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ORIGINAL RESEARCH

Iron Overload and Its Impact on Liver Function and Lipid Profiles in Transfusion-Dependent β-Thalassemia Patients in Sana'a City

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Background: β-thalassemia major (βTM) is a severe genetic blood disorder that necessitates regular blood transfusions, which often lead to iron overload and associated complications, including liver dysfunction and dyslipidemia.

Objective: To investigate the relationship between iron overload, liver function abnormalities, and lipid profile disturbances in transfusion-dependent β-thalassemia patients in Sana'a, Yemen.

Methods: A cross-sectional study was conducted among 53 participants recruited from the Yemeni Association for Thalassemia Patients and Genetic Blood Disorders in Sana'a City. Participants were divided into four groups: healthy controls, β-thalassemia patients receiving regular blood transfusions with or without iron chelation therapy (ICT), and nontrans fused thalassemia patients. Clinical data were collected using structured questionnaires, and Biochemical and haematological parameters, including serum ferritin, serum iron, GPT (ALT), bilirubin, triglycerides (TG), HDL, LDL, cholesterol, hemoglobin (Hb), and white blood cell (WBC) counts, were measured. The data were analyzed using SPSS Version 20. Normality was assessed with the ShapiroWilk test. Parametric tests, including independent sample ttests and ANOVA, were used to compare continuous variables. Categorical data were analyzed with the chi-square test. A Bonferroni correction was applied to adjust for multiple comparisons.

Results: Serum ferritin levels above 1,000 ng/mL were considered elevated, and iron levels were significantly higher in transfusion-dependent patients, particularly those receiving blood for >5 years or >250 mL per transfusion. Group II (patients receiving blood transfusions with ICT) and Group III (patients receiving blood transfusions without ICT) showed significantly elevated ferritin and serum iron levels compared to Group IV (non-transfused patients). Patients with high ferritin levels also exhibited significantly elevated GPT and direct bilirubin, indicating liver damage, with the highest levels observed in Group II and Group III. Furthermore, these patients had higher triglycerides and lower HDL, LDL, and total cholesterol, consistent with dyslipidemia. Haematological parameters showed reduced hemoglobin and RBCs, and increased WBCs among patients with iron overload.

Conclusion: Iron overload is strongly associated with liver dysfunction and dyslipidemia in transfusion-dependent β-thalassemia patients. The findings suggest that iron chelation therapy helps reduce the impact of iron overload on liver function and lipid metabolism. Routine monitoring of ferritin, liver enzymes, and lipid profiles is essential for managing these complications. Effective iron chelation therapy is critical, and improving access to ICT and establishing better follow-up strategies are needed to mitigate the long-term consequences of iron overload.

Keywords: β-thalassemia, iron overload, liver damage, dyslipidaemia, serum ferritin, transfusion, Yemen, chelation therapy

Introduction

Thalassemia syndromes, particularly β-thalassemia major (βTM), remain a significant public health concern globally and are especially prevalent in the Mediterranean region, the Middle East, Southeast Asia, and the Indian subcontinent. It is estimated that approximately 1.5% of the global population are carriers of β-thalassemia, with over 300,000 children born annually with severe hemoglobinopathies, including β-thalassemia and sickle cell anemia.[1,2] In Yemen, thalassemia

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continues to pose a considerable burden on the healthcare system, with around 700 new cases diagnosed each year and tens of thousands living with the condition.[3] β-thalassemia major is an autosomal recessive disorder characterized by a severe reduction or absence of β-globin chain synthesis, leading to ineffective erythropoiesis, chronic haemolytic anaemia, and a lifelong dependence on regular blood transfusions.[4] While transfusion therapy is essential for patient survival, it inevitably results in progressive iron overload, particularly in the liver, heart, and endocrine organs, unless adequately managed with iron chelation therapy.[5] Iron overload is a leading cause of morbidity and mortality in transfusion-dependent βTM patients. Excess iron catalyzes the formation of reactive oxygen species (ROS), leading to oxidative stress and damage to cellular structures, particularly in the liver, where hepatotoxicity is often observed.[6] In addition to liver damage, iron overload has been implicated in dyslipidemia, characterized by elevated triglyceride levels and decreased levels of HDL and LDL cholesterol, further complicating the clinical management of thalassemia.[7] Moreover, dysregulation of lipid metabolism in βTM patients is thought to be exacerbated by chronic oxidative stress, inflammation, and impaired liver function, all of which are associated with iron accumulation.[8] The interplay between iron overload, lipid abnormalities, and hepatic dysfunction highlights the need for continuous monitoring and timely intervention in these patients. Given the limited data available from low-resource settings such as Yemen, where access to comprehensive care and iron chelation therapy may be inconsistent, also no prior studies have comprehensively examined the relationship between iron overload and both lipid abnormalities and liver dysfunction in Yemeni β-thalassemia patients. So, this study aims to investigate the association of iron overload with dyslipidemia and liver damage among transfusion-dependent β-thalassemia patients attending the Yemeni Association for Thalassemia Patients and Genetic Blood Disorders in Sana'a City.

Methodology

Study Design and Setting

This cross-sectional study was conducted between January 2023 and December 2023 at the Yemeni Association for Thalassemia Patients and Genetic Blood Disorders in Sana'a City, Yemen. A total of 53 participants were included, grouped into four categories to allow comparison of different levels of transfusion dependency and iron overload:

1. Group I (Healthy controls, n=20): Healthy individuals without any history of thalassemia or related medical conditions. They were included to provide baseline data for comparison against the β-thalassemia patient groups.
2. Group II (Transfusion-dependent β-thalassemia patients with iron chelation therapy (ICT), n=15): β-thalassemia patients receiving regular blood transfusions and undergoing ICT. This group helped assess the effects of transfusion-related iron overload and the role of ICT in managing these complications.
3. Group III (Transfusion-dependent β-thalassemia patients without ICT, n=14): β-thalassemia patients receiving blood transfusions but not on ICT. This group was included to examine the impact of iron overload without the potential mitigating effect of ICT, providing a comparison to Group II.
4. Group IV (Non-transfused β-thalassemia patients, n=4): β-thalassemia patients who were not receiving regular blood transfusions. This small group was included to assess the baseline condition of patients without transfusion-induced iron overload, providing additional context to the other groups.

Note: While Group IV had a small sample size, it was included for comparison purposes, especially to examine the impact of transfusion-related iron overload. However, due to its small size, detailed statistical analysis of this group was limited.

Sample Size Determination

The sample size for Groups I, II, and III was determined using standard statistical power analysis methods, with the goal of ensuring adequate power (≥80%) to detect significant differences between groups at a significance level of 0.05. Based on this analysis, Groups I, II, and III were adequately powered to allow meaningful comparisons. However, Group IV had a smaller sample size (n=4), which did not meet the minimum required sample size for robust statistical analysis on

its own. Group IV was included for comparison purposes, but its small size limits its statistical power, and it was not used for detailed statistical analysis.

Inclusion Criteria

- Confirmed diagnosis of β-thalassemia by a haematologist or medical records.
- Patients of all genders and aged >2 years.
- Transfusion dependent or non-transfusion dependent thalassemia status.
- Voluntary informed consent obtained from participants or guardians.

Exclusion Criteria

- Patients with chronic liver diseases unrelated to thalassemia (eg, viral hepatitis B or C, autoimmune hepatitis).
- Individuals with metabolic disorders (eg, Cushing's syndrome, pancreatitis).
- Participants on medications affecting lipid or liver metabolism (eg, corticosteroids, estrogens).
- Incomplete clinical or biochemical data.

Data Collection and Biochemical Assays

Laboratory Data Collection: Laboratory data, including biochemical and haematological parameters, were collected after the participants' most recent blood transfusion. These parameters were selected to assess iron overload, liver function, lipid profile, and overall haematological health.

1. Serum Ferritin: Serum ferritin levels were measured using an enzyme linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. The assay was performed to ensure accurate readings. Calibration was done using ferritin standards provided with the kit, following the standard calibration procedures Compared with the normal reference range of 30–300 ng/mL for healthy individuals.
2. GPT (ALT): GPT (ALT) levels were measured using a commercially available \[Brand] colorimetric assay kit. The analysis was performed on an automated analyzer. The kit included standardized calibrators, and the calibration was done according to the manufacturer's protocol to ensure accuracy and consistency of the results. Compared with the normal reference range of 7–56 U/L.
3. Lipid Profile (Triglycerides, HDL, LDL, Total Cholesterol): The lipid profile was measured using automated lipid assay kits, according to the manufacturer's instructions. Calibration of the equipment and assay kits was performed using standard lipid calibrators, following the protocol recommended by the kit manufacturer to ensure reliable and precise measurements.

All assays were performed following the standard laboratory procedures and protocols. The quality control samples were used for each assay to confirm the consistency and reliability of the results:

- Hepatic Dysfunction is defined as any abnormality in liver function, typically indicated by elevated levels of liver enzymes such as ALT, which may signal liver injury or inflammation.
- Bilirubin (Total, Direct, and Indirect): Compared with the normal reference range for total bilirubin (0.3–1.2 mg/dL), direct bilirubin (0.1–0.3 mg/dL), and indirect bilirubin (0.2–0.8 mg/dL).
- Triglycerides (TG): Compared with the normal reference range of 40–150 mg/dL.
- HDL (High Density Lipoprotein): Compared with the normal reference range of 40–60 mg/dL.
- LDL (Low Density Lipoprotein): Compared with the normal reference range of 50–100 mg/dL.
- Total Cholesterol (TCH): Compared with the normal reference range of 120–200 mg/dL.
- Hemoglobin (Hb): Compared with the normal reference range of 12–16 g/dL for females and 14–18 g/dL for males.
- Red Blood Cell Count (RBCs): Compared with the normal reference range of 4.2–5.4 million cells/μL for females and 4.7–6.1 million cells/μL for males.
- White Blood Cell Count (WBCs): Compared with the normal reference range of 4,500–11,000 cells/μL.

Altered Lipid Composition is defined as any significant deviation in the concentration of blood lipids, such as triglycerides, cholesterol, LDL, or HDL, from normal reference values. Dyslipidemia, often observed in patients with iron overload, is marked by elevated triglycerides, reduced HDL, and altered LDL levels, all of which contribute to increased cardiovascular risk Fasting for Lipid Measurement: Lipid parameters (triglycerides, HDL, LDL, and total cholesterol) were measured after an overnight fasting period of at least 8 hours to ensure accurate results, as fasting is required for standard lipid testing to avoid postprandial variations. These parameters were selected to assess iron overload, liver function, lipid profile, and overall haematological health. The results were compared with their respective reference values to determine any deviations that might indicate complications associated with β-thalassemia and transfusion-related iron overload.

Statistical Analysis

The data were analyzed using SPSS Version 20. Normality of continuous variables was assessed using the Shapiro–Wilk test. For normally distributed data, parametric tests, including independent sample tests and ANOVA, were used to compare means between groups. Nonparametric tests were applied when the data were not normally distributed. The Chi-square test was employed to analyze categorical variables, such as gender, family history of thalassemia, and type of thalassemia. To account for multiple comparisons, a Bonferroni correction was applied where necessary to adjust the significance level and control for Type I errors. Differences were considered statistically significant when the p value was less than 0.05.

Result

Table 1 shows the sample was predominantly young, with 64.2% of participants being under 10 years of age. A significant majority (79.2%) were male, and 43.4% had no formal education, being classified as illiterate. Additionally, 98.1% of the participants were unemployed, highlighting the socio-economic difficulties faced by thalassemia patients in Yemen.

Table 2 demonstrates that Thalassemia patients exhibited significantly elevated levels of ferritin (P = 0.000), serum iron (P = 0.000), and GPT (ALT) (P = 0.000), suggesting the presence of iron overload and liver dysfunction. Additionally, the patients displayed dyslipidemia, characterized by reduced HDL, LDL, and total cholesterol levels (P = 0.004, 0.001, 0.000, respectively), along with increased triglyceride levels (P = 0.015). Anemia was evidenced by significantly lower hemoglobin (Hb) (P = 0.000) and red blood cell (RBC) counts (P = 0.000).

Table 1 The Sociodemographic Characteristics of the Studied Participants

The Sociodemographic Characteristics		N	%
Age	Less than 10 years	34	64.2
	Between 1018 year	15	28.3
	Between 1927 year	2	3.8
	More than or equal to 28 year	2	3.8
Sex	Male	42	79.2
	Female	11	20.8
Educational Level	Illiterate	23	43.4
	Primary	22	41.5
	Preparatory school	3	5.7
	Secondary school	4	7.5
	Bachelor	1	1.9
Job	Employee	1	1.9
	Not employee	52	98.1
Cases	Group I (Healthy people) as control one	20	37.7
	Group II (Patients receiving blood and using ICT) as cases	15	28.3
	Group III (Patients receiving blood without using ICT) as control two	14	26.4
	Group IV (Patients did not received blood and ICT) as control three	4	7.5

Table 2 Mean of Some Physical, Biochemical and Haematological Parameters Among Patients with Thalassemia, Healthy People, Transfusion Dependent and Non-Transfusion Dependent β-Thalassemia Patients

Tests	(Group I)		Patients with Thalassemia		P. value	(Group II and Group III)		(Group IV)		P Value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Ferritin	62.88	40.64	1505.39	734.57	0	1679.8966	595.19333	240.25	144.7305	0
Serum iron	7.73	3.36	46.69	15.9	0	51.3103	9.76913	13.25	10.5317	0
BMI	31.59	15	46.65	41.91	0.129	50.4581	43.39816	19.0697	2.19924	0.164
LDL	96.9	38.88	64.6	25.32	0.001	65.931	25.13525	55	28.36665	0.427
HDL	45.15	4.83	41.93	2.97	0.004	41.931	2.78941	42	4.69042	0.966
TG	118.65	111.05	215.63	75.35	0	179	85.71798	206.75	144.44693	0.806
TCH	150.45	52.71	109.96	24.01	0	112.8276	25.74195	109.25	38.06464	0.95
GPT	13.8	5.28	53.81	25.16	0	35.4483	28.07717	33.25	23.85197	0.081
Tbilirubin	0.97	0.82	1.49	1.09	0.2	1.5	1.14455	1.2	0.94163	0.576
Dbilirubin	0.27	0.11	0.51	0.47	0.043	0.4724	0.39087	0.3	0.18257	0.333
PLT	331.4	115.3	359.6	247.96	0.635	329.3448	170.60151	579	557.82494	0.058
RBCs	5.08	0.42	3.21	0.84	0	3.0069	0.54046	4.725	1.21758	0
WBCs	7.71	2.63	10.63	4.76	0.015	10.1517	5.17588	8.9	0.86023	0.445
Hb	13.29	1.44	7.65	1.64	0	7.3586	1.30562	9.8	2.43447	0

Notes: (Group I) = Healthy people, (Group II and group III) = Patients receiving blood, (Group IV) = Patients did not received blood.

Table 3 indicates that patients who received more than 250 mL of blood exhibited significantly higher ferritin (P = 0.027) and GPT (P = 0.049) levels, suggesting increased iron overload and liver damage. Additionally, these patients had a lower BMI (P = 0.006), which may reflect poorer overall health associated with larger blood transfusions.

Table 3 Mean of Some Physical, Biochemical and Haematological Parameters Among Transfusion-Dependent β-Thalassemia Patients According to Blood Receiving Volume

Tests	Less than or Equal to 250 mL		More than 250 mL		P. value
	Mean	SD	Mean	SD	
BMI	70.8910	41.48658	28.5656	24.71515	0.006
LDL	60.3333	24.83277	71.9286	24.93519	0.221
HDL	42.4667	3.04412	41.3571	2.46848	0.293
TG	153.2000	87.41625	206.6429	77.49303	0.094
TCH	109.8667	27.57293	116.0000	24.23919	0.531
Ferritin	1448.0667	459.58296	1928.2857	638.03634	0.027
Serum Iron	51.6667	11.72705	50.9286	7.55965	0.843
GPT	25.7333	19.17017	45.8571	32.81148	0.049
T bilirubin	1.1333	0.64771	1.8929	1.43123	0.073

(*Continued*)

Table 3 (Continued).

Tests	Less than or Equal to 250 mL		More than 250 mL		P. value
	Mean	SD	Mean	SD	
D bilirubin	0.3933	0.24919	0.5571	0.49725	0.267
PLT	344.6000	185.37869	313.0000	158.50067	0.627
RBCs	2.9000	0.46291	3.1214	0.60913	0.278
WBCs	11.6933	6.29381	8.5000	3.05966	0.097
PCV	21.6267	3.25367	23.7571	4.62064	0.160
Hb	7.0733	1.12597	7.6643	1.45317	0.230

Table 4 reveals that patients with more than 5 years of transfusions exhibited significantly higher ferritin levels (P = 0.011), along with lower platelet count (P = 0.041) and BMI (P = 0.025). These findings suggest long-term iron overload and a progressive decline in health over time.

Table 5 shows that Group II (transfusion + ICT) exhibited significantly higher ferritin (P = 0.000) and serum iron (P = 0.000) levels, indicating ongoing iron overload despite iron chelation therapy (ICT). Additionally, RBC count (P = 0.001) and hemoglobin (Hb) levels (P = 0.022) were significantly lower, suggesting that ICT does not fully prevent anemia.

Table 4 Comparison of Biochemical and Hematological Parameters in Transfusion-Dependent β-Thalassemia Patients Based on Duration of Blood Transfusion

Test	Period of Receiving Blood				P Value
	Less than or Equal to 5 Years		More than 5 Years		
	Mean	SD	Mean	SD	
BMI	67.8805	44.64134	18.8550	3.93852	0.025
LDL	58.6842	23.55149	75.8000	23.99375	0.164
HDL	42.5263	2.87457	41.0000	2.64575	0.296
TG	155.7895	79.30712	214.2000	80.18541	0.158
TCH	107.1579	26.30645	120.0000	23.46274	0.333
Ferritin	1458.2632	485.28718	2238.0000	814.47529	0.011
Serum Iron	50.9474	11.66892	51.0000	6.20484	0.992
GPT	40.6842	25.54311	55.2000	21.83346	0.259
Tbilirubin	1.4737	1.23866	1.4000	0.90277	0.903
Dbilirubin	0.5132	0.46840	0.3800	0.17889	0.545
PLT	356.1053	170.32514	183.4000	84.36409	0.041
RBCs	3.0263	0.62525	2.8200	0.25884	0.484
WBCs	11.3316	5.59385	8.2800	2.34137	0.252
PCV	22.5789	4.37957	21.1400	3.42972	0.505
Hb	7.3474	1.39896	7.0200	1.26372	0.640

Table 5 Comparison of Biochemical and Hematological Parameters Between Transfusion-Dependent β-Thalassemia Patients with and without Iron Chelation Therapy (ICT)

Tests	Group II (Patients Receiving Blood and Using ICT)		Group IV (Patients did not Received Blood and ICT)		P.value
	Mean	SD	Mean	SD	
Ferritin	2005.0667	555.51205	240.2500	144.73050	0.000
Serum Iron	51.6000	6.66333	13.2500	10.53170	0.000
BMI	25.2405	24.64018	19.0697	2.19924	0.630
LDL	73.9333	21.81895	55.0000	28.36665	0.164
HDL	41.1333	2.61498	42.0000	4.69042	0.624
TG	212.0000	78.50296	206.7500	144.44693	0.922
TCH	118.0667	20.83084	109.2500	38.06464	0.535
GPT	45.0000	31.61148	33.2500	23.85197	0.89
Tbilirubin	1.7467	1.43221	1.2000	0.94163	0.484
Dbilirubin	0.5133	0.49116	0.3000	0.18257	0.414
PLT	324.4667	172.63623	579.0000	557.82494	0.127
RBCs	2.9733	0.67132	4.7250	1.21758	0.001
WBCs	9.7733	3.22811	8.9000	0.86023	0.606
Hb	7.2667	1.62334	9.8000	2.43447	0.022

Table 6 demonstrates that Group III (transfusion without ICT) had significantly higher ferritin (P = 0.000) and serum iron (P = 0.000) levels compared to Group IV. Additionally, Group III showed significantly lower RBC count (P = 0.000) and hemoglobin (Hb) levels (P = 0.018), indicating that iron overload in the absence of ICT exacerbates anemia.

Table 6 Comparison of Biochemical and Hematological Parameters Between Transfusion-Dependent β-Thalassemia Patients with and without ICT

Tests	Group III (Patients Receiving Blood without Using ICT)		Group IV (Patients did not Receive Blood and ICT)		P. value
	Mean	SD	Mean	SD	
Ferritin	1331.5000	421.85264	240.2500	144.73050	0.000
Serum iron	51.0000	12.55143	13.2500	10.53170	0.000
BMI	77.4769	43.39101	19.0697	2.19924	0.018
LDL	57.3571	26.36317	55.0000	28.36665	0.878
HDL	42.7857	2.80600	42.0000	4.69042	0.675
TG	143.6429	81.15380	206.7500	144.44693	0.729
TCH	107.2143	29.90544	109.2500	38.06464	0.599
GPT	25.2143	20.09278	33.2500	23.85197	0.50

(*Continued*)

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Table 6 (Continued).

Tests	Group III (Patients Receiving Blood without Using ICT)		Group IV (Patients did not Receive Blood and ICT)		P. value
	Mean	SD	Mean	SD	
Tbilirubin	1.2357	0.68344	1.2000	0.94163	0.793
Dbilirubin	0.4286	0.25549	0.3000	0.18257	0.290
PLT	334.5714	174.74188	579.0000	557.82494	0.154
RBCs	3.0429	0.37563	4.7250	1.21758	0.000
WBCs	12.0571	6.36018	8.9000	0.86023	0.000
Hb	7.4571	0.90189	9.8000	2.43447	0.018

Table 7 Relationship Between Liver Function, Lipid Levels, Hematological Parameters, and Iron Overload in Transfusion-Dependent β-Thalassemia Patients

Test	Ferritin Level among Transfusion Dependent β-Thalassemia Patients				P Value
	High		Normal		
	Mean	SD	Mean	SD	
GPT	48.7500	28.75593	14.1905	5.45545	0.000
Tbilirubin	1.4656	1.10208	1.0429	0.80404	0.294
Dbilirubin	0.5234	0.48343	0.2762	0.21290	0.043
LDL cholesterol	66.0938	24.22124	93.0952	41.72278	0.004
HDL cholesterol	41.7500	2.81700	45.2857	45.2857	0.001
Triacyl glyceride	185.8125	91.31174	116.4286	116.4286	0.015
Total cholesterol	113.8438	25.85706	146.4286	146.4286	0.005
Hb	7.5781	1.60939	13.1381	1.57050	0.000
Platelets (PLTs)	329.1250	178.38066	379.1905	246.15638	0.395
RBCs	3.1438	0.75389	5.1048	0.42009	0.000
WBCs	10.6938	4.4826	7.7619	2.57924	0.014

Table 7 illustrates that elevated ferritin levels were significantly associated with higher GPT (ALT) (P = 0.000), direct bilirubin (P = 0.043), and triglycerides (TG) (P = 0.015), confirming iron-induced liver damage and dyslipidemia. Moreover, lower hemoglobin (Hb) (P = 0.000) and RBC count (P = 0.000), along with higher white blood cell (WBC) count (P = 0.014), were correlated with iron overload, suggesting anemia and immune dysregulation.

Discussions

This study aimed to investigate the relationship between iron overload, liver dysfunction, and lipid abnormalities in transfusion-dependent β-thalassemia patients. The findings indicate that iron overload, as measured by elevated serum ferritin and serum iron levels, is strongly associated with liver dysfunction and lipid abnormalities in transfusion-dependent β-thalassemia patients. These results support the growing evidence that excessive iron accumulation due to

chronic transfusions contributes to various complications in β-thalassemia patients, particularly liver damage and dyslipidemia.[9,10]

The findings of this study provide important insights into the relationship between iron overload, liver dysfunction, and dyslipidemia in transfusion-dependent β-thalassemia patients. The groups in this study were created based on key clinical characteristics to better understand the impact of regular blood transfusions and iron chelation therapy (ICT) on these parameters.

Group I (Healthy controls): This group was essential for comparison to assess the baseline levels of ferritin, iron, liver enzymes, and lipids in individuals without thalassemia. This allowed us to distinguish between abnormalities arising from thalassemia and those seen in the general population. The importance of using a healthy control group to provide baseline values in studies of thalassemia has been emphasized in previous research.[4]

Group II (Transfusion-dependent β-thalassemia patients with ICT): This group was included to evaluate the effects of both iron overload due to regular transfusions and the potential protective effects of iron chelation therapy. Studies have demonstrated that ICT can reduce iron levels and mitigate organ damage in thalassemia patients.[5] By including this group, we aimed to investigate whether ICT could mitigate some of the negative impacts of transfusions on liver function and lipid profiles.[6]

Group III (Transfusion-dependent β-thalassemia patients without ICT): This group was critical for assessing the effect of iron overload in the absence of ICT. It helped us understand how iron accumulation contributes to liver damage and dyslipidemia when chelation therapy is not available or effective. Previous studies have shown that the absence of proper chelation therapy exacerbates iron overload and related complications, such as liver damage and dyslipidemia.[8,9]

Group IV (Non-transfused β-thalassemia patients): Although small in sample size, this group was included to compare the parameters of non-transfused thalassemia patients with those receiving transfusions. While its statistical analysis was limited due to the small number of participants, it provided valuable insight into the baseline condition of β-thalassemia patients who are not exposed to the added burden of transfusion-related iron overload. The inclusion of non-transfused patients allows for a comparison of iron overload levels, lipid profiles, and liver function between transfused and non-transfused patients, which has been previously highlighted as an important comparison.[11]

The groups were carefully selected to reflect different clinical realities encountered in thalassemia management, particularly in resource limited settings. By comparing these groups, we were able to assess the cumulative effects of transfusions and ICT on iron overload, liver function, lipid metabolism, and haematological parameters. The differentiation of the groups based on transfusion status and ICT use is consistent with recommendations in the literature regarding the need for detailed subgroup analysis in thalassemia studies.[2,12]

Our study found that transfusion-dependent patients had significantly higher serum ferritin and serum iron levels compared to healthy controls. Elevated levels of liver enzymes (GPT and bilirubin) were also significantly higher in transfusion-dependent patients, suggesting the detrimental effect of iron overload on liver function. This is consistent with previous studies that have demonstrated the negative impact of iron accumulation on liver function, leading to hepatotoxicity, liver fibrosis, and cirrhosis.[6,7] In thalassemia patients, iron overload in the liver occurs when the body's capacity to sequester excess iron exceeds its removal, primarily due to ineffective chelation therapy or inadequate management.[5] Our findings emphasize the importance of routine monitoring of liver function markers, particularly in patients receiving regular transfusions, to detect early signs of liver injury and prevent irreversible damage.

The lipid profiles of transfusion-dependent β-thalassemia patients showed significant alterations compared to healthy controls. Specifically, these patients had elevated triglyceride levels and reduced HDL cholesterol, consistent with dyslipidemia commonly seen in patients with iron overload. Similar findings have been reported in previous studies, where iron overload in β-thalassemia patients was found to be associated with lipid metabolism disturbances, potentially increasing cardiovascular risk.[8,13] Dyslipidemia in thalassemia patients is thought to result from iron induced oxidative stress and liver dysfunction, which impairs lipid metabolism.[14,15] Iron overload can directly affect lipid synthesis in the liver, leading to an increase in triglycerides and a decrease in HDL levels. These findings further highlight the need for routine lipid monitoring in thalassemia patients, particularly those with high ferritin levels, to manage and mitigate cardiovascular risk.

Our study also examined the role of ICT in mitigating iron overload and its associated complications. Patients who received ICT (Group II) had significantly lower ferritin levels and comparatively better liver function and lipid profiles compared to those who did not receive ICT (Group III). These findings underscore the importance of effective iron chelation therapy in managing iron overload and preventing complications such as liver dysfunction and dyslipidemia. Several studies have shown that ICT significantly reduces serum ferritin levels and improves liver function by preventing iron accumulation in the liver[4]. However, the results from our study also suggest that while ICT improves iron control, it does not completely normalize lipid profiles, highlighting the need for a multifaceted approach to managing thalassemia-related complications, including dietary and lifestyle interventions to address dyslipidemia.

Thalassemia is a major public health burden in Yemen, with approximately 700 new cases diagnosed annually and thousands living with the condition (WHO, 2020). In our cohort, 54.7% of participants had received transfusions, yet only 28.3% reported using ICT, and nearly half had no structured follow-up. This reflects systemic challenges in resource limited settings, including restricted access to chelation, fragmented care, and limited patient education.[2,5,6] The majority of participants were children under 10 years of age (64.2%) and male (79.2%), with low educational attainment—factors that may influence health seeking behavior, treatment adherence, and followup attendance.[1,8]

Given that 64.2% of participants were under 10 years of age, the potential impact of β-thalassemia on neurocognitive development and academic performance is a critical consideration. Chronic anemia, iron overload, and associated complications can impair concentration, memory, and school performance, as shown in lower grades and standardized scores in other pediatric thalassemia cohorts.[1,4] Although our study did not assess academic performance, incorporating cognitive and educational evaluations into future research would provide valuable insight into the broader quality of life burden in this vulnerable age group. Although this study focused on transfusion history, ICT use, and laboratory parameters, other patient-related factors such as comorbid illnesses and nutritional status are important considerations in interpreting the results. β-thalassemia patients in low-resource settings like Yemen may face recurrent infections, micronutrient deficiencies, and varying degrees of undernutrition, all of which can affect hematologic indices, lipid metabolism, and liver function. For example, chronic infections can elevate inflammatory markers and alter lipid levels, while malnutrition can exacerbate anemia and impair immune responses. Although these variables were not systematically assessed in the present study, future research should incorporate detailed medical history and nutritional assessments to better account for their potential confounding effects on biochemical and clinical outcomes.

One of the main limitations of this study is the small sample size, particularly in Group IV (non-transfused β-thalassemia patients), which had only 4 participants. The small sample size in this group significantly limits the statistical power of the analysis and weakens the ability to draw robust conclusions from comparisons with the other groups. The lack of statistical power in Group IV means that the results should be interpreted with caution. Larger studies with more balanced group sizes are needed to validate these findings and improve the reliability of comparisons between transfused and non-transfused patients.

Moreover, the cross-sectional design of this study limits the ability to establish causal relationships between iron overload, liver dysfunction, and lipid abnormalities. Longitudinal studies, which follow patients over time, would be better suited to determine the directionality and causality of these associations. Future research should focus on larger cohorts, especially non-transfused patients, to clarify the long-term effects of iron overload in β-thalassemia patients and the role of ICT in mitigating these complications. Additionally, the potential role of genetic factors and their interaction with iron overload in contributing to liver dysfunction and dyslipidemia should be explored.

Conclusions

This study highlights significant associations between iron overload, liver dysfunction, and lipid abnormalities in transfusion-dependent β-thalassemia patients. Elevated serum ferritin levels, indicating iron overload, were strongly linked to liver dysfunction as evidenced by increased liver enzymes (GPT) and bilirubin. Additionally, dyslipidemia, characterized by higher triglycerides and lower HDL, was prevalent among transfusion-dependent patients, underscoring the impact of iron overload on lipid metabolism. The findings suggest that iron chelation therapy (ICT) plays a pivotal role in mitigating these complications, as patients receiving ICT exhibited lower ferritin levels and better liver function and lipid profiles compared to those not receiving ICT. However, due to the cross-sectional design, the study only

identifies associations, not causal relationships. The small sample size, especially in Group IV (non-transfused patients), limits the statistical power of subgroup comparisons, and the results from this group should be interpreted with caution. Larger studies with more robust sample sizes, particularly in non-transfused groups, are necessary to confirm these findings. In light of these results, we recommend routine ferritin monitoring, enhanced access to ICT, and comprehensive follow up strategies for transfusion-dependent β-thalassemia patients to prevent the long-term complications of iron overload. These measures are crucial for improving patient outcomes, especially in settings where access to treatment may be limited. Further longitudinal studies are required to validate the causal relationships between iron overload, liver dysfunction, and lipid abnormalities and to refine treatment protocols for this patient population.

Data Sharing Statement

All data included in the manuscript are available upon request from corresponding author.

Ethics Approvals

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Intuitional Review Board in the Ethics Committee of the Faculty of Medicine and Health Science, Sanaa university, Yemen (Research code: REC**1224**).

Consent to Participate

Informed consent was obtained from all individuals participants included in the study. For participants under 18 years of age, written informed consent was obtained from a parent or legal guardian.

Consent to Publish

Patients signed informed consent regarding publishing their data to the journal.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors of this study do not report any conflict of interest.

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