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# Disturbances of Lipid Profile and Serum Ferritin Levels in Thalassemic Children

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## ABSTRACT

*Background/Aim:* Beta-thalassemia is considered to be the most frequent hereditary blood disorder worldwide. Lipid abnormalities have been detected in different types of beta-thalassemia. The aim of this study is to assess the lipid profiles and their relation with serum ferritin in beta-thalassemia major (TM) and beta-thalassemia intermedia (TI) patients. *Subjects and methods:* The study group consisted of 34 TM patients and 30 TI patients. The control group included 30 sex-and age-matched healthy participants. Serum lipids profiles (total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol) as well as hemoglobin (Hb) and ferritin, were compared between the three groups. P value < 0.05 was considered statistically significant. *Results* There were no significant differences between TM and TI patients regarding age or sex. Mean triglyceride and LDL-cholesterol concentration was significantly higher while HDL-cholesterol was significantly lower in patients with TM and TI in comparison with controls ($p < 0.001$). Serum cholesterol was found to be significantly higher in TM patients compared to BTI patients. There were a positive significant correlation between serum ferritin and LDL-cholesterol, also a negative correlation between it and HDL- cholesterol was found. *Conclusion:* hypertriglyceridaemia, hypocholesterolemia and low HDL-cholesterol levels in major and intermediate thlassemic children put them at higher risk for cardiovascular complications and correlate significantly with serum ferritin.

***Key words:*** Thalassemia, Cholesterol, LDL, HDL, Triglycerides, Ferritin

## Introduction

Beta-thalassemia major (TM) is an autosomal recessive hereditary anemia, which is incurable, caused by defective synthesis of hemoglobin, ineffective erythropoiesis, and rapid erythrocyte breakdown (Pirinççioðlu *et al.,* 2011). Beta-thalassemia major patients frequently end up with iron overload because of hemolysis and repeated blood transfusion (Fahmey *et al.,* 2013).

Thalassemia intermedia (TI) is a term used to define a group of patients with β thalassemia in whom the clinical severity of the disease is somewhere between the mild symptoms of β-thalassemia trait and the severe manifestations of BTM. The diagnosis is a clinical one made on the basis of the patient maintaining a satisfactory Hb level of at least 6-7 g/dl without the need for regular blood transfusions (Aessopos *et al.,* 2007).

Lipid abnormalities have been detected in different types of beta thalassemia, and also in various hematological disorders including sickle cell disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, spherocytosis, aplastic anemia and myelodysplastic syndrome (Ammirabile *et al.,* 2009).The pathogenesis of these abnormalities is not exactly clear, but there are many suggested mechanisms including plasma dilution due to anemia, accelerated erythropoiesis resulting in increased cholesterol uptake by macrophages and histiocytes of the reticulo-endothelial system, defective liver functioning due to iron overload, macrophage system activation with cytokine release, and hormonal disturbances (Shalev *et al.,* 2007).

A high incidence of thrombo-embolic event has been observed in patients with β thalassemia. Thrombotic events are more frequent in β-thalassemia patients who are not receiving regular transfusions or in β-thalassemia patients who have undergone splenectomy, strongly supporting the pro-coagulant activity of circulating damaged red blood cells (Cappellini *et al.,* 2005).

Vascular dysfunction with increased arterial stiffness and endothelial dysfunction have been found in patients with β thalassemia (Cheung, 2005). Endothelial dysfunction occurs in thalassemic children because of peroxidative tissue injury because of continuous blood transfusions. Children with β thalassemia are at risk of developing premature atherosclerosis because of dyslipidemia (Tantawy *et al.,* 2009).

Abnormal lipid profiles, including low total cholesterol, low high-density lipoprotein cholesterol (HDL-C), low low-density lipoprotein cholesterol (LDL-C), and high triglycerides, have long been observed in

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β thalassemia (Al-Quobaili and AbouAsali, 2004). Awareness of physicians to these abnormalities is helpful to avoid unnecessary work up in these patients. The aim of this research is to assess the lipid profiles in two groups of patients with BTM and BTI and to compare the findings to those in healthy control participants and also to find any correlation between serum ferritin and lipid profile.

## Subjects and Methods

The present study included Sixty-four children with β thalassemia (34 thalassemia major and 30 thalassemia intermedia). Their age ranged from 4 to 15 years, mean age 9.8 ± 5.6 years. Patients with a diagnosis of thalassemia were recruited from Hematology Unit, Abu El Rish Hospital, Cairo University. Thirty normal, healthy children were included as controls. Informed consents were obtained from the parents of the children studied and the study was approved by the medical ethical committee of the National Research Center, Cairo, Egypt.

## Exclusion criteria:

None of the participants had any acute illness or diabetes mellitus; presence of other chronic or inflammatory disease; presence of known renal disease at time of testing. All patients and controls were subjected to the following:

1. Full history was taken from the parents including the onset of hemolysis, duration of disease, frequency of blood transfusion and presence of complication especially hypersplenism and splenectomy.
2. Thorough clinical examination and anthropometric measurements were done.
3. Laboratory investigations: Morning venous blood sample was withdrawn after 12 hours over night fasting into plane tube and left to colt. The serum was separated by centrifugation for 10 minutes at 5000 rpm, and stored at – 20 until assays done. Determination of serum levels of total cholesterol (Allain *et al.,* 1974), triglycerides (Wahlefeld, 1974), and HDL-C (Warnick *et al.,* 1982) was carried out using auto analyzer Olympus 400 (AU400, Japan). Serum LDL-C levels were calculated using the Friedewald formula [LDL-C = Total cholesterol - HDL-C- (Triglyceride/5)] (Friedewald *et al.,* 1972). Serum level of ferritin was assessed using the ELISA technique from Alpha Diagnostic International Company according to the method of Theurl (Theurl, 2009).

Data entry was carried on excel sheet and statistical analysis was done using SPSS software program version 18.0. Chi square was done for qualitative data that presented by numbers and percentages. T-test was done for comparison between two means and one way ANOVA for more than two means. P value was considered statistically significant when P was <0.05 and considered statistically highly significant when its value was<0.01.

**Results:**

The mean age of studied thalassemic children and control group were 9.55±3.85, 9.83 ± 2. 63 years, respectively and the mean hemoglobin level (Hb) of thalassemic children was 7.43 ± 1.14gm/dl vs.12.23 ± 0.55gm/dl in control group with a highly significant difference (P < 0.0000). Table (1) shows comparison between thalassemic subgroups and control group. There was a significant difference between them regarding all lipid profile (P < 0.0000). Each of the thalassemic subgroups (TM, TI) had significantly higher serum ferritin level, and serum triglycerides level and LDL-C with significantly lower serum total cholesterol and HDL-C compared with the control group. Also, the TI group had significantly lower serum total cholesterol levels and ferritin level compared with the TM group, and a higher significant difference between both groups in LDL-C and Hb level.

**Table 1:** Hemoglobin content, lipid profile, and ferritin levels in thalasemic major and intermediates children under study.

| | Thalassemia major(n=34) Mean ± SD | Thalassemia intermedia(n=30) Mean ± SD | Control group (n=30) Mean ± SD | P1 | P2 | P3 |
|---|---|---|---|---|---|---|
| Age (years) | 8.88 ± 3.79 | 10.30 ± 3.85 | 9.83± 2.63 | 0.254 | 0.585 | 0.143 |
| Hb (g/dL) | 7.13 ± 0.96 | 7.77 ± 1.24 | 12.23 ± 0.55 | 0.000* | 0.000* | 0.024* |
| Serum cholesterol (mg/dl) | 141.21 ± 46.68 | 92.96 ± 23.63 | 156.80 ± 26.66 | 0.112 | 0.000* | 0.000* |
| Serum triglyceride (mg/dl) | 148.41 ± 20.00 | 150.60 ± 28.52 | 133.20 ± 22.80 | 0.006* | 0.012* | 0.721 |
| Serum HDL (mg/dl) | 34.41 ± 9.18 | 32.20 ± 11.97 | 67.27 ± 9.02 | 0.000* | 0.000* | 0.407 |
| Serum LDL (mg/dl) | 94.24 ± 37.31 | 121.13 ± 32.95 | 67.47 ± 18.58 | 0.001* | 0.000* | 0.003* |
| Serum ferritin (ng/ml) | 1936.24 ± 953.71 | 903.15 ± 705.93 | 90.80 ± 33.30 | 0.000* | 0.000* | 0.008* |

*All data are represented as mean± SD, * P< 0.05 is significant HDL = High density lipoprotein LDL = Low Density lipoprotein*
*P1 Comparison between thalassemia major and control, P2 Comparison between thalassemia intermedia and control,P3 Comparison between thalassemia major and intermedia.*

Table (2) shows a positive correlation between serum ferritin and LDL-C (fig1) while a negative correlation was seen between serum ferritin and HDL-C (fig 2) in thalassemic children.

Multiple linear regression analysis in table (3) shows the effect of lipid profile parameters as independent variables on serum ferritin level as a dependent variable in all thalassemic groups after adjustment for age and sex. Serum cholesterol and HDL were found to be significant independent predictors of serum ferritin ($p<0.005$) and serum triglycerides and LDL were found to be insignificant independent predictors of serum ferritin ($p>0.005$).

**Table 2:** Correlation coefficients between serum ferritin and lipid profile in thalassemic children.

| Variables | Serum Ferritin | |
|---|---|---|
| | Pearson correlation | P value |
| Total cholesterol | 0.115 | 0.270 |
| Triglycerides | 0.011 | 0.915 |
| HDL | -0.326 | 0.001* |
| LDL | 0.301 | 0.003* |

**: P< 0.05 is significant*
*HDL = High density lipoprotein LDL = Low Density lipoprotein*

**Table 3:** Multiple Linear regression analysis showing the effect of lipid profile (independent variables) on serum ferritin in thalassemic children after adjustment for age and sex

| | Unstandardized B coefficient | Standardized B coefficient | t | p |
|---|---|---|---|---|
| Cholesterol | 11.901 | 0.357 | 3.302 | 0.001* |
| Triglyceride | -5.005 | -0.086 | -0.851 | 0.397 |
| HDL | -36.274 | -0.470 | -4.070 | 0.000* |
| LDL | 6.844 | 0.177 | 1.786 | 0.078 |

**P< 0.05 is significant HDL = High density lipoprotein LDL = Low Density lipoprotein*

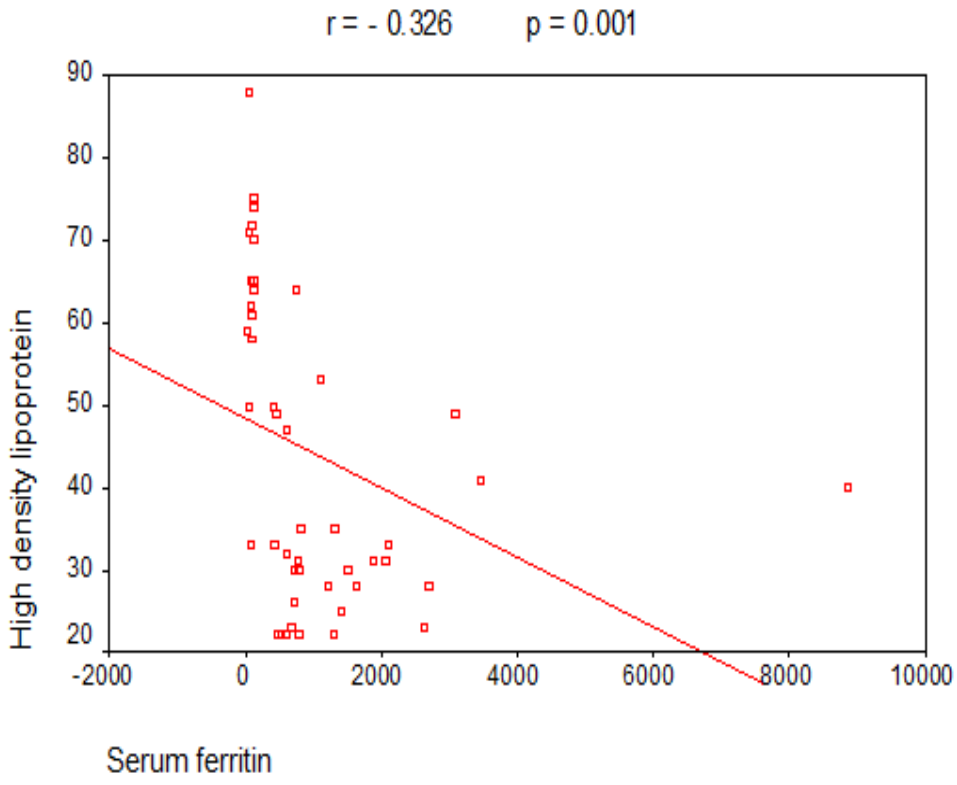


**Fig.1** Correlation between serum ferritin and high density lipoprotein

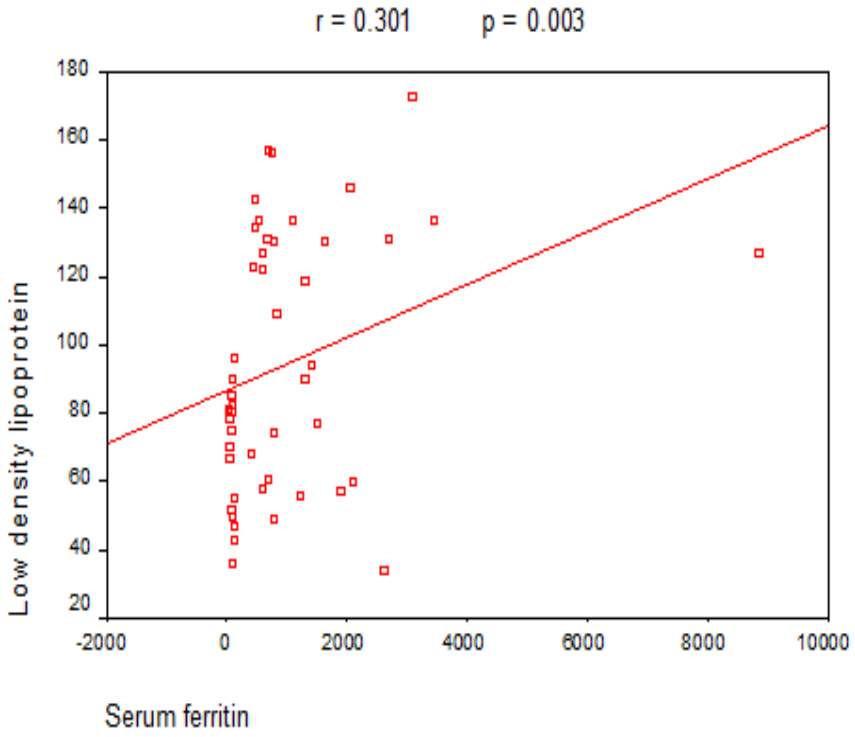


**Fig.2** Correlation between serum ferritin and low density lipoprotein

## Discussion

The aim of this research was to assess the lipid profile in two groups of patients with TM and TI in comparison with a group of healthy individuals. Several studies have reported conflicting results on lipid profiles in thalassemic children. Some have reported atherogenic profiles (Tantawy *et al.,* 2009); (Dwivedi and Kumar, 2007), while others have reported anti-atherogenic profiles in the thalassemic children (Hartman *et al.,* 2002); (Al-Quobaili and AbouAsali, 2004) and (Tselepis *et al.,* 2010).

The results of this study showed that the thalassemic children had significantly lower total serum cholesterol and HDL-C level, with higher serum triglycerides, compared with the control group; this is in agreement with previous studies showing similar results (Hartman *et al*., 2002); (Al-Quobaili and AbouAsali, 2004) and (Tselepis *et al.,* 2010).

Hypocholesterolemia has been detected in different types of beta thalassemia. In our study, we found lower levels of total cholesterol in TI than TM, which is in agreement with Ricchi *et al*.,( 2009), but different with other studies which showed similar values in TM and TI patients (Amendola *et al*., 2007). The pathophysiology of hypocholesterolemia is obscure in these hematologic disorders, in which anemia is a common characteristic. The purposed mechanisms include increased erythropoietic activity resulting in increased cholesterol requirements, liver injury due to iron overload, and macrophage system activation with cytokine release (Shalev *et al.,* 2007). It seems that the main mechanism of hypocholestrolemia in TM is severe iron overload and oxidative stress, but in TI the major mechanism is accelerated erythropoiesis and enhanced cholesterol consumption (Patne *et al*., 2012).

The present study revealed increase in triglyceride levels in both major and intermediate thalassemic children than control participants, which is similar to Hartman *et al.,* (2002) and Ricchi *et al.,*(2009) studies, who reported that triglycerides were elevated in association with diseases such as thalassemia, probably due to extra hepatic lipolytic activity, but differs from other studies which found that triglyceride levels were similar in patients and control participants (Amendola *et al.,* 2007).

HDL-cholesterol was lower in children with major and intermediate thalassemia than in the control group, like other reports have noted. This subject could be considered as a predictive value of cardiovascular risk in patients with thalassemia. Studies proved that the risk for myocardial infarction is high when HDL-C is

low. Thalassemic patients are at a much higher coronary risk than their matched controls because of the low HDL-C production; even total cholesterol is normal (Ragab *et al.,* 2014).

Our results showed that, the only lipid profile parameter that differed between TM and TI was the serum cholesterol, being significantly higher in TM compared with TI children. This result is in contrast with that of Haghpanah *et al.,* (2010) who found no significant difference between TM and TI in lipid profiles. On the other hand Ricchi *et al.,* (2009) found lower levels of triglyceride and LDL-C in TI than TM.

Thalassemic children had significantly higher serum ferritin levels compared with the controls. A significant difference was found between TM and TI in serum ferritin. This is not in agreement with Ali *et al.,* 2008 and Vladislav *et al.,* 2008, who found no significant difference between different groups. The iron overload in thalassemic patients can be attributed to multiple life-long transfusions and enhanced iron absorption resulting in secondary hemosiderosis, with a resultant increase in serum ferritin (Ragab *et al.,* 2014).

There were a positive significant correlation between serum ferritin and LDL- cholesterol, a negative correlation between it and HDL- cholesterol, but no correlation was found between serum ferritin and total cholesterol or triglyceride which is in contrast to the study made by Arica *et al.,* (2012) who found a significant positive correlation between triglyceride and serum ferritin levels.

In conclusion, our study revealed that thalassaemic children had disturbed lipid profile which is closely related to serum ferritin. These findings should be a motive for concern of better evaluation of the cardiovascular risk factors in these patients as they are at a much higher risk for coronary diseases than their matched controls; however more future researches are needed for confirmation and explanation of this relationship.

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