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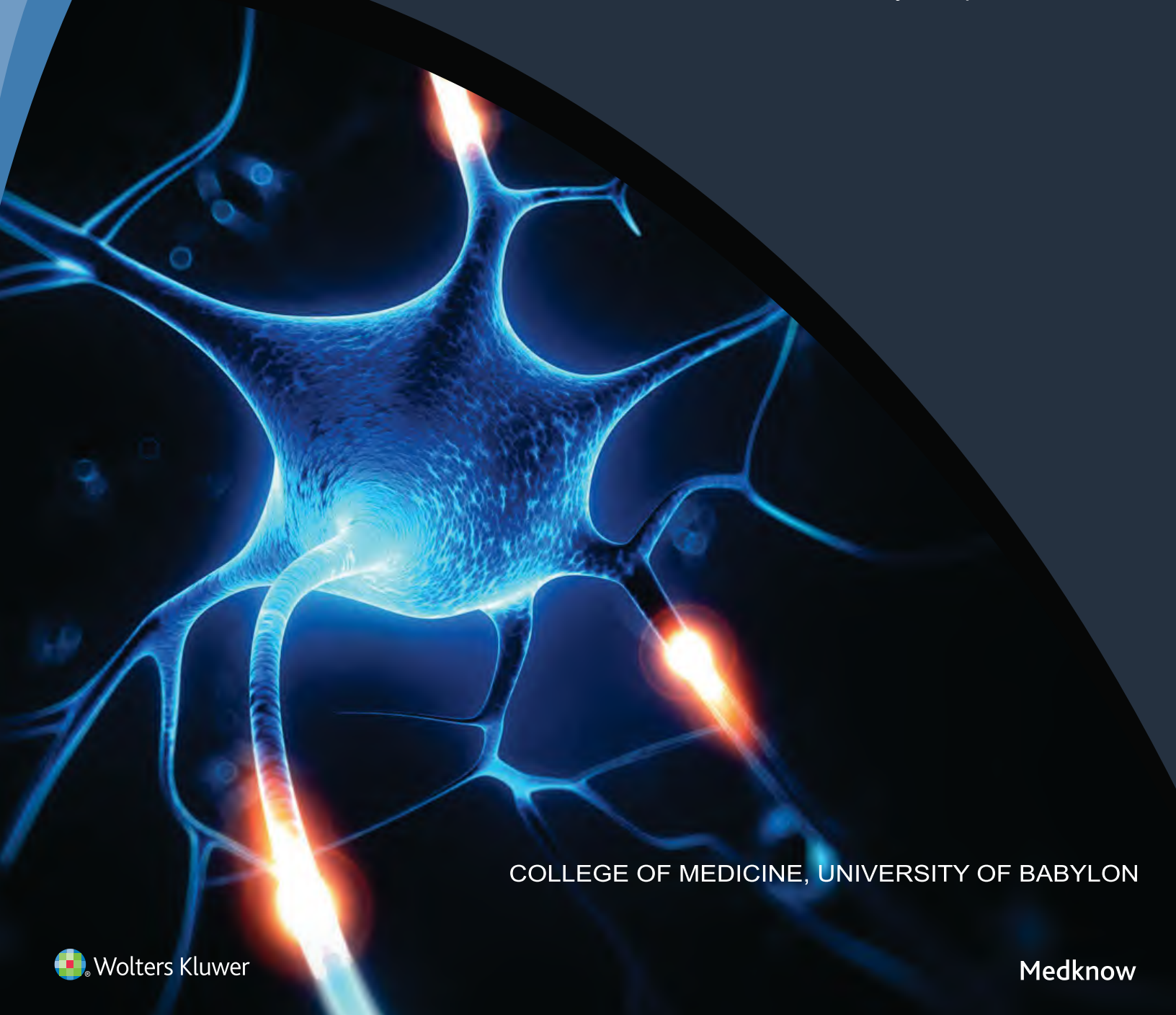

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Original Article

Role of Carotid Ultrasound in the Evaluation of Atherosclerotic Changes in Beta Thalassemia Major Patients

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Abstract

Background: Iron overload in beta thalassemia patients may lead to the alteration of arterial structures together with hyperlipidemia and other risk factors that may lead to the atherosclerotic changes and thickening of carotid arteries. Carotid ultrasound is easy, noninvasive, and rapid test that can detect atherosclerotic changes by the assessment of carotid intima-media thickness, which is a structural marker of atherosclerosis, and it correlates well with vascular risk factors and its relation with stroke and coronary artery disease. **Aim:** The aim was to evaluate the role of carotid ultrasound in the assessment of atherosclerotic changes in iron-overloaded beta thalassemia major patients. **Patients and Methods:** This is a case–control study done in Babylon Gynecology and Children Teaching Hospital from July 1 to December 31, 2018 on 60 patients with beta thalassemia major and 30 normal children as a control group. Their age ranges from 3 to 14 years old. Carotid ultrasound examination was done on all patients and the control group. **Results:** In this study, carotid intima-media thickness was significantly higher in patients than in controls ($P < 0.001$). Carotid intima-media thickness significantly increases in patients with beta thalassemia major with increasing duration of blood transfusion ($P < 0.001$), with increasing serum ferritin ($P = 0.004$), and with increasing serum cholesterol ($P < 0.001$). The study also showed no correlation between body mass index and blood pressure with carotid intima-media thickness. **Conclusion:** Carotid ultrasound is useful in the assessment of carotid intima-media thickness, which is a marker of atherosclerosis and has a strong positive correlation with markers of iron overload and hyperlipidemia.

Keyword: Atherosclerotic changes, beta thalassemia major, carotid ultrasound

Introduction

Thalassemia syndromes describe all the inherited genetic abnormalities that affect the synthesis of α- or β-globin chains and consequently normal erythropoiesis and oxygen-carrying capacity of blood. This condition inherited as an autosomal recessive disorder and can be classified into two main categories: α- and β-thalassemia. Patients with thalassemia commonly develop chronic hemolytic anemia and ineffective erythropoiesis because of an imbalanced globin synthesis. The severity of anemia is linked to the number of genetic aberrations, the specific combination of affected genes, other genetic and environmental modifiers, and physiological stressors.[1]

Atherosclerosis

Atherosclerosis is a lipid-driven chronic inflammatory disease of vessel wall in which both innate and adaptive immune responses play a role. Immune cells and their mediators directly cause chronic arterial inflammation that is a hallmark of atherosclerosis. It is clinically and experimentally reported that postinflammatory vascular remodeling induces the development of arteriosclerosis or an early onset of atherosclerosis.[2]

Iron overload has been documented to cause endothelial dysfunction via oxidative damage, causing early and accelerated atherosclerosis. Vascular events such as thrombotic occlusions of the cerebral, portal, retinal, and

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coronary circulations are described in patients with excess iron, although there are currently sparse data and a lack of studies regarding the mechanism of such events.[3]

Carotid intima-media thickness

Carotid intima-media thickness (CIMT) is defined as the distance between the lumen–intima interface and the media–adventitia interface of the artery wall. CIMT is an early marker of atherosclerosis and predicts future cardiovascular events.[4]

CIMT is a preclinical marker for cardiovascular disease (CVD) and is a quantitative index for evaluating the severity and progression of atherosclerosis and the prediction of coronary heart disease and stroke. CIMT is also associated with several cardiovascular risk factors including blood pressure (BP), dyslipidemia, and health behaviors such as smoking and physical activity.[5]

Normal CIMT for pediatrics age group considered to be 0.2–0.4 mm and according to the following equation: [intima-media thickness (IMT) in millimeters = (0.009 × age in years) + 0.35].[6]

Carotid atherosclerosis plays a large role in the etiology of stroke and CVD. Carotid Doppler has been widely used to detect subclinical carotid atherosclerosis by quantifying CIMT and carotid plaque. Both CIMT and carotid plaque have been proposed as surrogate imaging biomarkers of subclinical atherosclerosis.[7]

The aim of this study was to assess of the role of carotid ultrasound examination of carotid intima-media thickness measurement as a predictor of atherosclerotic changes in beta thalassemia major patients with iron overload and evaluate their clinical and laboratory findings as risk factors.

Patients and Methods

This is a case–control study done in Babylon Gynecology and Children Teaching Hospital in Babylon, Iraq from July 1 to December 31, 2018 on 60 patients with thalassemia major, and 30 normal children were taken as a control group. Oral consent was taken from parents and older children before doing the tests. Inclusion criteria include patients with B-thalassemia major in the age range of 3–14 years who are iron overloaded (more than one year history of frequent blood transfusion or those with serum ferritin more than 1000 µg/dL) and on iron chelation therapy.

The patients with chronic illness such as cardiac, hypothyroidism, and diabetes mellitus were excluded.

History and physical examination were performed on patients and controls. The history included age, gender, medical diseases, and the duration of illness since first blood transfusion, frequency of blood transfusion, and intake of iron-chelating agent.

Full clinical examination was done, BP was measured using age-appropriate cuff size BP devices, and the weight in kg and height in cm were measured.

Laboratory analysis

After appropriate cleaning and good antiseptic measures and after fasting of at least 8 h, 5 mL of blood was taken from median cubital vein and put in a tube containing an anticoagulant and then transferred to the lab for doing investigations; after 3 min of centrifugation, blood was taken for the assessment of packed cell volume by using centrifuge and special chart, whereas serum was taken for serum ferritin assessment using MINI VIDUS coinstrument and serum cholesterol assessment using spectrophotometry.

Carotid Doppler study

All patients and controls were subjected to B-mode ultrasonography (GE vulsion machine) of their extracranial carotid arteries after the explanation of procedure to parents and children.

All ultrasound examinations were performed by a single radiologist who was unaware of the clinical and laboratory details of the examined children.

The examined children were placed in a supine position with the head extended and rotated for up to 45 degree away from examiners side.

The examination was started by locating the common carotid artery in the lower part of the neck in the transverse plane; the artery is followed upward till it widens to form the carotid bulb where it bifurcates into internal and external carotid arteries.

Intima-media thickness was measured in 1-cm segment distal to the dilation of carotid bulb and always in a plaque-free segment; for each subject, CIMT measurement was done on both sides and frames were taken in end-diastolic images.

Values for both right and left arteries were then averaged; two frames were selected and analyzed for mean CIMT.

The average reading from these two frames was calculated for both right and left internal carotid arteries; the average of the two sides was considered as the patient's overall CIMT.

Statistical analysis

The data were collected, organized, and tabulated using the SPSS software version 23. The results were expressed in the form of numbers, ranges, and the mean ± standard deviation (SD). Independent t-test and Qi square test were used to analyze the differences between the two groups.

P value < 0.05 was considered statistically significant.

Some variables were assessed by scatter plots to determine the relationship between them in a linear manner by using

R value (correlation coefficient) with values between 0.1 and 0.3 signify a small association, values between 0.3 and 0.5 signify a medium association, and values between 0.5 and 1 signify a large association.

Ethical approval

The study was conducted in accordance with the ethical principles that have their declaration of Helsinki. It was carried out with patients' verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number (732 in June 15, 2018) to get this approval.

Results

The study was done on 60 patients with thalassemia major: 33 male and 27 females; male-to-female ratio was 1.2:1; and their mean age was 9.93 in Babylon Gynecology and Pediatrics Hospital and compared with the control group: 17 male and 13 females; male-to-female ratio was 1.3:1; and their mean age was 9.7 and compared statistically as shown in Table 1.

Table 1: Demographic data of patients and controls

Group	Age (years), mean ± SD	Gender	
		Male, *n* (%)	Female, *n* (%)
Patients group	9.93 ± 2.99	33 (55%)	27 (45%)
Control group	9.7 ± 3.09	17 (56.7%)	13 (43.3%)
P value	0.543	0.078	

The study shows a significant difference between patients and controls regarding measurements of Hb, serum ferritin, and serum cholesterol ($P < 0.001$). There is no significant difference regarding measurements of body mass index (BMI) ($P = 0.459$), systolic BP ($P = 0.064$), and diastolic BP ($P = 0.092$) between patients and controls as shown in Table 2.

The relation between CIMT and the age, sex, and type of chelation therapy were studied as shown in Table 3.

Showing that CIMT increase with age, no change in CIMT regarding gender and increase CIMT in patients taking oral chelation therapy only compared with patients taking mixed therapy.

CIMT increases in a linear manner with increasing duration of blood transfusion in years, R value = 0.8, *P* value < 0.001 as shown in Figure 1.

CIMT increases in a linear manner with increasing serum ferritin, R value = 0.4, *P* value = 0.004 shown in Figure 2.

CIMT increases in a linear manner with increasing serum cholesterol, R value = 0.6, *P* value < 0.001 as shown in Figure 3.

The study shows that the mean of CIMT of the patients (0.50 mm) is more than CIMT of the control group (0.34 mm) and there was significant difference regarding CIMT measurement ($P < 0.001$) as shown in Table 4.

By using the receiver operating characteristics curve to qualify the effectiveness of CIMT as screening test and by comparison between patients and controls, we found that the cut-off value of CIMT was 0.45, the sensitivity was 80%, and specificity was 100% as shown in Figure 4.

Table 2: Clinical and laboratory data of patients and controls

Variable		Cases (mean ± SD)	Control (mean ± SD)	*P* value
BP (mmHg)	Systolic	115 ± 9.75	111.3 ± 6.5	0.064
	Diastolic	75 ± 8.05	72 ± 8.15	0.092
Hb (g/dL)		7.11 ± 1.28	12.5 ± 0.85	<0.001
S. ferritin (µg/dL)		2500 ± 1205	79 ± 14	<0.001
S. cholesterol (mg/dL)		265 ± 137.6	82.2 ± 16.9	<0.001
Body mass index (kg/m^2)		20.11 ± 1.98	20.46 ± 2.34	0.459

Table 3: Correlation of CIMT with the age, gender, and type of chelation therapy

Patients		*n* (%)	CIMT		*P* value
			Mean	SD	
Age group (years)	<7	14 (23.3%)	0.409	0.030	<0.001
	7–9	18 (30%)	0.483	0.039	
	>9	28 (46.6%)	0.551	0.051	
Sex	Male	33 (55%)	0.506	0.066	0.507
	Female	27 (45%)	0.519	0.079	
Type of chelation	Oral	44 (73.3%)	0.491	0.068	<0.001
	Mixed	16 (26.7%)	0.569	0.048	

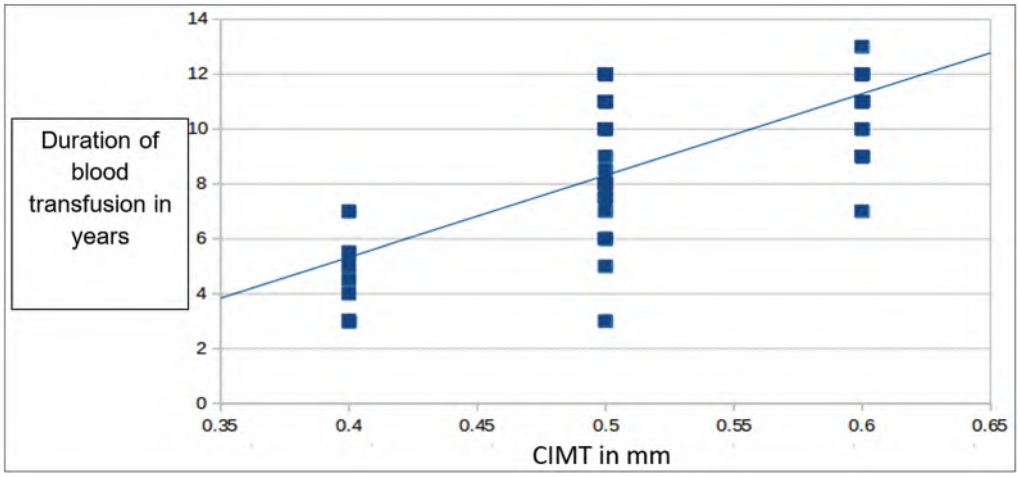

Figure 1: Scatter plot of CIMT versus the duration of blood transfusion in years

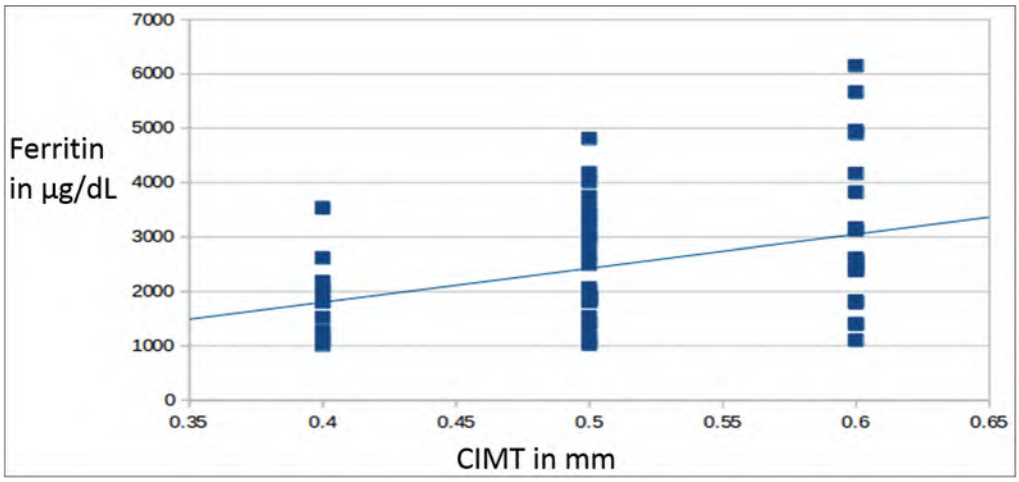

Figure 2: Scatter plot of CIMT versus serum ferritin

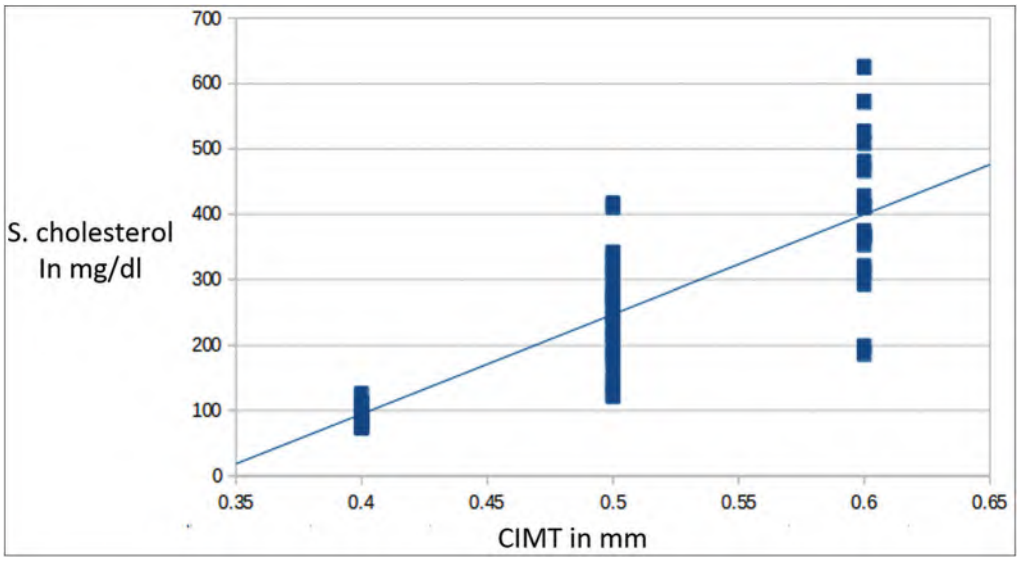

Figure 3: Scatter plot of CIMT versus serum cholesterol

Table 4: The difference in CIMT measurements between patients and controls

Groups	CIMT range (mm)	Mean ± SD	*P* value
Patients	0.4–0.6	0.51 ± 0.071	<0.001
Controls	0.2–0.4	0.34 ± 0.073	

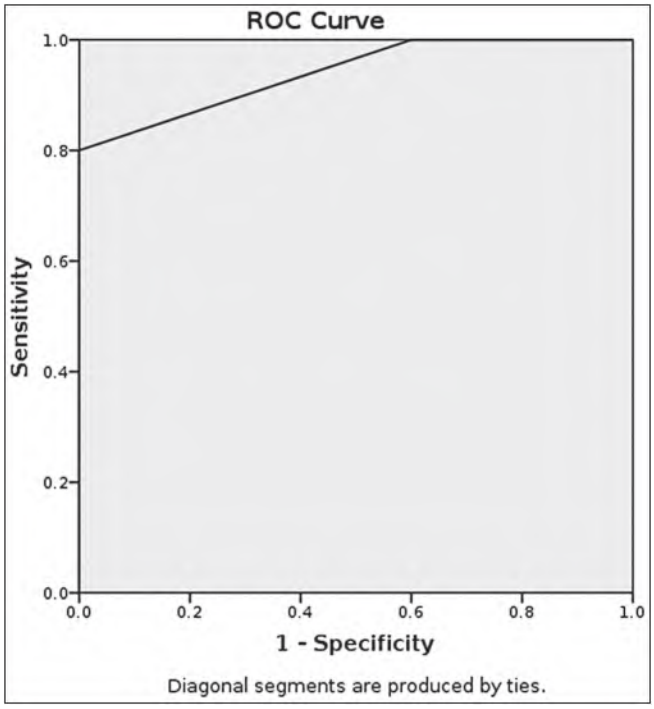

Figure 4: The receiver operating characteristics curve of CIMT between patients and controls

Discussion

In this study, carotid Doppler examination was done to evaluate the CIMT in 60 patients with thalassemia major who are iron overloaded, and their clinical and laboratory findings were compared with the control group.

The results of CIMT measurements of thalassemia patients were significantly higher than those of the control group ($P < 0.001$).This study was in agreement with Abdelsamei *et al.*,[8] Dogan and Citak,[9] and Abaza *et al.*[10] who found that CIMT was significantly higher in patients with thalassemia, and disagree with Piccione *et al.*[11] who has shown no significant difference in the CIMT measurement between thalassemia patients and controls.

The study has shown that the CIMT increases in a linear manner with age, which was in agreement with Su *et al.*,[12] which shows similar results and that [IMT in millimeters = (0.009 × age in years) + 0.35]. The study also shown that there were no significant differences in the CIMT measurement between male and female, which was in agreement with Doyon *et al.*,[6] which shows that there was no effect of gender on CIMT measurement.

The results of serum ferritin and serum cholesterol were significantly higher in patients than in controls ($P < 0.001$). CIMT was significantly high with increasing duration from the first blood transfusion ($P < 0.001$). Significant negative correlation with hemoglobin level ($P < 0.001$) as hemoglobin level measured before blood transfusion on the day of examination, and there is no correlation with BMI ($P = 0.459$) as compared with the control group and where in agreement with Abdelsamei *et al.*[8]

There is no significant correlation between CIMT and BP, which matches with Soltani *et al.*[13] who has shown that ambulatory BP monitoring in thalassemia patients is lower than controls because of lower BMI and disagreed with Day *et al.*[14] who has shown that BP had a positive correlation with CIMT as a risk factor for atherosclerosis.

The differences in readings may be due to a single reading of BP was taken while serial ambulatory readings are required for the proper assessment.

The correlation between the type of chelation therapy and CIMT was significant as 73.3% of patients were on oral chelating agent and 26.7% of patients were on mixed oral and subcutaneous medications and $P < 0.001$, which may be due to that patients with more severe iron overload are on mixed chelating agents, whereas patients with less severe iron overload are on oral medications only.

In patients with thalassemia, CIMT increases with increasing serum level of ferritin ($P < 0.001$) and also increases with increasing serum cholesterol level ($P < 0.001$). Juonala *et al.*[15] and Gursel *et al.*[16] showed similar results regarding the relationship of CIMT in thalassemia patients with serum ferritin and serum cholesterol and their etiological role in the development of atherosclerosis.

Conclusion

CIMT has increased in patients with beta thalassemia as well as markers of iron overload and hyperlipidemia, which all increase with increasing duration from the first blood transfusion, and all are risk factors for atherosclerosis.

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Conflicts of interest

There are no conflicts of interest.

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