Correlation Of Serum Ferritin with Lipid Profile in Multiple Transfusion Dependent Beta Thalassemia Patient

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KEYWORDS

Beta Thalassemia, Serum Ferritin, Lipid Profile, Iron Overload, HDL Cholesterol

ABSTRACT:

Background: Beta thalassemia major patients require regular blood transfusions leading to iron overload, which may impact lipid metabolism. This study investigated the correlation between serum ferritin and lipid profile parameters in transfusion-dependent beta thalassemia patients.

Methods: In this cross-sectional study, 86 transfusion-dependent beta thalassemia patients were enrolled. Serum ferritin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured after a 12-hour fast. Patients were categorized into four groups based on ferritin levels. Statistical analysis included correlation coefficients and multiple linear regression.

Results: The median serum ferritin was 2763 ng/mL, with 33.7% of patients having severe iron overload (>5000 ng/mL). Significant inverse correlations were observed between serum ferritin and TC ($r=-0.463$, $p<0.001$), HDL-C ($r=-0.512$, $p<0.001$), and LDL-C ($r=-0.487$, $p<0.001$), while TG showed a positive correlation ($r=0.248$, $p=0.021$). Multivariate analysis confirmed serum ferritin as an independent predictor of lipid parameters after adjusting for age, gender, BMI, splenectomy status, and chelation therapy type. Splenectomized patients exhibited significantly higher TG and lower HDL-C levels compared to non-splenectomized patients, while deferasirox therapy was associated with more favorable HDL-C levels.

Conclusion: Iron overload in transfusion-dependent beta thalassemia is associated with a distinctive dyslipidemic pattern characterized by reduced TC, HDL-C, and LDL-C alongside elevated TG. Regular monitoring of both iron status and lipid parameters is essential for comprehensive management of these patients, with effective iron chelation potentially mitigating adverse effects on lipid metabolism.

INTRODUCTION

Beta thalassemia represents one of the most common hereditary hemoglobinopathies worldwide, characterized by reduced or absent synthesis of beta-globin chains leading to ineffective erythropoiesis and chronic hemolytic anemia [1]. Patients with beta thalassemia major require regular blood transfusions to maintain adequate hemoglobin levels and sustain normal growth and development [2]. However, these life-saving transfusions result in progressive iron accumulation in various organs, as the human body lacks an efficient physiological mechanism to eliminate excess iron [3]. Iron overload, assessed primarily through serum ferritin levels, is a major complication in transfusion-dependent beta thalassemia patients [4]. The excessive iron deposits in vital organs such as the heart, liver, and endocrine glands, leading to significant morbidity and mortality if left untreated [5]. Despite advances in iron chelation therapy, iron-related complications remain prevalent among these patients [6]. Growing evidence suggests that iron overload may significantly impact lipid metabolism in beta thalassemia patients [7]. Several studies have documented alterations in lipid profiles, including decreased

total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels in these patients [8, 9]. These lipid abnormalities may contribute to the increased risk of cardiovascular complications observed in long-term survivors of beta thalassemia [10]. The relationship between serum ferritin levels and lipid profile parameters in transfusion-dependent beta thalassemia patients remains incompletely understood, with conflicting findings reported in the literature [11, 12]. Some studies suggest an inverse correlation between serum ferritin and lipid parameters [13], while others report no significant association [14]. Additionally, factors such as age, transfusion frequency, splenectomy status, and chelation therapy regimens may influence both iron overload and lipid metabolism in these patients [15]. Understanding the precise nature of the relationship between iron overload and lipid abnormalities in beta thalassemia could provide valuable insights into the pathophysiology of iron-related complications and potentially guide optimization of therapeutic strategies [16]. Therefore, this study aims to investigate the correlation between serum ferritin levels and lipid profile parameters in multiple transfusion-dependent beta thalassemia patients, considering various clinical and demographic factors that may influence this relationship.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional analytical study was conducted at Haematology outpatient department of Bangabandhu Sheikh Mujib Medical University from January 2021 to December 2021. A total of 86 transfusion-dependent beta thalassemia major patients were enrolled using a consecutive sampling technique. The diagnosis of beta thalassemia major was confirmed based on clinical features, complete blood count, hemoglobin electrophoresis, and family history. Patients receiving regular blood transfusions (at least 8 transfusions per year) for a minimum of 2 years were included in the study. Exclusion criteria comprised patients with other hemoglobinopathies, concomitant liver disease unrelated to iron overload, diabetes mellitus, thyroid dysfunction, or those receiving medications known to affect lipid metabolism such as statins or steroids.

Data Collection

Demographic data including age, gender, age at diagnosis, duration of transfusion therapy, transfusion frequency, and chelation therapy details were collected using a structured questionnaire and verified from medical records. Anthropometric measurements including height and weight were obtained using standardized techniques, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Clinical examination was performed to assess hepatomegaly, splenomegaly, or previous splenectomy status.

Laboratory Investigations

Blood Sampling

After obtaining informed consent, blood samples were collected following a 12-hour overnight fast. For all participants, blood samples were collected just before their scheduled transfusion (at least 2 weeks after the previous transfusion) to minimize the influence of recent transfusions on laboratory parameters. Venous blood samples (10 ml) were drawn using standard venipuncture techniques under aseptic conditions and distributed into appropriate tubes for different analyses.

Hematological Parameters

Complete blood count including hemoglobin level, red blood cell indices, white blood cell count, and platelet count was determined using an automated hematology analyzer. Pre-transfusion hemoglobin levels were recorded for the assessment of transfusion adequacy.

Serum Ferritin Measurement

Serum ferritin levels were measured using electrochemiluminescence immunoassay (ECLIA) on an automated analyzer. The reference range for serum ferritin in our laboratory was 24-336ng/mL for males and 25-200ng/mL for females. To account for acute phase fluctuations, C-reactive protein (CRP) was simultaneously measured, and patients with elevated CRP levels were either excluded or underwent repeated testing after resolution of acute inflammation.

Lipid Profile Analysis

Serum lipid profile components including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using standardized enzymatic methods on an automated clinical chemistry analyzer. Very-low-density lipoprotein cholesterol (VLDL-C) was calculated using the Friedewald formula when triglyceride levels were <400 mg/dL. Additionally, non-HDL cholesterol and various atherogenic indices (TC/HDL-C, LDL-C/HDL-C, and TG/HDL-

C ratios) were calculated. Quality control measures were implemented according to laboratory standards, with internal controls run with each batch of samples and participation in external quality assessment programs.

Liver Function Tests
Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total protein, albumin, and total bilirubin were performed to assess hepatic function using standard methods.

Statistical Analysis
Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation for normally distributed data and median with interquartile range for non-normally distributed data. Categorical variables were presented as frequencies and percentages. Normality of data distribution was assessed using the Shapiro-Wilk test. Patients were stratified into different groups based on serum ferritin levels: <1000 ng/mL, 1000-2500 ng/mL, 2501-5000 ng/mL, and >5000 ng/mL, to evaluate the relationship between iron burden severity and lipid profile parameters. Comparisons between groups were made using one-way analysis of variance (ANOVA) with post-hoc Tukey's test for normally distributed variables and Kruskal-Wallis test with post-hoc Dunn's test for non-normally distributed variables.
Correlation between serum ferritin levels and lipid profile parameters was assessed using Pearson's or Spearman's correlation coefficient based on data distribution. Multiple linear regression analysis was performed to identify independent predictors of lipid profile parameters, adjusting for potential confounding variables including age, gender, BMI, splenectomy status, and type of chelation therapy. Multicollinearity was assessed using variance inflation factor. Additionally, subgroup analyses were performed based on age groups, gender, splenectomy status, and chelation therapy regimens to evaluate potential modifiers of the ferritin-lipid relationship. A p-value <0.05 was considered statistically significant for all analyses.

RESULTS
Demographic and Clinical Characteristics
A total of 86 patients with transfusion-dependent beta thalassemia major were included in the study. The demographic and clinical characteristics of the study population are presented in Table 1. The mean age of the participants was 15.3 ± 6.8 years, with a slight male predominance (53.5%). The mean age at diagnosis was 1.2 ± 0.9 years, and the mean duration of transfusion therapy was 14.1 ± 6.7 years. The majority of patients (68.6%) were receiving transfusions at 2–4-week intervals, with a mean pre-transfusion hemoglobin level of 8.2 ± 1.1 g/dL.

Table 1: Demographic and Clinical Characteristics of Study Population (n=86)

Parameter	Value
Age (years), mean ± SD	15.3 ± 6.8
Gender, n (%)	
Male	46 (53.5%)
Female	40 (46.5%)
Age at diagnosis (years), mean ± SD	1.2 ± 0.9
Duration of transfusion therapy (years), mean ± SD	14.1 ± 6.7
Transfusion frequency, n (%)	
Every 2 weeks	30 (34.9%)
Every 3 weeks	18 (20.9%)
Every 4 weeks	11 (12.8%)
Variable frequency	27 (31.4%)
Pre-transfusion hemoglobin (g/dL), mean ± SD	8.2 ± 1.1
Splenectomy status, n (%)	
Splenectomized	36 (41.9%)
Non-splenectomized	50 (58.1%)
BMI (kg/m²), mean ± SD	17.9 ± 3.1
Chelation therapy, n (%)	
Deferasirox	39 (45.3%)
Deferiprone	22 (25.6%)
Deferoxamine	8 (9.3%)
Combination therapy	12 (14.0%)
No chelation	5 (5.8%)

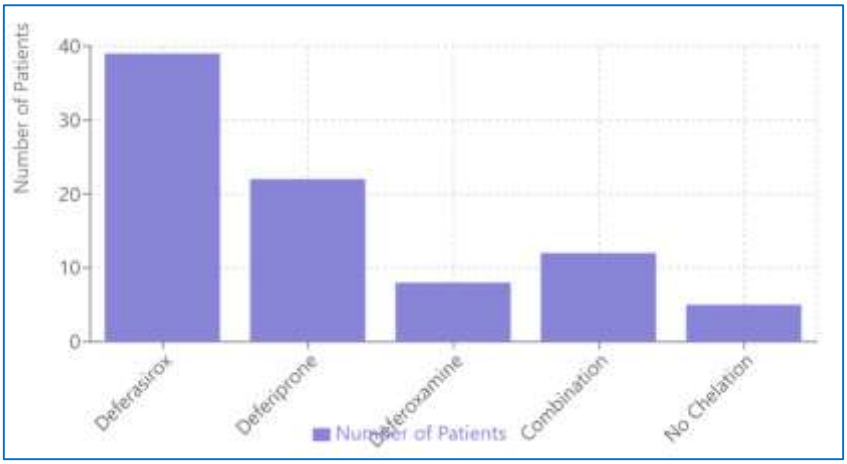

Fig 1: A bar graph showing the distribution of patients by chelation therapy type would be appropriate here.

Serum Ferritin Levels and Iron Overload Status

The median serum ferritin level of the study population was 2763 ng/mL (interquartile range: 1524-4835 ng/mL), indicating significant iron overload in the majority of patients. Based on serum ferritin levels, patients were categorized into four groups as shown in Table 2. Only 8.1% of patients had ferritin levels below 1000 ng/mL, while 33.7% had severe iron overload with ferritin levels exceeding 5000 ng/mL.

Table 2: Distribution of Patients According to Serum Ferritin Levels

Serum Ferritin (ng/mL)	Number of Patients (%)
<1000	7 (8.1%)
1000-2500	32 (37.2%)
2501-5000	18 (20.9%)
>5000	29 (33.7%)

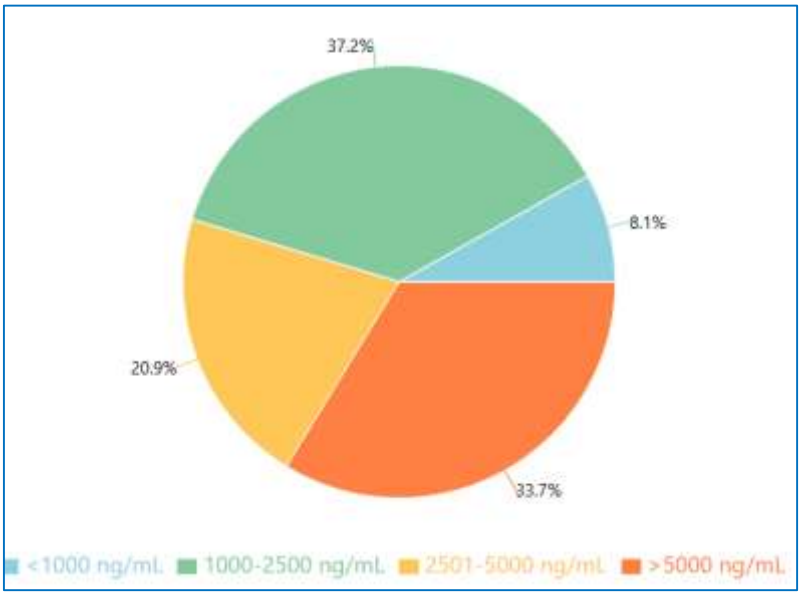

Fig 2: A pie chart illustrating the distribution of patients according to serum ferritin categories

Lipid Profile Parameters

The lipid profile parameters of the study population are summarized in Table 3. Overall, the mean values of total cholesterol, LDL-C, and HDL-C were lower than reference ranges for age-matched controls, while triglyceride levels were within normal limits.

Table 3: Lipid Profile Parameters of the Study Population

Parameter (mg/dL)	Mean ± SD	Reference Range*
Total Cholesterol	128.6 ± 26.7	150-200
Triglycerides	112.4 ± 48.3	<150
HDL-C	32.8 ± 9.4	>40
LDL-C	73.3 ± 24.5	<100
VLDL-C	22.5 ± 9.7	<30
Non-HDL-C	95.8 ± 25.9	<130
TC/HDL-C ratio	4.1 ± 1.3	<4.5
LDL-C/HDL-C ratio	2.3 ± 0.9	<3.0
TG/HDL-C ratio	3.6 ± 1.9	<3.5

*Reference ranges for age-matched controls from institutional laboratory guidelines

Correlation Between Serum Ferritin and Lipid Profile Parameters

Analysis of lipid profile parameters across different ferritin categories revealed a significant inverse relationship between serum ferritin levels and total cholesterol, HDL-C, and LDL-C (Table 4). Patients with higher ferritin levels demonstrated progressively lower values of these parameters ($p<0.01$). Triglyceride levels, however, showed a positive correlation with serum ferritin, with higher TG levels observed in patients with severe iron overload ($p=0.038$).

Table 4: Lipid Profile Parameters According to Serum Ferritin Categories

Parameter (mg/dL)	Ferritin <1000 ng/mL (n=7)	Ferritin 1000-2500 ng/mL (n=32)	Ferritin 2501-5000 ng/mL (n=18)	Ferritin >5000 ng/mL (n=29)	p-value
Total Cholesterol	156.3 ± 23.8	138.7 ± 25.2	124.1 ± 20.4	113.5 ± 22.3	<0.001
Triglycerides	98.6 ± 35.2	103.8 ± 42.7	114.7 ± 51.3	125.9 ± 53.6	0.038
HDL-C	41.9 ± 8.7	35.4 ± 9.1	31.2 ± 8.3	28.3 ± 7.9	<0.001
LDL-C	94.7 ± 21.3	82.6 ± 24.1	70.0 ± 19.8	59.9 ± 21.5	<0.001
VLDL-C	19.7 ± 7.0	20.8 ± 8.5	22.9 ± 10.3	25.2 ± 10.7	0.042
Non-HDL-C	114.4 ± 22.1	103.3 ± 24.5	92.9 ± 20.6	85.2 ± 23.1	<0.001
TC/HDL-C ratio	3.7 ± 0.8	3.9 ± 1.1	4.0 ± 1.2	4.5 ± 1.6	0.026
LDL-C/HDL-C ratio	2.3 ± 0.6	2.3 ± 0.8	2.2 ± 0.7	2.4 ± 1.1	0.872
TG/HDL-C ratio	2.4 ± 0.9	3.0 ± 1.4	3.8 ± 1.8	4.5 ± 2.2	<0.001

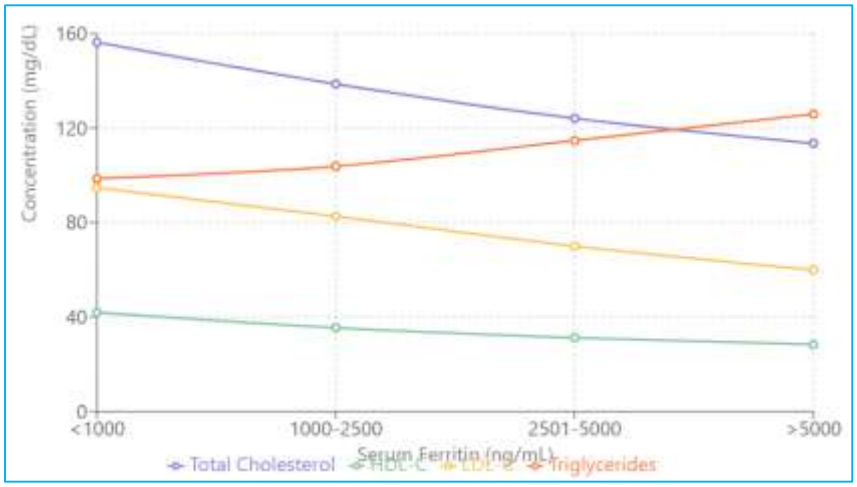

Fig 3: A line graph showing the trends of TC, HDL-C, LDL-C, and TG across different ferritin categories

Correlation analysis confirmed significant negative correlations between serum ferritin and total cholesterol (r=-0.463, p<0.001), HDL-C (r=-0.512, p<0.001), and LDL-C (r=-0.487, p<0.001), while a positive correlation was observed with triglycerides (r=0.248, p=0.021) and TG/HDL-C ratio (r=0.413, p<0.001) as shown in Table 5.

Table 5: Correlation Between Serum Ferritin and Lipid Profile Parameters

Parameter	Correlation Coefficient (r)*	p-value
Total Cholesterol	-0.463	<0.001
Triglycerides	0.248	0.021
HDL-C	-0.512	<0.001
LDL-C	-0.487	<0.001
VLDL-C	0.252	0.019
Non-HDL-C	-0.414	<0.001
TC/HDL-C ratio	0.272	0.011
LDL-C/HDL-C ratio	0.078	0.475
TG/HDL-C ratio	0.413	<0.001

*Spearman's correlation coefficient was used as serum ferritin values were not normally distributed

Multivariate Analysis

Multiple linear regression analysis was performed to identify independent predictors of lipid profile parameters after adjusting for potential confounding variables including age, gender, BMI, splenectomy status, and type of chelation therapy (Table 6). Serum ferritin remained a significant independent predictor of total cholesterol (β=-0.409, p<0.001), HDL-C (β=-0.487, p<0.001), and LDL-C (β=-0.442, p<0.001) after adjustment for these variables.

Table 6: Multiple Linear Regression Analysis for Predictors of Lipid Profile Parameters

Dependent Variable	Independent Predictor	Standardized β Coefficient	p-value	95% CI	Adjusted R^2
Total Cholesterol	Serum Ferritin (log)	-0.409	<0.001	-24.82 to -11.63	0.324
	Age	0.186	0.048	0.02 to 1.25	
	BMI	0.204	0.032	0.13 to 2.72	
	Splenectomy	-0.112	0.243	-12.63 to 3.22	
HDL-C	Serum Ferritin (log)	-0.487	<0.001	-9.53 to -4.37	0.376
	Gender (female)	0.217	0.017	0.71 to 7.08	
	Age	0.096	0.289	-0.12 to 0.39	
	BMI	0.148	0.106	-0.09 to 0.95	
LDL-C	Serum Ferritin (log)	-0.442	<0.001	-22.58 to -10.27	0.338
	Age	0.169	0.071	-0.05 to 1.09	
	BMI	0.193	0.042	0.04 to 2.31	
	Chelation (Deferasirox)	0.187	0.049	0.05 to 13.71	
Triglycerides	Serum Ferritin (log)	0.231	0.026	1.43 to 22.75	0.192
	Age	0.169	0.097	-0.17 to 1.96	
	BMI	0.181	0.066	-0.07 to 2.97	
	Splenectomy	0.238	0.016	3.01 to 28.64	

CI = Confidence Interval

Subgroup Analysis

Effect of Splenectomy Status

Subgroup analysis based on splenectomy status revealed that splenectomized patients had significantly higher triglyceride levels (129.6 ± 53.1 vs. 99.7 ± 40.4 mg/dL, p=0.003) and lower HDL-C levels (29.4 ± 8.6 vs. 35.3 ± 9.3 mg/dL, p=0.004) compared to non-splenectomized patients. The negative correlation between serum ferritin and HDL-C was stronger in splenectomized patients (r=-0.582, p<0.001) compared to non-splenectomized patients (r=-0.421, p=0.002).

Table 7: Comparison of Lipid Profile Parameters According to Splenectomy Status

Parameter (mg/dL)	Splenectomized (n=36)	Non-splenectomized (n=50)	p-value
Total Cholesterol	124.2 ± 25.9	131.8 ± 27.0	0.188
Triglycerides	129.6 ± 53.1	99.7 ± 40.4	0.003
HDL-C	29.4 ± 8.6	35.3 ± 9.3	0.004
LDL-C	69.0 ± 23.8	76.5 ± 24.8	0.158
VLDL-C	25.9 ± 10.6	19.9 ± 8.1	0.003
TG/HDL-C ratio	4.5 ± 2.1	2.9 ± 1.4	<0.001

Effect of Chelation Therapy

Analysis based on chelation therapy type showed that patients on deferasirox had significantly higher HDL-C levels (35.7 ± 9.6 mg/dL) compared to those on deferiprone (31.4 ± 8.9 mg/dL) or deferoxamine (30.2 ± 8.3 mg/dL) (p=0.027). Patients not receiving any chelation therapy had the lowest HDL-C levels (24.8 ± 6.1 mg/dL) and highest TG/HDL-C ratio (5.3 ± 2.4).

Table 8: Lipid Profile Parameters According to Chelation Therapy Type

Parameter (mg/dL)	Deferasirox (n=39)	Deferiprone (n=22)	Deferoxamine (n=8)	Combination (n=12)	No Chelation (n=5)	p-value
Total Cholesterol	134.5 ± 27.3	128.2 ± 24.9	126.4 ± 26.6	119.7 ± 25.7	112.8 ± 24.1	0.087
Triglycerides	107.8 ± 46.5	111.6 ± 49.2	113.5 ± 51.0	118.9 ± 47.8	129.7 ± 54.3	0.452
HDL-C	35.7 ± 9.6	31.4 ± 8.9	30.2 ± 8.3	33.6 ± 9.5	24.8 ± 6.1	0.027
LDL-C	77.2 ± 25.1	74.5 ± 23.6	73.4 ± 24.7	62.3 ± 23.3	62.1 ± 21.7	0.096
TG/HDL-C ratio	3.1 ± 1.5	3.7 ± 1.8	3.9 ± 2.0	3.7 ± 1.9	5.3 ± 2.4	0.011

Age and Gender Effects

Further stratification by age groups revealed that the negative correlation between serum ferritin and HDL-C was stronger in adolescents (13-18 years) and adults (>18 years) compared to children (<13 years). Gender-specific analysis showed that females had significantly higher HDL-C levels than males (35.2 ± 9.7 vs. 30.7 ± 8.7 mg/dL, p=0.028), despite similar serum ferritin levels.

Table 9: Correlation Between Serum Ferritin and HDL-C According to Age Groups

Age Group	Number of Patients	Correlation Coefficient (r)	p-value
<13 years	31	-0.385	0.032
13-18 years	32	-0.529	0.002
>18 years	23	-0.567	0.005

DISCUSSION

Our study demonstrates significant alterations in lipid metabolism associated with iron overload in transfusion-dependent beta thalassemia patients. We found strong inverse correlations between serum ferritin and total cholesterol (r=-0.463, p<0.001), HDL-C (r=-0.512, p<0.001), and LDL-C (r=-0.487, p<0.001), while triglycerides showed a positive correlation (r=0.248, p=0.021). The hypocholesterolemia observed in our cohort aligns with findings by Suman et al. [17] and Mansi et al. [18], who documented reduced cholesterol synthesis in thalassemia patients with iron overload. Multiple mechanisms likely contribute to this phenomenon, including iron-mediated inhibition of HMG-CoA reductase [19], increased erythropoietic activity with enhanced cholesterol consumption, and accelerated cholesterol catabolism [20]. Particularly concerning was the significant reduction in HDL-C levels, especially in patients with severe iron overload (ferritin >5000 ng/mL). This finding is consistent with studies by Al-Quobaili et al. [9] and Asif et al. [21], who reported similar inverse

correlations. The mechanisms responsible include oxidative modifications of HDL particles [22], reduced apolipoprotein A-I synthesis by iron-damaged hepatocytes, and increased HDL clearance due to binding with plasma hemoglobin released during chronic hemolysis [23]. In contrast to cholesterol parameters, we observed higher triglyceride levels in severely iron-overloaded patients, creating an atherogenic lipid profile characterized by elevated TG/HDL-C ratios. This pattern, also reported by Soliman et al. [24], may contribute to the increased cardiovascular risk in long-term thalassemia survivors despite reduced total cholesterol and LDL-C levels [25]. Our multivariate analysis confirmed serum ferritin as an independent predictor of lipid parameters after adjusting for potential confounders. Additionally, subgroup analyses revealed that splenectomy status and chelation therapy type significantly influence lipid profiles, with splenectomized patients showing more pronounced dyslipidemia and deferasirox therapy associated with higher HDL-C levels compared to other chelation regimens [26, 27]. These findings have important clinical implications. The paradoxical dyslipidemia pattern observed may contribute to accelerated atherosclerosis in thalassemia patients, necessitating regular monitoring of both iron status and lipid parameters. Optimizing iron chelation therapy not only prevents iron-related organ damage but may also improve lipid profiles, potentially reducing cardiovascular risk in this vulnerable population.

CONCLUSION

Our study demonstrates a significant correlation between serum ferritin levels and lipid profile parameters in transfusion-dependent beta thalassemia patients. Iron overload is associated with a unique dyslipidemic pattern characterized by reduced total cholesterol, HDL-C, and LDL-C, alongside elevated triglycerides and atherogenic indices. This relationship persists after adjusting for potential confounding variables, with serum ferritin emerging as an independent predictor of lipid parameters.

The inverse correlation between serum ferritin and HDL-C is particularly strong and may have significant implications for cardiovascular risk assessment in these patients. Additionally, clinical factors including splenectomy status and chelation therapy type significantly influence the relationship between iron overload and lipid metabolism. These findings highlight the importance of comprehensive monitoring of both iron status and lipid parameters in transfusion-dependent thalassemia patients. Effective iron chelation strategies should be implemented not only to prevent iron-related organ damage but also to potentially mitigate adverse effects on lipid metabolism. Further longitudinal studies are warranted to establish causality and evaluate whether improved iron control translates to normalized lipid profiles and reduced cardiovascular risk in this vulnerable population.

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