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Evaluation of Serum Ferritin as a Surrogate Marker of Hyperlipidemia in Children with Beta Thalassemia Major

[1]Pritish Mohapatra, [2]Subash Chandra Majhi, [3]Prakash Chandra Panda, [4]Chandrakant Poddar and [5]Deepak Ranjan Bhol

[1-5]Department of Pediatrics, VIMSAR, Burla, Sambalpur, Odisha, India

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Corresponding Author
Subash Chandra Majhi,
Department of Pediatrics, VIMSAR, Burla, Sambalpur, Odisha, India

Author Designation
[1]Senior Resident
[2]Associate Professor
[3]Professor
[4,5]Assistant Professor

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ABSTRACT
Thalassemia refers to a group of genetic disorders of globin chain production in which there is imbalance between the alpha- globin and beta-globin chain production. Thalassemia is one of the major hemoglobinopathies among the population all around the world. It has been reported that now a days approximately 1 out of 14 people are carriers for different subtypes of thalassemia. 1lakh thalassemia children are born every year in the world with birth rate of 22.8/10000. In India 10000 thalassemia children are born every year. To find out the correlation between serum ferritin and lipid profile status in beta thalassemia major patients in 5-14 years age group. A cross sectional analytical study was conducted where 227 children with beta thalassemia major in the age group 5-14 years from the Thalassemia unit of Veer Surendra Sai Institute of Medical Science and Research (VIMSAR) who were on regular blood transfusion and oral iron chelators were enrolled. Serum ferritin levels, lipid profile status and baseline red cell indices were investigated and their correlation assessed. Out of total 227 children, 141 (62.1%) were of 11 years or above, with male predominance of 60.4% among 227 patients. Only 46 (20.3%) had a history of consanguinity which was statistically significant with a $p<0.0001$. Hematological tests showed the mean pre-transfusion haemoglobin level was 6.0863 g dL^{-1} with a standard deviation of 1.10. Mean MCHC was on the lower side at 25.26 g dL^{-1} (SD:2.24) and mean MCV was 87.32fl (SD:2.25). The mean value of Serum ferritin was 2924.79±1697.12 ng mL^{-1}. Mean value of Total cholesterol, HDL- cholesterol, LDL-cholesterol were 139.94±15.23, 41.92±5.86, 103.04±7.32 mg dL^{-1}, respectively and their correlation with serum ferritin were negative ($r = -0.909$, $r = -0.935$ and $r = -0.882$, respectively). Mean value of serum Triglyceride was 188.06±26.43 and it had positive correlation with serum ferritin with $r = 0.860$. We observed that, there was significant derangement in lipid profile status correlating with serum ferritin values in a beta thalassemia major patient. As the serum ferritin value increases serum triglyceride level increases and serum total cholesterol, HDL cholesterol, LDL cholesterol value decreases.

INTRODUCTION

Thalassemia refers to a group of genetic disorders of globin chain production in which there is imbalance between the alpha-globin and beta-globin chain production. Thalassemia is one of the major hemoglobinopathies among the population all around the world. It has been reported that now a days approximately 1 out of 14 people are carriers for different subtypes of thalassemia. One lakh thalassemia children are born every year in the world with birth rate of 22.8/10000.In India 10000 thalassemia children are born every year[1].

Patients with beta thalassemia major are at risk of an iron overload in various organs, which is through repeated blood transfusions and increased iron absorption from the gastrointestinal tract. In beta thalassemia major, liver damage accounts for the low total cholesterol (TC), low high-density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) serum levels[2]. Thalassaemic patients are also subjected to peroxidative tissue injury. It has been documented that circulating low density lipoprotein C(LDL C) in thalassaemic patient show marked oxidative modification that could represent an event leading to pathogenesis. Free radical production is increased in patients with iron overload. Iron loaded patients have high levels of thiobarbituric acid reactants and increased hepatic levels of aldehyde-protein adducts, indicating lipid peroxidation which in turn is responsible for the major cardiovascular complications. Due to scarcity of studies on serum lipid profile and high prevalence of beta thalassemia major in population of Western Odisha , they intend to study the detailed serum lipid profile levels in correlation with serum ferritin levels in patients of thalassemia major.

Thalassemia is one of the most common hereditary diseases that interfere with the synthesis of the normal globin chain, occurring in no less than 2.4 out of every 1000 live births, globally[3]. Ineffective erythropoiesis and hemolysis encompass the main reason of anemia in thalassemia. Severe anemia from early life is characteristic of thalassemia major thus requiring routine blood transfusion to survive. However, a continuous load of iron due to repeating transfusion will result in iron overload because the body has no active elimination pathway for iron. Therefore, to reduce iron accumulation and its related complications, iron chelation therapy is needed[4].

Iron is one of the essential minerals for cellular function however, iron overload, as happen in thalassemia patients, may result in cell injury. Iron could initiate free radical reaction and potentially impair cellular metabolism, including carbohydrates, proteins, lipids, and nucleic acids[5]. A chronic inflammatory condition existed in patients with thalassemia major. Inflammatory state resulted from reactive oxygen species production, lipid peroxidation, and other metabolic changes due to iron toxicity are risk factors for cardiac dysfunctions, such as heart failure and left ventricular dysfunction.

MATERIALS AND METHODS

Place of study: The study was conducted in Department of Paediatrics, Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla, District-Sambalpur, Odisha, India with latitude and longitude-21.4888°N, 83.8844°E. This is a 1600 bedded tertiary hospital catering to the western districts of state of Odisha in eastern coast of India.

Study setting: In patient department (IPD) at Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla in the department of Paediatrics

Period of study:

- **Study phase 1:**
  Preparation (October 2020- December 2020): During the period a blueprint of the proposed dissertation was made. Data regarding the prevalence of the various aspects related to the study was collected like frequency of blood transfusions, dose of oral iron chelating agents, duration of oral iron chelation therapy, pre-transfusion Hb levels, Serum Ferritin levels in patients receiving repeated blood transfusions. From the above data we calculated the sample size using n-master V 2.0 (BRTC, Vellore) software
- **Study phase 2:**
  Data collection (January 2021-November 2022): Each patient was enrolled in study after taking informed consent form the parents or the local guardian. Case proforma for each patient was filled and required data was collected from the sheet
- **Study phase 3:**
  Data analysis and interpretation (November 2022-December 2022): For statistical analysis data were entered into a Microsoft excel spreadsheet and then analysed by SPSS (version 27.0, SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variable and the result was interpreted
- **Study phase 4:**
  Presentation and report writing (December 2022-January 2023): A final review of the study was done before the institutional ethical committee and any modification needed was done after the expert opinion of the ethical board. Finally, the study was ready and results were reported in form of thesis dissertation, paper publication in standard scientific journals of various countries of the world including India

Study design: Cross sectional analytical study.

Study population: Any child between age group of 5-14 years of either sex attending their IPD with the clinical diagnosis of Beta thalassemia major by HPLC.

Inclusion criteria: HPLC confirmed subjects of Beta-thalassemia major children of either gender aged between 5×14 years.

Exclusion criteria:

- Critically ill patients
- Patients with hereditary hyperlipidaemia screened by family history at the time of admission
- Patients with diabetes mellitus screened by HbA1c levels or other endocrine abnormalities like Hyperthyroidism, hypothyroidism, hyper/ hypoparathyroidism
- Diagnosed case of Nephrotic syndrome or any other disease currently on steroid therapy for >2 years
- Those who are already on Anti-lipidemic drugs, OCPS etc
- Any chronic or acute inflammatory condition like sepsis
- Vitamin D deficiency/insufficiency

RESULTS AND DISCUSSIONS

Thalassemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the α-globin and β-globin chain production. B-thalassemia syndromes result from a decrease in β-globin chains and relative excess of α-globin chains. β-thalassemia major is primarily due to absence of production of β-globin. The primary pathology in the thalassemia syndromes stems from the quantity of globin produced. Ineffective erythropoiesis and hemolysis encompass the main reasons of anemia in thalassemia. The excess α-globin chains form tetramers (α4) which appear as RBC inclusions which in turn damage the RBC membrane and shorten RBC survival leading to anemia and increased erythroid production.

This two year cross-sectional analytical study was conducted from November 2020-October 2022 at Department of Paediatrics, Veer Surendra Sai Institute of ±Pincode: 768017. 227 study subjects were selected as per inclusion and exclusion criteria by consecutive sampling. Their demographic and anthropometric parameters along with history of previous blood transfusions and oral chelation was recorded. Serum ferritin and lipid profile status of each patient was evaluated and a correlation was established.

In our study majority of the children were in the age group of 12-14 years (49%) and age was statistically significant (p<0.00001). (z = 5.1626). The mean Age (years) of patients was [10.7357±2.0931]. When age was correlated with serum ferritin and lipid profile levels, it was found out that age had a positive correlation with serum ferritin (r = 0.086) and triglyceride (r = 0.066) i.e., as the age increases serum ferritin and triglyceride values also increase but these values were not significant with p-value of 0.195 and 0.323, respectively. Also age had a negative correlation with serum total cholesterol, HDL-cholesterol, LDL-cholesterol with r = -0.033, r = -0.004, -0.122, respectively but these were not significant with p-value of 0.622, 0.947, 0.067 respectively. Arsang-Jang *et al*.[6] and Fianza *et al*.[7] also evaluated age as a risk factor for iron overload associated complication and their mean age was 21.4±7.5 (range 8-39) and 21.9±8.0 years, respectively (Table 1-5).

Table 1: Distribution of mean MCHC of the subjects (g dL^{-1})

MCHC of the subjects (g dL^{-1})	Male		Female		Total	
20-25	92		38		130	
26-30	45		52		97	
>30	0		0		0	
	Total	Mean	SD	Minimum	Maximum	Median
MCHC (g dL^{-1})	227	25.2643	2.2402	20.0000	28.0000	25.0000

Table 2: Distribution of mean Sr. ferritin of the subjects (ng mL^{-1})

Serum ferritin of the subjects (ng mL^{-1})	Male		Female		Total	
0-2000	44		40		84	
2001-4000	60		27		87	
4001-6000	26		20		46	
6001-8000	7		1		8	
>8000	0		2		2	
	No.	Mean	SD	Minimum	Maximum	Median
Sr. Ferritin (ng mL^{-1})	227	2924.7974	1697.1256	448.0000	9700.0000	2500.0000

Table 3: Distribution of mean total cholesterol of the subjects (mg dL^{-1})

Total cholesterol of the subjects (mg dL^{-1})	Male		Female		Total	
100-120	7		7		14	
121-140	72		41		113	
141-160	44		27		71	
161-180	14		15		29	
>180	0		0		0	
	No.	Mean	SD	Minimum	Maximum	Median
Total cholesterol (mg dL^{-1})	227	139.9471	15.2384	120.0000	170.0000	137.0000

Table 4: Distribution of mean HDL-cholesterol of the subjects (mg dL^{-1})

Serum HDL-cholesterol of subjects (mg dL^{-1})	Male		Female		Total	
>50	0		0		0	
41-50	78		57		135	
31-40	53		31		84	
≤30	6		2		8	
	No.	Mean	SD	Minimum	Maximum	Median
HDL-Cholesterol	227	41.9295	5.8638	30.0000	50.0000	42.0000

Table 5: Distribution of mean LDL-cholesterol of the subjects (mg dL^{-1})

Serum LDL-Cholesterol of subjects (mg dL^{-1})	Male		Female		Total	
81-90	9		9		18	
91-100	36		15		51	
101-110	92		66		158	
>110	0		0		0	
	No.	Mean	SD	Minimum	Maximum	Median
LDL-Cholesterol	227	103.0441	7.3218	81.0000	110.0000	107.0000

We found that male population 137 (60.4%) was higher than female population 90 (39.6%). Male: Female ratio was 1.52:1. Sex was statistically significant ($p<0.00001$). ($z = 4.4116$). Nandi *et al*.[8] in similar study also found male predominance with 55.88% male patients while Arsang-Jang *et al*.[6] and Suman *et al*.[9] showed female predominance with 53.54 and 56.4% female patients, respectively.

Also our study showed that majority of the subjects (53.3%) were from the lower socio-economic class while 19.8, 16.7 and 10.1% of the subjects were from lower middle class, middle class and upper class respectively and it was statistically significant ($p<0.00001$). ($z = 9.8831$). Nandi *et al*.[8] also found in a similar study that 69.61% children came from lower socio-economic class. This lays emphasis on providing proper education and spreading awareness about the disease, frequency of blood transfusion and oral iron chelation therapy, more in the lower socio-economic class.

In our study, mean weight (kg) of patients was [28.3436±6.4249], mean height (cm) of patients was [129.7357±11.9542], mean Age at diagnosis (months) of patients was [7.3128±1.3934], mean Duration of chelation therapy (years) of patients was [6.4969±2.5663], mean Dose of deferasirox (mg kg^{-1} day^{-1}) of patients was [18.0396± 4.9861], mean Pre- transfusion Hb (g dL^{-1}) of patients was [6.0863±1.1037], mean MCHC (g dL^{-1}) of patients was [25.2643±2.2402] and mean MCV (fl) of patients was [87.3260±2.2458].

Of the many parameters used to monitor iron overload in thalassemia major patients such as serum ferritin, liver biopsy, SCQID, and T2 MRI assessment of liver and cardiac iron, serum ferritin level is the most commonly used parameter. It correlates with cardiac impairment and survival but can be elevated by many confounding factors, including acute phase reactants such as infections, inflammation, or malignancy or by hepatic damage.

In our study all the patients had elevated serum ferritin levels which ranged from 448 ng mL^{-1} to 9700 ng mL^{-1} with a mean of 2924.7974±1697.1256. In similar study conducted by Koreti *et al*.[10] where from a study population of 60 patients all had elevated serum ferritin levels with range from 1050 to 5029 ng/ml with a mean value of 3879 ng mL^{-1}. Also in our study we found a positive correlation between serum ferritin and age ($r = 0.086$, $p = 0.195$), weight ($r = 0.072$, $p = 0.279$), age at diagnosis ($r = 0.035$, $p = 0.600$), dose of deferasirox ($r = 0.021$, $p = 0.750$) but these were not statistically significant. Ferritin also showed positive correlation with duration of chelation therapy ($r = 0.201$, $p = 0.002$) which was statistically significant (Fig. 1a-d).

In our study we also evaluated the lipid profile status of the beta-thalassemia major patients. In our study serum triglyceride values (mg dL^{-1}) of the subjects range between 140-200 with a mean of 188.0617±26.4320, serum total cholesterol values (mg dL^{-1}) range between 120-170 with a mean value of 139.9471±15.2384, serum HDL-cholesterol values (mg dL^{-1}) range between 30-50 with a mean value of 41.9295±5.8638 and serum LDL-cholesterol values (mg dL^{-1}) range between 81-110 with a mean value of 103.0441±7.3218. Thus TG values were higher in thalassemia patients while total cholesterol, HDL-cholesterol and LDL-cholesterol values are lower in thalassemia patients.

A similar study by Suman *et al*.[9] also had similar findings with Mean cholesterol level, high density lipoprotein (HDL), low density lipoprotein (LDL) levels were on lower side of the range with values of 124.47±19.81 mg dL^{-1}, 36.58±12.22 mg dL^{-1}, 63.94±4.57 mg dL^{-1}, respectively. The mean triglyceride level (TG) was on higher side with an average of 142.93±33.7 mg dL^{-1}. The average serum ferritin levels were 2130.33±859.85 ng mL^{-1}.

Suman *et al*.[9] examined that β-thalassemia major is a secondary iron load state. The high serum ferritin accounts for abnormal lipid profile. Mean cholesterol level, high density lipoprotein (HDL), low density lipoprotein (LDL) levels were on lower side of the range with values of 124.47±19.81 mg dL^{-1}, 36.58±12.22 mg dL^{-1}, 63.94±4.57 mg dL^{-1}, respectively. The mean triglyceride level (TG) was

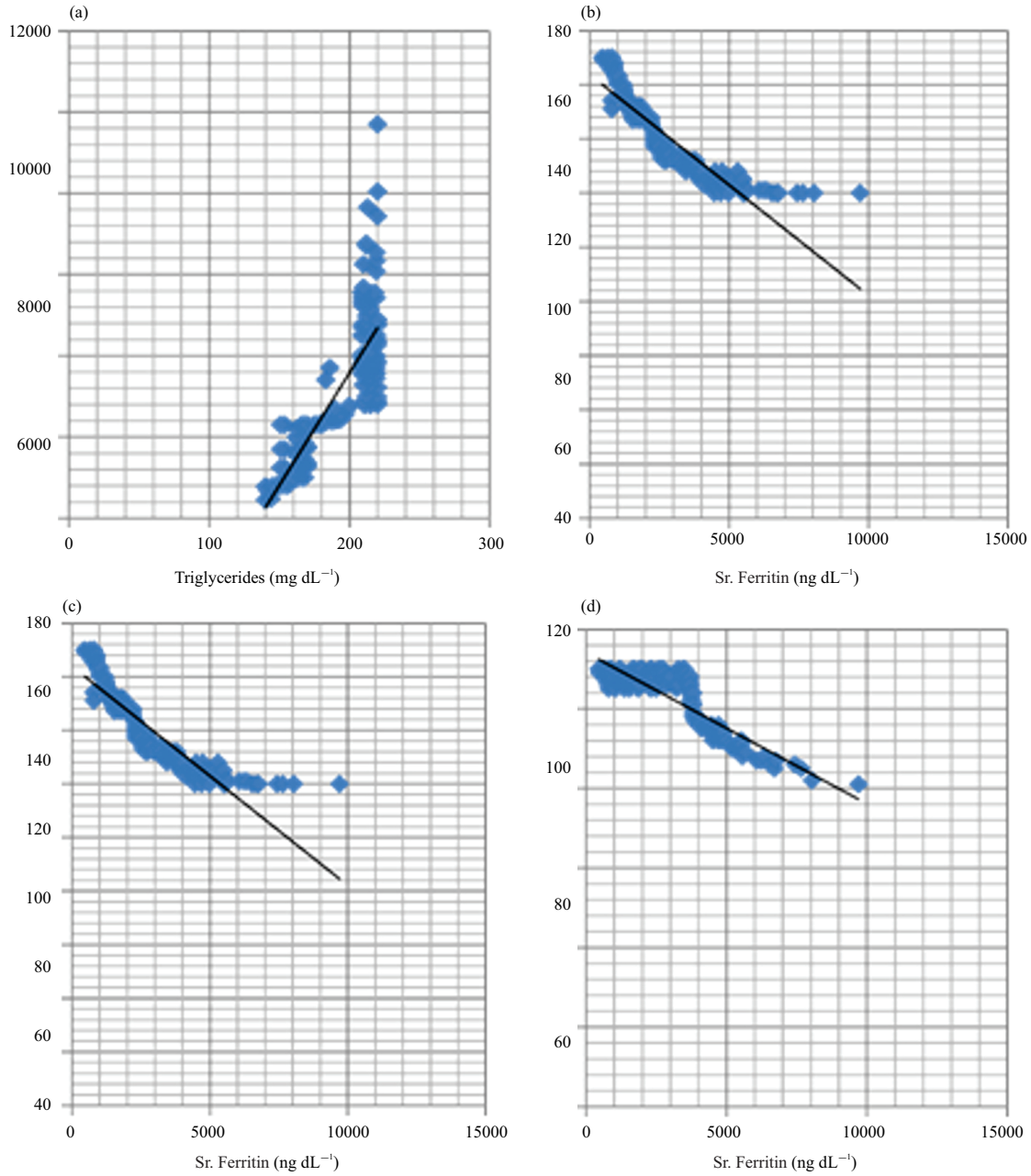

Fig. 1(a-d): Correlation plots showing correlations of serum ferritin (ng mL^{-1}) with serum triglyceride (mg dL^{-1}), HDL-cholesterol (mg dL^{-1}), total cholesterol (mg dL^{-1}), LDL-cholesterol (mg dL^{-1}), respectively

on higher side with an average of 142.93±33.7 mg dL^{-1}. The average serum ferritin levels were 2130.33±859.85 ng mL^{-1}.

Sherief *et al*.[11] found that early vascular alteration, atherosclerosis and coronary artery disease have emerged as important cardiovascular complications among beta-thalassemia major (B-TM) patients. On the contrary, total serum cholesterol (116±16 vs 143±5, p<0.001), low density lipoprotein-cholesterol (LDL-C) (44±9 vs 73±6, p<0.001) and high density lipoprotein cholesterol (HDL-C) (39±2 vs 61±5, p<0.001), were significantly lowered in patients versus normal peers.

Now coming to the correlation between serum ferritin level of subjects and the lipid profile status of the subjects, we observed that as the serum ferritin value was increasing, the serum triglyceride value was also increasing with a Pearson correlation coefficient r = 0.860 with a p<0.0001 which is statistically significant. Similarly, as the serum ferritin value was increasing there was a decrease observed in the serum values of total cholesterol, HDL-cholesterol, LDL-cholesterol with Pearson correlation coefficient r = -0.909, r = -0.935, r = -0.882 with p<0.0001 for each, which is statistically significant.

Suman *et al*.[9] also had similar results. They found out that the high serum ferritin accounts for abnormal lipid profile. There was negative correlation of total cholesterol, HDL, LDL with serum ferritin with coefficient of correlation (r = -0.77, -0.55, -0.72) respectively. The serum triglyceride had positive correlation with serum ferritin with coefficient of correlation (r = +0.85).

However, similar study done by Nandi *et al*.[8] had different results. They observed that the mean value of serum ferritin was 2263.53±833.904 ng mL^{-1}. The average value of serum total cholesterol, LDL and HDL were 153.84±5.428 mg dL^{-1} and 97.16±3.982 mg dL^{-1} and 29.45±4.445 mg dL^{-1}, respectively and their correlation with serum ferritin were negative (r = -0.941 and r = -0.964 and r = -0.751, respectively). Average value of serum triglyceride and VLDL were 206.22±67.407 mg dL^{-1} and 36.16±3.385 mg dL^{-1}, respectively and their correlation with serum ferritin were positive (r = +0.606 and r = +0.973, respectively).

Thus serum ferritin can be used as a marker of dyslipidemia in β-thalassemia major patients and can serve as a tool for early detection and intervention for dyslipidemia like lifestyle changes, early initiation of lipid lowering agents like statins so as to prevent major cardiovascular complications.

CONCLUSION

The aim of this dissertation was to contribute new insight to the lipid profile derangements and their correlation with serum ferritin values in beta thalassemia major patients. Despite the high prevalence of thalassemia major in the paediatric population and major cardiovascular risks associated with it, this disease is often overlooked or undertreated. Patients with thalassemia major are at risk of iron overload in various organs due to repeated blood transfusions, leading to devastating complications. Major cause of death in thalassemia patients is cardiac arrhythmias, congestive cardiac failure and myocardial infarction. Deranged lipid profile status is a major predictor of the above complications in thalassemia major patients. Beta thalassemia major patients have low HDL-cholesterol levels and high Triglycerides level. Early detection of these patients with a deranged lipid profile is required to avoid thrombotic and atherogenic complications. Since, it is impossible to predict these changes clinically and, in a resource, limited country like India, it is not cost effective to carry out regular blood lipid profile levels, serum ferritin levels may be used to predict dyslipidaemia. Such patients with deranged lipid profile status should undergo dietary and lifestyle modifications and maybe started on lipid lowering agents. Our study found a positive correlation between Serum ferritin levels and Triglycerides while a negative correlation between serum ferritin and total cholesterol, HDL-cholesterol, LDL-cholesterol was assessed. We believe that tables presented in this study will be of help for early detection of dyslipidemia and prevention of major cardiovascular hazards.

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