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RESEARCH ARTICLE

Estimation of Serum Homeostasis Model Assessment-Insulin Resistance and Lipid Profile in Beta-thalassemia Major Patients and their Correlation with Iron Overload in Koya City

Kochar K. Saleh*, Saman R. Abdullah, Rukhosh E. Mekha

Department of Community Health, Koya Technical Institute, Erbil Polytechnic University, Erbil, Kurdistan Region – Iraq

***Corresponding author:**
Kochar K. Saleh,
Department of Community Health, Koya Technical Institute, Erbil Polytechnic University, Kurdistan Region, Iraq.
Phone: 07503492248.
E-mail: kochar.saleh@epu.edu.iq

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ABSTRACT

The current study focused on 43 patients who suffer from major βeta-thalassemia at the hospital of shaheed Dr. Khaled in the Koya city. Out range, age of cases was 8.03 ± 4.0 and of controls was 7.81 ± 3.11 years. Our aim is to observe the prevalence of homeostasis model assessment-insulin resistance and other physiological and biochemical changes in major beta-thalassemia. While we a significant changes confirm that serum glucose concentration was significantly higher in the patients than in the controls ($P \leq 0.01$) and lipid abnormality occurs in βeta-thalassemia major patients, which include high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), serum total cholesterol (TC), serum triglycerides (TG), and very-low-density lipoprotein (VLDL) levels compared with normal healthy controls. There was no significant difference between the serum insulin level of cases and controls ($P = 0.214$), the mean values of serum HDL-C, LDL-C, TC, TG, and VLDL in cases were 29.5 ± 7.8, 65.2 ± 1.9, 121.9 ± 36.7, 182.09 ± 43.1, and 26.47 ± 12.13 mg/dl, respectively. Moreover, the mean values of serum HDL-C, LDL-C, TC, TG, and VLDL in controls were 48.6 ± 4.2, 79.7 ± 14.5, 178.7 ± 14.6, 124.14 ± 12.1, and 23.52 ± 5.47 mg/dl, respectively. In conclusion, the results suggested that revealed that beta-thalassemia patients had hypertriglyceridemia, hypocholesterolemia, and low LDL-C, and HDL-C levels.

Keyword: Homeostasis model assessment-insulin resistance; Lipid profile and iron overload; Major βeta-thalassemia

INTRODUCTION

Major βeta-thalassemia is a very serious blood condition since individuals with it are unable to make enough healthy red blood cells and depend on blood transfusions all their life (Khattak and Khan, 2004). It is the most prevalent type of thalassemia as it is common in certain populations and causes severe anemia in its homozygous state (Thein, 2005). Thalassemia represents the most common single gene disorder causing a major public health problem. βeta-thalassemia major characterized by progressive anemia manifested during the 2nd 6 months of life, associated with splenomegaly and chronic hemolytic anemia that sustain life (Danjou et al., 2011; Driscoll et al., 2003). B-thalassemia major is caused by the complete absence of beta-globin chain production resulting from reduced synthesis of one or more globin chains, which can be caused by different globin gene mutation resulting in ineffective hematopoiesis, increased hemolysis, and early onset anemia. Most types of βeta-thalassemias are due to point mutations, and deletion mutations found in rare cases, many mutations associated with β-thalassemia either reduce ß-globin gene expression (β^+-type) or completely suppress beta-globin gene (β^o-type) (Haghi et al., 2009).

Major β-thalassemia is the most prevalent type of thalassemia, because of anemia caused in thalassemia major, patients are pale, fatigue, and have a slower rate of growth (Ambekar et al., 2001). Lipid abnormalities have been detected in different types of beta-thalassemia, and in various hematological disorders including sickle cell disease, glucose-6-phosphate dehydrogenase deficiency, spherocytosis, aplastic anemia, and myelodysplastic syndrome (Sutay, 2016; Ricchi 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 of the reticuloendothelial system, defective liver functioning due to iron overload, and macrophage system activation with cytokine release and hormonal disturbances (Al-Quobaili

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and Asali, 2004). Our aim and objectives in the present study to show what are the main physiological changes occur in patients that suffer with major βeta-thalassaemia and what are the main significant correlations between each parameter.

MATERIALS AND METHODS

The design of the present investigations is composed of 86 subjects divided equally between two groups; the first group is the patient group, which included 43 major β-thalassemia children, who were managed for the clinical symptoms and treatments at the hospital of shaheed Dr. Khaled in the Koya city. The second group is a control group, which included 43 apparently healthy children randomly, selected, who served as a control group of the study. The control groups were age- and sex-matched to the patients, the mean age of the patients (9.1 ± 2.2 and controls 8.8 ± 1.9 years). Six milliliters sample of venous blood taken from each patient before the scheduled blood transfusion using a disposable syringe. Then, it used for the estimation of serum homeostasis model assessment-insulin resistance and lipid profile in major B-thalassemia patients and their correlation with iron overload by used full-automated (cobas e 411 and cobas c 111) instruments used for assessment each parameter, which include lipid profiles, serum insulin, and glucose. Statistical analysis: SPSS (Statistical Package for the Social Sciences) (Version 20) statistical software was used to analyze the data. Differences in mean values between two groups were analyzed by two samples *t*-test (independent Student's *t*-test between healthy and thalassemia patients and paired sample *t*-test between male thalassemia and female thalassemia) and correlation coefficient. Probably level of $P < 0.05$ level of significant was considered to be statistically significant.

RESULTS

The result of the current study showed significant changes in the iron overload, serum glucose concentration, and in the insulin resistance index (IRI) of the major β-thalassemia patients as compared with healthy control groups in the same ages and sex, while there are no significant changes in the serum insulin concentration of the 43 βeta-thalassemia. Major patients were managing at the hospital of shaheed Dr. Khaled in Koya city, as shown in Table 1 and Figure 1.

The insulin resistance index was significantly higher in βeta-thalassemia major patients compared to control groups (3.90 ± 5.7) versus (2.90 ± 1.2), ($P = 0.048$). There was not any correlation between insulin resistance and other biochemical factors such as iron overload except glucose and insulin, as shown in Table 2 and Figure 2.

There is no significant difference between the ages of patients and controls, in the 43 βeta-thalassemia. Major patients, which include 23 male and 21 female patients that mean age of βeta-thalassemia major patients was 8.03 ± 4.0 years and healthy control groups was 7.81 ± 3.11 years, which include 86 healthy control groups which sex and ages were matched with patients, as shown in Figures 3 and 4.

In patients, the fasting serum glucose correlated with the iron overload indicators like serum iron overload, there is no correlation seen with serum glucose ($r = 0.002$), as shown in Table 3and Figure 5. About 6.9% ($n = 3$) of patients had a serum glucose level equal to or higher than 5.5 mmol/L. A fasting glucose level of 53.4% ($n = 23$) of patients was more than 6.5 mmol/L among whom 20.9% ($n = 9$) were determined as diabetes mellitus and 18.6 % ($n = 8$) as a prediabetic state with repeated tests, and all controls had a normal fasting serum glucose except one participant with a serum glucose of 6.2 mmol/L.

There was no significant difference between the serum insulin level of Beta-thalassemia major patients and control groups ($P = 0.215$), but slightly decrease of the serum insulin level of Beta-thalassemia major patients as compared with healthy control groups. About 5% of the patients ($n = 2$) and 11.6% of the controls ($n = 5$) had a serum insulin higher than 24 μIU/mL. There is no

Table 1: Demographic and general characterization of the study population

Mean ages	Mean ages of patients/ male (Mean±SE)	Mean ages of controls/ male (Mean±SE)	Mean ages of patients/ female (Mean±SE)	Mean ages of controls/ female (Mean±SE)	*p*
Beta-thalassemia major patients	8.22±0.6	8.1±0.4	7.84±0.4	7.52±0.9	*NS
Gender (M/F)	22/21	43/43	22/21	43/43	*NS
	Beta-thalassemia majors		**Healthy control groups**		
Random serum glucose (mmol/L)	6.6±0.1		4.2±0.1		0.001**
Serum insulin (μIU/mL)	14.7±1		15.1±1.2		*NS
Insulin resistance index	3.90±0.8		2.90±0.1		0.048*
Iron (ng/ml)	167.1±0.06		112.3±0.1		0.01*

* NS: Non-significant differences between controls and patients (male and female)

significant correlation seen between serum insulin levels and serum iron overload ($r = -0.159$), as shown in Table 4.

A significant changes confirmed in the lipid profile of 43 βeta-thalassemia. Major patients as showed in the previous result that serum glucose concentration was significantly higher in the βeta-thalassemia major patients than in the controls ($P = 0.01$), as shown in Table 5.

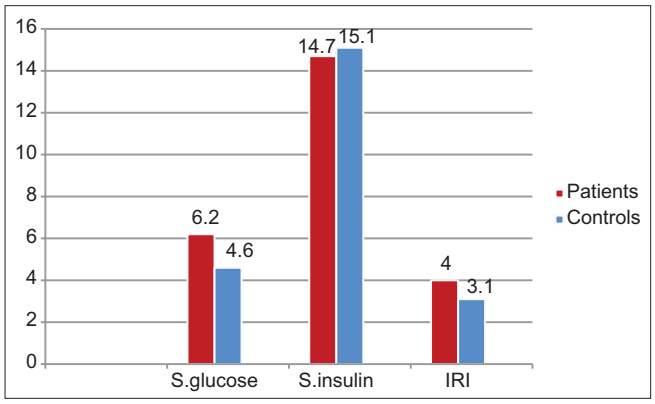


Figure 1: Standard error of the mean changes in homeostasis model assessment-insulin resistance in the study population

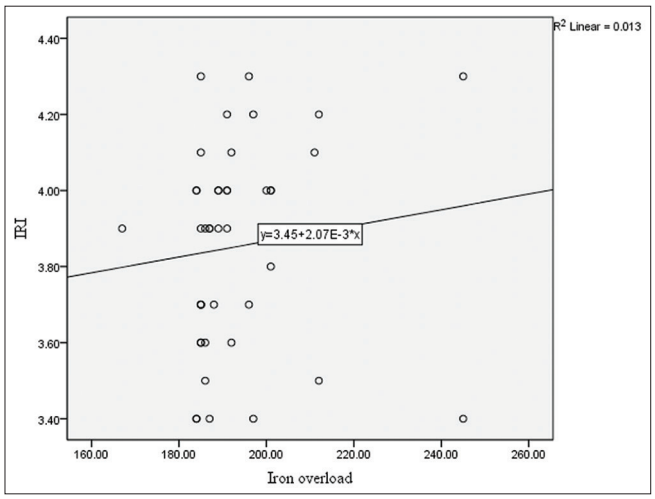


Figure 2: Correlation between iron overload and insulin resistance index

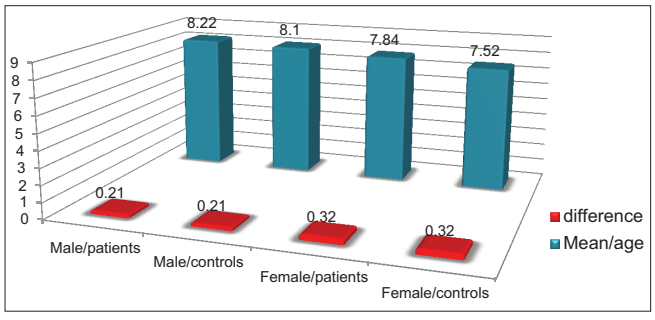


Figure 3: Standard error of the mean ages distribution of the studied populations

Lipid abnormality occurs in βeta-thalassemia major patients, which includes serum total cholesterol (TC) (121.9 ± 36.7 mg/dl), serum triglycerides (TG) (182.09 ± 43.1 mg/dl), low-density lipoprotein-cholesterol (LDL-C) (65.2 ± 1.9 mg/dl), high-density lipoprotein-cholesterol (HDL-C) (29.5 ± 7.8 mg/dl), and very-low-density lipoprotein (VLDL) (23.47 ± 12.13 mg/dl) levels compared with normal healthy controls, as shown in the following Figures 6-9.

There are no significant changes confirmed in the lipid profile of the healthy control groups, as shown in

Table 2: Correlation between iron overload and IRI

Correlations	Iron	IRI
Iron		
Pearson correlation	1	0.113
Sig. (two-tailed)		0.472
n	43	43
IRI		
Pearson correlation	0.113	1
Sig. (two-tailed)	0.472	
n	43	43

IRI: Insulin resistance index

Table 3: Correlation between iron overload and serum glucose

Correlations	Iron	Serum glucose
Iron		
Pearson correlation	1	0.002
Sig. (two-tailed)		0.988
n	43	43
Serum glucose		
Pearson correlation	0.002	1
Sig. (two-tailed)	0.988	
n	43	43

Table 4: Correlation between iron overload and serum insulin

Correlations	Iron	Serum insulin
Iron		
Pearson correlation	1	−0.159
Sig. (two-tailed)		0.308
n	43	43
Serum insulin		
Pearson correlation	−0.159	1
Sig. (two-tailed)	0.308	
n	43	43

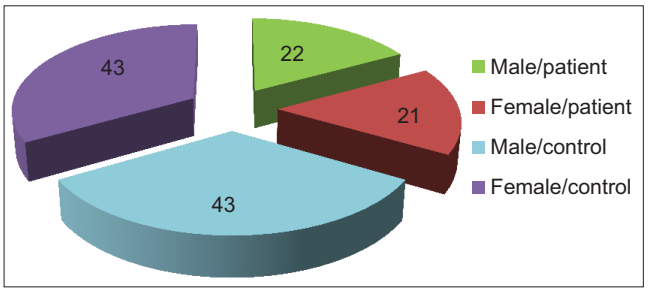


Figure 4: Gender distribution among the study population

Table 5: Analysis of lipid profile in patients

Parameters	TC (mg/dl)	TG (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)
Maximum	183	357	116	54	189
Minimum	56	41	18	10	7
Std. deviation	25.678	54.123	21.198	7.978	21.658
Median	114.30	97.30	66.30	25.10	22.20
Mean	121.9±36.7	182.09±43.1	65.2±1.9	29.5±7.8	23.47±12.13

TC: Total cholesterol, TG: Triglycerides, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, VLDL: Very-low-density lipoprotein

Table 6: Analysis of lipid profile in controls

Parameters	TC (mg/dl)	TG (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	VLDL-C (mg/dl)
Maximum	145	105	100	54	36
Minimum	95	55	50	40	13
Std. deviation	14.981	16.735	15.816	4.138	7.103
Median	126.10	77.00	78.40	46.10	22.00
Mean	178.7±14.6	124.14±12.1	79.7 ±14.5	48.6±4.2	26.52±5.47

TC: Total cholesterol, TG: Triglycerides, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, VLDL: Very-low-density lipoprotein

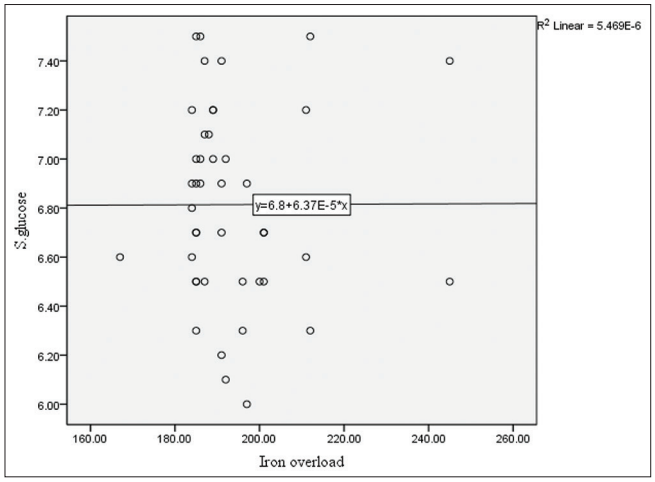


Figure 5: Correlation between iron overload and serum glucose

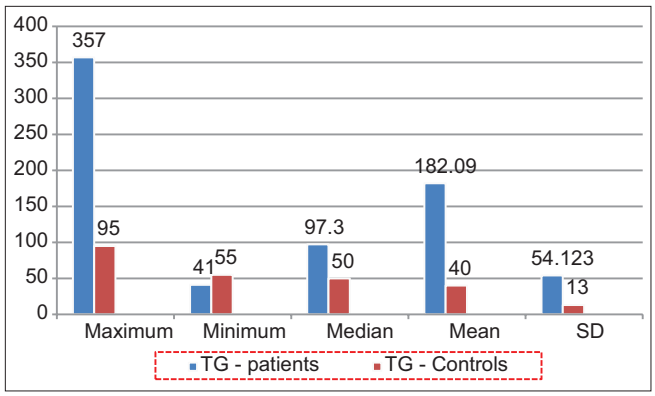


Figure 6: Standard error of the mean serum triglycerides in the study population

Table 6. While the present study showed, lipid profile was significantly higher in the βeta-thalassemia major patients than in the healthy control groups ($P = 0.01$).

Lipid profile occurs in healthy control groups, which includes serum TC (178.7 ± 14.6 mg/dl), serum TG (124.14 ± 12.1.1 mg/dl), LDL-C (79.7 ± 14.5 mg/dl), HDL-C (48.6 ± 4.2 mg/dl), and VLDL (26.52 ± 5.47 mg/dl) levels compared patients. The serum cholesterol (TC) it had no significant correlation with iron overload about ($r = 0.139$, $P = 0.374$), as shown in Table 7 and Figure 10, while serum cholesterol (TC) was significantly lower in βeta-thalassemia. Major patients compared with healthy control groups (121.9 ± 36.7 mg/dl) versus (178.7 ± 14.6 mg/dl), respectively, ($P = 0.000$), as shown in Table 8. Close to 9.3% ($n = 4$) of patients had a cholesterol level <(80 ± 46.7 mg/dl) and 4.6% ($n = 2$) more than (150 ± 72.7 mg/dl). Only three of the controls had a cholesterol level more than 190 ± 1.6 mg/dl.

There is no significant correlation seen between iron overload and serum TG, as shown in Table 9. Serum TG were significantly higher in βeta-thalassemia. Major patients compared with healthy control groups (182.09 ± 43.1 mg/dl) versus (124.14 ± 12.1 mg/dl), respectively, ($P = 0.000$), as shown in Table 8. About 25% of patients had a TG more than (231.09 mg/dl), while in the controls, this percentage was 4.6%. The serum TG in female patients and male patients was no significantly higher than each other were. There is no significant correlation seen between iron overload and serum TG.

There is no significant correlation seen between iron overload and serum TG, as shown in Table 10 and Figure 11. Serum LDL-C was significantly lower in βeta-thalassemia. Major patients compared with healthy control groups (65.2 ± 1.9 mg/dl) versus (79.7 ± 14.5 mg/dl), respectively, ($P = 0.001$), as shown in Table 8. Close to 13.9% ($n = 6$) of patients had a serum LDL-C levels more than 70 ± 2.7 mg/dl and 86% ($n = 37$) of patients less than 65 ± 2.7 mg/dl. Seven percent of the controls had a serum LDL-C level less than 55 ± 2.4 mg/dl.

There is no significant correlation seen between iron overload and serum TG, as shown in Table 11 and

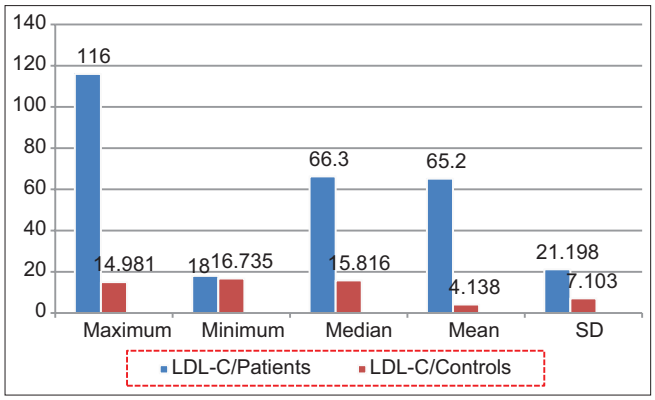


Figure 7: Standard error of the mean of low-density lipoprotein-cholesterol in the study population

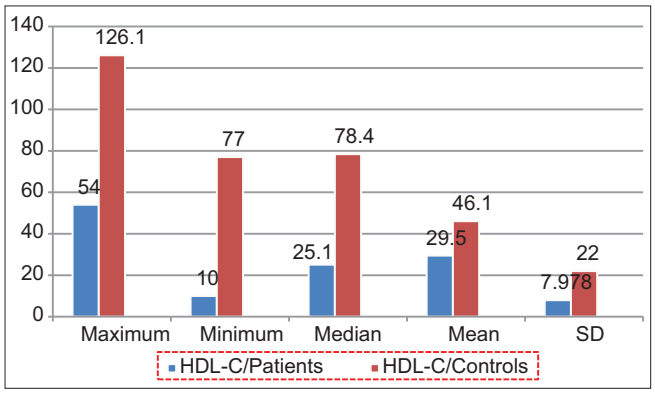


Figure 8: Standard error of the mean of high-density lipoprotein-cholesterol in the study population

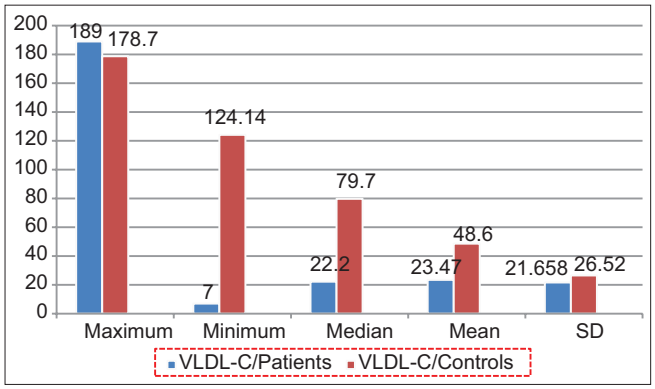


Figure 9: Standard error of the mean of very-low-density lipoprotein-cholesterol in the study population

Figure 12. HDL-C was significantly lower in βeta-thalassemia. Major patients compared with healthy control groups (29.5 ± 7.8 mg/dl) versus (48.6 ± 4.2 mg/dl), respectively, (P = 0.000), as shown in Table 8. Around 23.25% (n = 10) of patients had a serum HDL-C levels less than 25 ± 2.6 mg/dl and 76.74% (n = 33) of patients less than 35 ± 5.7mg/dl. Eight percent of the controls had a serum HDL-C level less than 45 ± 2.4 mg/dl.

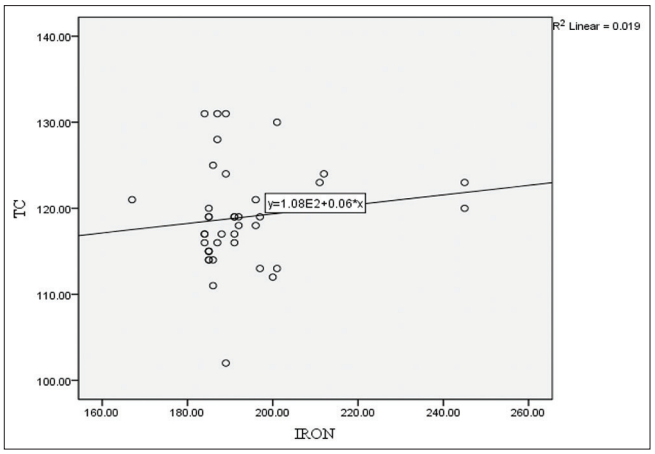


Figure 10: Correlation between iron overload and total cholesterol

Table 7: Correlation between iron overload and total cholesterol

Correlations	TC	Iron
TC		
Pearson correlation	1	0.139
Sig. (two-tailed)		0.374
n	43	43
Iron		
Pearson correlation	0.139	1
Sig. (two-tailed)	0.374	
n	43	43

TC: Total cholesterol

Table 8: SEM comparison of lipid profile between patients and control group

Parameters	Beta-thalassemia major patients		Healthy control groups		*p*
	Mean	SE	Mean	SE	
TC (mg/dl)	121.9±36.7	3.916	178.7±14.6	2.284	0.000
TG (mg/dl)	182.09±43.1	8.254	124.14±12.1	2.552	0.000
LDL-C (mg/dl)	65.2±1.9	3.232	79.7±14.5	2.412	0.001
HDL-C (mg/dl)	29.5±7.8	1.216	48.6±4.2	0.631	0.000
VLDLC (mg/dl)	23.47±12.13	3.303	26.52±5.47	1.083	0.167

SEM: Standard error of the mean, TC: Total cholesterol, TG: Triglycerides, LDL-C: Low-density lipoprotein-cholesterol, HDL-C: High-density lipoprotein-cholesterol, VLDL: Very-low-density lipoprotein

There is no significant correlation seen between iron overload and serum TG, as shown in Table 12 and Figure 13. VLDL was lower in βeta-thalassemia. Major patients as compared with healthy control groups (23.47 ± 12.13 mg/dl) versus (26.52 ± 5.47 mg/dl), respectively, but there are no significant differences between patients and healthy controls (P = 0.167), as shown in Table 8. Approximately 18.6% (n = 8) of patients had a VLDL levels more than 25 ± 2.6 mg/dl and 79% (n = 34) of patients less than 24 ± 4.7 mg/dl, while only one patients had a VLDL level less than 20 ± 1.2 mg/dl.

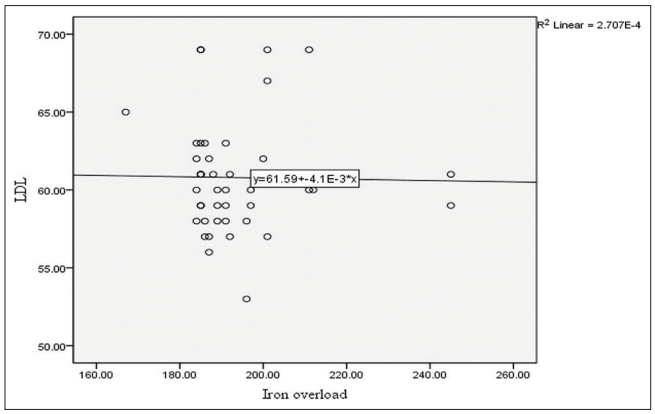


Figure 11: Correlation between iron overload and low-density lipoprotein

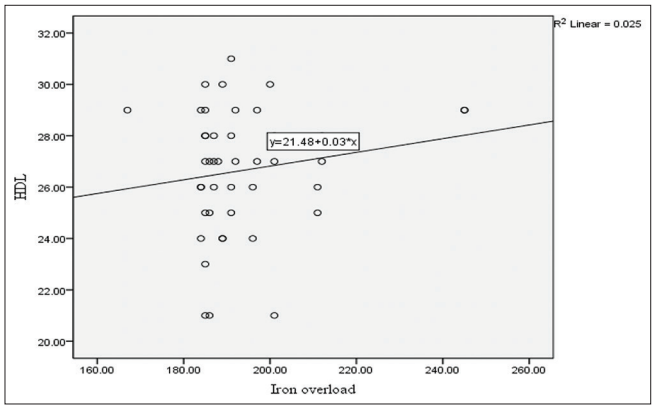


Figure 12: Correlation between iron overload and high-density lipoprotein

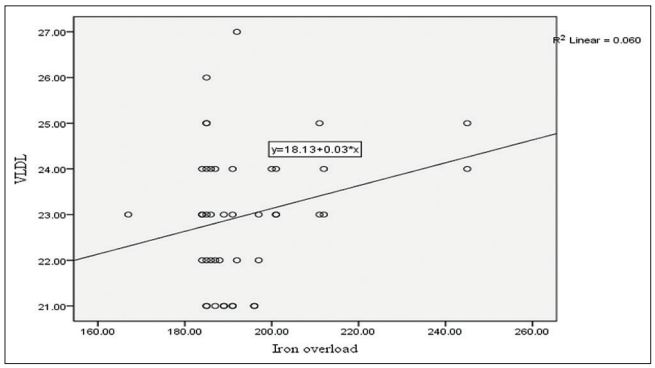


Figure 13: Correlation between iron overload and very-low-density lipoprotein

DISCUSSION

Many studies explain the mechanism of changes in serum insulin, glucose, and lipid profile of thalassemia particularly in Beta-thalassemia major such as the previous of (Shams et al., 2010), this alteration due to abnormality in hepatic biosynthesis that include anemia and iron overload (Ambekar et al., 2001; Calandra et al., 2004). In current study showed that there are significant differences have been detected between the values of Beta-thalassemia major patients and healthy control groups. It was appear that in Beta-thalassemia major patient's serum levels of iron overload (P = 0.01) significantly higher than healthy control groups, this result supported by numerous reports that published on iron overload and endocrine problems in Beta-thalassemia major such as Ariffin et al., 2017, its related with frequent blood transfusions for increased life expectancy and improved the quality of health and life for the patients with B-thalassemia major, but this frequent blood transfusions cause progressive iron overload, which is a major clinical complication of the patients and lead to damages to the liver and other organs of the body (Khaleel et al., 2013).

On the other hand, serum glucose and IRI significantly higher in B-thalassemia major patients rather than healthy control groups; it is related with pancreatic failure because normally the islet cells must produce more insulin to overcome hyperglycemia (Agarwal et al., 2003). It is likely that an increased levels of iron overload cause iron toxicity in the liver and pancreas and insulin dysregulation, due to hepatic and pancreatic dysfunction, which is most likely the cause of impaired glucose metabolism in Beta-thalassemia major patient this result agreement with the finding of Ambekar et al., 2001, while serum insulin there is no significant differences (P = 0.048) between B-thalassemia patients and control groups. In the lipid profile of B-thalassemia major patient's serum levels which included TC, HDL-C, and LDL-C was low as compared to healthy control groups.

In addition, total TG levels in B-thalassemia major patient were higher than healthy control groups, it is because of many factors that related with complication of iron overload in the body of thalassemia patients, while the VLDL-C (P = 0.167) does not show any significant changes and differences in the values that mean neither low nor high as compared with healthy control groups, frequently reported on lipid abnormality in Beta-thalassemia but its pathophysiology is not totally clear (Al-Quobaili and Asali, 2004; Weatherall, 2001), however results of present study correlate well with previous study (Seddon et al., 1994) and Maioli et al. in their results published from 1984 to 1997 suggested that liver damage, accelerated erythropoiesis, and an increased uptake of LDL by macrophages and histiocytes of the reticuloendothelial system are the main causes of low plasma cholesterol in thalassemia (Hashemieh et al., 2011). In 1991, Goldfarb et al. found low plasma cholesterol and abnormality in the structure and composition of lipoproteins in Beta-thalassemia major. In our study, hypertriglyceridemia and hypocholesterolemia were observed. It seems that the main mechanism of hypocholestrolemia in beta-thalassemia

Table 9: Correlation between iron overload and total triglyceride

Correlations	Iron	TG
Iron		
Pearson correlation	1	−0.072
Sig. (two-tailed)		0.648
n	43	43
TG		
Pearson correlation	−0.072	1
Sig. (two-tailed)	0.648	
n	43	43

TG: Triglyceride

Table 10: Correlation between iron overload and LDL

Correlations	Iron	LDL
Iron		
Pearson correlation	1	−0.016
Sig. (two-tailed)		0.917
n	43	43
LDL		
Pearson correlation	−0.016	1
Sig. (two-tailed)	0.917	
n	43	43

LDL: Low-density lipoprotein

Table 11: Correlation between iron overload and HDL

Correlations	Iron	HDL
Iron		
Pearson correlation	1	0.158
Sig. (two-tailed)		0.311
n	43	43
HDL		
Pearson correlation	0.158	1
Sig. (two-tailed)	0.311	
n	43	43

HDL: High-density lipoprotein

Table 12: Correlation between iron overload and VLDL

Correlations	Iron	VLDL
Iron		
Pearson correlation	1	0.245
Sig. (two-tailed)		0.114
n		
VLDL	43	43
Pearson correlation	0.245	1
Sig. (two-tailed)	0.114	
n	43	43

VLDL: Very-low-density lipoprotein

major is severe iron overload these abnormalities can be caused by many mechanisms including plasma dilution because of anemia, accelerated erythropoiesis resulting in increased cholesterol uptake by macrophages and histiocytes of the reticuloendothelial system, defective liver functioning because of iron overload, macrophage system activation with cytokine release and hormonal disturbances (Amendola et al., 2007) while some researchers observed that the lipid profile in thalassemia major patients is not influenced by age, sex, liver injury, and hemoglobin or ferritin levels (Haghi et al., 2009). The higher erythroid bone marrow activity with enhanced cholesterol consumption could be the dominant mechanism implicated in the lipid abnormalities of thalassemia major patients (Tuzmen and Schechter, 2001). Our findings of hypocholesterolemia and hypertriglyceridemia in patients of beta-thalassemia major were supported by other studies (Sutay, 2016; Patne et al., 2012).

CONCLUSION

Results in our study revealed that Beta-thalassemia patients had hypertriglyceridemia, hypocholesterolemia, and low LDL-cholesterol and HDL-cholesterol levels, while VLDL-cholesterol was not significantly changed, so it must be a screening for concern of better evaluation of the cardiovascular risk factors in these patients. Therefore, the prevalence's of lipid abnormality are useful to avoid unnecessary evaluation in patients with Beta-thalassemia major. The mean in serum glucose concentrations increased in Beta-thalassemia major patients and developments of diabetes mellitus appeared. In addition, hypertriglyceridemia and hypocholesterolemia revealed among children suffering from Beta-thalassemia major, while away serum insulin level was not significant changes.

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