrin and ferritin, and it also serves as the primary organ for iron storage. Free ferrous iron is very toxic since iron is generally protein-bound in the liver. Free radicals are produced by unbound iron, which has been linked to lipid peroxidation and hepatotoxicity [15]. In routinely transfused thalassemia patients, the liver is the first location of iron build-up and a common source of morbidity. Iron overload occurs in both hepatocytes and reticuloendothelial cells. The Fenton reaction increases free radical production in those who have an excess of iron. These free radicals

build up in the liver, heart, and other organs, wreaking havoc on tissue and causing it to deteriorate [16]. Because iron levels and serum ferritin have a positive correlation, serum ferritin concentration is commonly used to assess iron overload in β- thalassemia patients [17]. As it explaining above the ferritin levels increase in the major thalassemia which explain the increase of case frequency have abnormal results of liver enzymes.

In the current investigation, we discovered higher levels of ALP, AST, and ALP, as well as a positive correlation of ALT and AST with the ferritin level. The current study's findings are thus consistent with the findings of prior investigations conducted by De Sanctis et al [18 and 15]. Despite the fact that various analysts have depicted the postulated component of activity, the best way is yet unknown. Seng Suk et al discovered that liver functions in β -thalassemia patients were three to four times higher than in healthy people [10]. In transfusion-dependent -thalassemia major, iron accumulation is related with increased oxidative stress, lipid peroxidation, and liver cell damage. Jensen et al. also discovered that when the iron level of the liver increases, so do serum transaminases and hepatic fibrosis [20].

We examined the lipid profile of patients with Thalassemia major and mild in this study. It was revealed that in frequently transfused thalassemia major patients with serum ferritin levels higher than minor patients, whereas cholesterol, HDL cholesterol, and LDL cholesterol levels were low, triglyceride levels were high. Total cholesterol, HDL, and LDL had a negative correlation with serum ferritin and liver enzymes, whereas serum triglycerides had a positive correlation with serum ferritin and liver enzymes. As a result, it appears that numerous variables, including iron overload (high ferritin levels), liver injury, and hormone instability, influence lipid pattern in these individuals. Mild erythroid hyperplasia also increases LDL clearance by bone marrow. The major causes of low plasma cholesterol levels include accelerated erythropoiesis, enhanced LDL absorption by macrophages, and reticuloendothelial system histiocytosis. Hepatic injury and iron excess produce low total cholesterol. Because these alterations are indicators of lipid peroxidation, the cause of the occurrence was investigated [21]. Papanastasiou et al, had shown that total cholesterol, HDL and LDL cholesterol were significantly lower in thalassemia patients compared to controls, but triglycerides were significantly higher. A positive correlation between age and triglyceride levels was also discovered [22]. According to Kaltwassen et al., an increase in triglyceride was detected with increasing ferritin readings, and there was a positive correlation between patient triglyceride and both age and oxidative LDL-C antibodies [23]. In a research done in Jordan in 2008, Kamal et al discovered significantly lower cholesterol, HDL, and LDL levels when compared to controls [24]. Louis et al. discovered a comparable reduction in total cholesterol [25]. Patne et al found that lipid abnormalities are more common in thalassemia children than in controls in their study [26]. During a study in Lebanon, Inati et al discovered that the lipid profile of patients with β-Thalassemia major is altered. Serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels are lower in thalassemia patients than in normal controls, however triglyceride (TG) levels are neither significantly different nor higher in thalassemia patients [27]. Our findings support earlier authors' theory that serum iron and triglycerides are both implicated in the development of LDL cholesterol oxidation. In the current investigation, we found a significant positive correlation between serum ferritin and triglycerides, a marker of a disordered lipid profile associated with aberrant iron overload and poor chelation [28].

CONCLUSIONS

The results in this study were found many abnormalities in the major thalassemia because of the overloud of ferritin compared to minor. However, even though there was no ferritin overloud, there was some abnormalities in the minor such as ALP levels was higher than the normal rang all patients with minor thalassemia, and some lipid profiles higher than normal range; 40% of them have abnormal higher level of BilD, 30% of them have abnormal higher level of the BilT and 20% have abnormal higher Trig.

As conclusion, liver enzymes and lipid profiles abnormality were caused by the ferritin overloud in the major thalassemia. However, there are abnormality in the minor thalassemia since there are abnormal value of ALP even though the normal AST and ALT, and abnormal of some lipid profiles in some patient with minor thalassemia. So, the prevailing belief that there is no need for health follow-up for patients with minor thalassemia is incorrect because there is a risk of liver disorder in them which need more research to find the exact reason of this disorder.

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