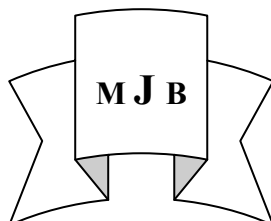


Lipid Profile in Thalassemia Major Patients on Desferrioxamine Therapy

Adnan A. Zainal

Mohammad A. Al-Kataan

Department of Clinical Pharmacy, College of Pharmacy, University of Mosul, Mosul, Iraq.



Abstract

Objectives: (a) To determine the differences in lipid profile parameters between thalassemia major (TM) patients not taking desferrioxamine (DFO) who show signs of iron overload (IOL) and those well-controlled TM patients on DFO therapy.

(b) To determine the effects of age and BMI on measured parameters in both groups.

Subjects and Methods: The study was conducted in Thalassemia Center at Ibn-Al-Atheer Pediatric Hospital in Mosul from October 2007 to April 2008. Twenty patients with TM were selected as follows: Ten patients on DFO therapy with no signs of IOL and ten TM patients not on DFO therapy and showing signs of IOL. Data were presented as mean $\pm$ SD; independent samples t-test was used in comparing both groups, while effects of age and BMI on measured parameters were determined by using Pearson correlation.

Results: Total cholesterol (TC), triglyceride (TG), Very low density lipoprotein (VLDL-C), low density lipoprotein (LDL-C) and atherogenic index (AI) showed significant increase in IOL group, while serum high density lipoprotein (HDL-C) showed significant reduction in IOL group, when compared to the second group. Age and BMI show no significant correlation with measured parameters in well-controlled group, while in IOL group, BMI showed positive correlation with LDL-C and AI.

Conclusion: Significant changes in lipid profile parameters were seen in TM patients not taking DFO therapy and showing signs of IOL compared to those well-controlled patients on DFO therapy.

الخلاصة

اهداف الدراسة: ١- بيان التغيرات الحاصلة في واجهة شحوم الدم عند مرضى التلاسيميا النوع الرئيسي غير الخاضعين لعلاج الدسفيروكسامين و المظهرين لاعراض فرط تحميل الحديد و المرضى الخاضعين لعلاج الدسفيروكسامين . ٢- بيان تأثير عامل العمر و معامل كتلة الجسم على المعايير المقاسة عند المجموعتين.

طرق العمل: انجزت هذه الدراسة في مركز التلاسيميا / مستشفى ابن الاثير للأطفال للفترة من تشرين الاول ٢٠٠٧ لغاية نيسان ٢٠٠٨. اختير عشرون مريضاً جميعهم مصابون بالتلاسيميا النوع الرئيسي و كما يلي: عشرة مرضى خاضعين لعلاج الدسفيروكسامين و لا يعانون من اعراض فرط تحميل الحديد و عشرة اخرين يعانون من اعراض فرط تحميل الحديد و غير خاضعين لعلاج الدسفيروكسامين.

تم تمثيل البيانات كوسط حسابي $\pm$ معامل الانحراف المعياري و باستخدام اختبار - ت للنماذج المستقلة ، كما قيس تأثير عاملي العمر و معامل كتلة الجسم على المعايير المأخوذة بواسطة معامل ارتباط بيرسون.

النتائج: اظهر كل من مستوى الكوليستيرول الكلي، الشحوم الثلاثية، كوليستيرول البروتين الشحمي وضيع الكثافة، كوليستيرول البروتين الشحمي واطي الكثافة، الدهون المفسفرة و معامل التصلب الشرياني زيادة معنوية ($p < 0.05$) عند المرضى غير الخاضعين لعلاج الدسفيروكسامين، على العكس من كوليستيرول البروتين الشحمي عالي الكثافة الذي اظهر انخفاضاً معنوياً ($p < 0.05$) عند نفس المجموعة.

لم يظهر كل من معامل كتلة الجسم و العمر ارتباطاً مع المعايير المقاسة عند المرضى الخاضعين لعلاج الدسفيروكسامين، في حين اظهر معامل كتلة الجسم ارتباطاً معنوياً موجباً مع كل من كوليستيرول البروتين الشحمي واطي الكثافة و معامل التصلب الشرياني.

الاستنتاج: تم ملاحظة فروقات معنوية في واجهة شحوم الدم بين مرضى التلاسيميا النوع الرئيسي ممن تظهر عليهم علامات فرط تحميل الحديد و لا يتعاطون الدسفيروكسامين مقارنة باولئك المرضى المستمرين على الدسفيروكسامين و جيدي الحالة السريرية.

Introduction

Thalassemia major (TM) is a genetic disorder characterized by impaired normal hemoglobin synthesis and such patients will depend on blood transfusion all their life. However, quality and duration of life of transfusion-dependent patients has transformed over the last few years with their life expectancy increasing into the third decade and beyond with a good quality of life [1].

Cardiac symptoms and premature death from cardiac causes are still major problems and are associated mainly with oxidative modification of LDL which plays a central role in the pathogenesis of atherosclerotic lesions [2].

TM patients are subjected to continuous blood transfusion and show peroxidative tissue injury through secondary iron overload (IOL). The alteration of oxidation/antioxidation balance might affect the susceptibility of LDL to oxidation and this promotes atherogenesis in arterial wall [3]. IOL cause many conditions associated with increased thromboembolism such as diabetes mellitus and complex cardiopulmonary abnormalities and alterations in liver function tests [2]. Low plasma and lipoproteins cholesterol caused by increased cholesterol consumption and abnormal lipoprotein structure have been frequently reported in TM patients [4]. Desferroxamine (DFO) is a chelating agent used for induction of negative iron balance by increasing iron urinary excretion and preventing free oxygen radical formation and inhibit catalyzing role of iron in Fenton reaction [5]. In this study, we evaluate the effect of DFO therapy on lipid profile parameters in TM patients.

Subjects and Methods

The study was conducted in Thalassemia Center at Ibn Al-Atheer Pediatrics Hospital in Mosul from October 2007 to April 2008. Twenty patients with TM were selected as follows: Ten patients (well-controlled, no signs of IOL) on DFO therapy (mean age $\pm$ SD, 15.2 ± 3.35 years) and ten patients not taking DFO therapy showing signs of IOL (mean age $\pm$ SD, 7.4 ± 3.56 years), both groups were receiving blood transfusion at a rate of one transfusion /month.

IOL was assessed by clinical examination by the specialist physician referring the patients for the study. History and DFO compliance were determined by questioning the patients and referring to patients medical records. IOL was not, however, the basis of patient assignment into either group (since it was only assessed by clinical examination) but rather was DFO therapy compliance.

Total serum cholesterol (TC), serum triglyceride (TG) and high density lipoprotein (HDL-C) were measured by enzymatic methods [6- 8], while very low density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C), atherogenic index (AI) and phospholipids were calculated from equations [9]. BMI was calculated as weight (in kilograms) divided by standing height (in square meters) [1]. Data are presented as mean $\pm$ SD. Independent samples t-test was used to compare both groups and the effects of age and BMI on measured parameters were obtained by Pearson's correlation.

Results

In the present study TG, VLDL-C, LDL-C and phospholipids showed

significant increase in IOL group as compared with DFO group ($P < 0.05$), also TC and AI showed significant increase in IOL group as compared with DFO group ($P < 0.01$), while HDL-C showed significant decrease as compared with DFO group ($P < 0.01$), as shown in Table 1.

Age and BMI did not show significant correlation with the measured parameters in DFO patients group, age also did show significant correlation with the parameters in the IOL group (Data not shown). BMI showed significant positive correlation to LDL-C (Figure1) and AI (Figure 2) in the IOL group.

Table1 Lipid profile, atherogenic index and BMI in DFO group and IOL group TM patients

Parameters	DFO patients	IOL patients
Total Cholesterol (mmol/L)	2.39 ± 0.5	$2.93 \pm 0.35^{**}$
Serum Triglyceride (mmol/L)	0.759 ± 0.111	$0.886 \pm 0.156^*$
HDL-C (mmol/L)	1.37 ± 0.33	$0.75 \pm 0.2^{**}$
VLDL-C (mmol/L)	0.33 ± 0.05	$0.39 \pm 0.07^*$
LDL-C (mmol/L)	1.39 ± 0.41	$1.46 \pm 0.55^*$
Phospholipids (mmol/L)	22.64 ± 0.14	$22.80 \pm 0.10^*$
AI	4.4 ± 1.83	$5.33 \pm 1.94^{**}$
BMI	22.43 ± 2.41	20.42 ± 3.72

* $P < 0.05$, ** $P < 0.01$

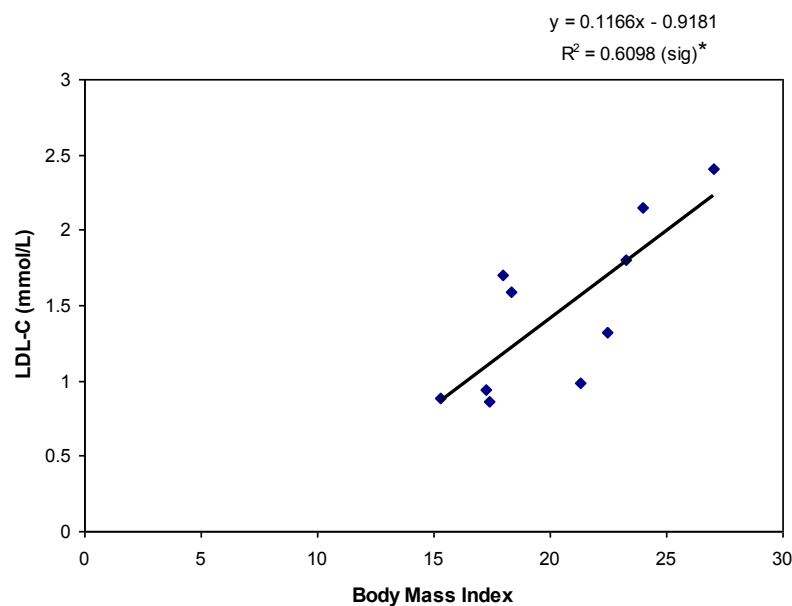


Figure 1 Correlation between BMI with LDL-C level in IOL group thalassemic patients, * $P < 0.01$

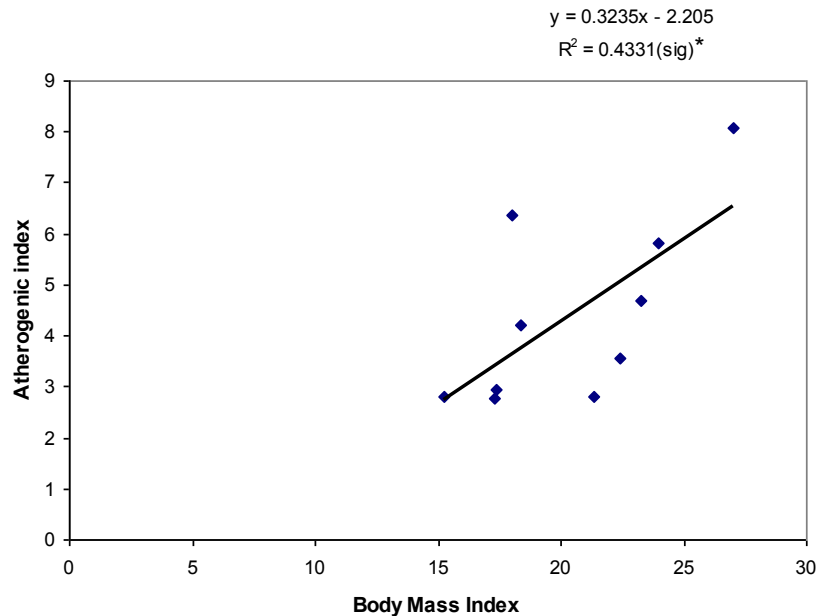


Figure 2 Correlation between BMI with atherogenic index in IOL group thalassemic patients, * $P < 0.05$

Discussion

The present study shows significantly higher TC, LDL-C and VLDL-C and significantly lower HDL-C levels in TM patients not taking DFO compared to TM patients on DFO therapy.

It is well established that TM is associated with changes in plasma lipids and lipoproteins. In TM patients, when compared to controls, low levels of TC, caused by a significant reduction of both LDL-C and HDL-C levels have been consistently reported whereas reports on TG levels were discordant [4, 10].

Brizzi *et al.* [3] reported significantly lower levels of TC, HDL-C, LDL-C and TG in TM patients receiving regular DFO therapy, as compared to controls. Similar findings in TM patients, except that TG was not significantly different [11, 12] or was significantly high [4, 13-16] were also reported. Similar findings regarding HDL-C and TC in TM patients on DFO [17,18] were also reported; TG did not significantly differ between study groups in another study [19]. Although

they indicate a major difference in lipid profile compared to general population; however, due to radically different study design, the above studies' findings bear little relevance to the present study findings.

Goldfarb *et al.* [12] reported lower TC and LDL-C and higher HDL-C levels in TI compared to TM patients. Hartman *et al.* [4] reported significantly higher levels of TC, HDL-C, LDL-C and TG in TM patients as compared to TI patients. These studies offer very little in clinical relevance to the present study findings, as no comparison was made between TM and TI patients in the present work.

It appears that many factors such as IOL, anemia, activated macrophage system, defective liver function and hormonal disturbances affect lipid patterns seen in TM [1, 14]. Dominant mechanisms suggested to explain altered lipid patterns in TM including accelerated erythropoiesis, increased uptake of LDL by macrophages and reticuloendothelial system [1, 19], IOL and oxidative stress [4].

Lipid peroxidation may contribute to lipid changes seen in TM. Oxidative stress leads to depletion of antioxidants within LDL, leading to LDL oxidation [2]. In TM patients, IOL depletes the blood from antioxidant substances [3], iron may play a catalytic role in the initiation of free radical reactions [11] and a significant correlation exists between ferritin level (a measure of IOL) and peroxidative stress [17]. Oxidative stress seen in TM leads to increased uptake of LDL-C and HDL-C by macrophage/ monocyte system [4, 5]. In TM, LDL and HDL particles themselves have abnormal lipid composition with low cholesterol and high TG [3, 5, 12]. A protective factor in TM patients is chelation therapy with DFO, because this treatment was shown to inhibit LDL oxidation independent of its iron chelation property [4, 20].

AI predicts coronary heart disease (CHD) risk regardless of absolute LDL-C and HDL-C [1]. A higher index implies an increased cardiovascular risk, and lowering this ratio has been shown to decrease this risk [21]. The present study demonstrated a significantly lower level of AI and plasma phospholipids in DFO group as compared to TM patients not taking DFO. Apart from previous studies reporting significantly lower serum phospholipids compared to controls [18] and higher AI in TM women than in men [1], no relevant study addressed such aspects as AI and phospholipids similarly to the current work; phospholipids are usually infrequently used in the context of lipid profile assessment.

BMI showed positive correlation with LDL-C and AI in TM patients not taking DFO, while no correlation was found between BMI and measured parameters in DFO group. No relevant findings in previous studies on lipid profile in TM supporting or

contradicting such correlations could be found. In the present study, no correlation was found between measured parameters and patients age, this is consistent with previous studies findings [1, 4, 12]. This was, however, inconsistent with Chrysohoou *et al.* [1] finding that age was positively and significantly correlated with all blood lipid measurements except HDL-C; also it is inconsistent with the positive correlation between patients age with TG found in a previous study [16].

Higher concentrations of LDL, VLDL, TG and lower concentrations of HDL are known to correlate positively with severe and premature atherogenesis [22]. A low level of plasma HDL is one of the strongest independent risk factors for CHD. HDL-C concentration is inversely correlated with risk of CHD [23]. A lower AI indicates a greater proportion of HDL-C and is a measure of CHD. Patients with lower AI are less predisposed to arteriosclerosis [24].

In the current study, LDL-C, VLDL, TG and AI were higher while HDL-C was lower, significantly, in TM patients not taking DFO treatment compared to DFO group. Thus it maybe assumed that TM patients on DFO treatment seem more protected against CHD than those not taking DFO treatment, although the small patients sample size poses a major limitation of the current study and makes it difficult to generalize such a conclusion.

A previous study suggested that differences in blood lipids and lipoproteins could also be attributed to adherence to a different life style and dietary habits in patients with TM [1]. Among other factors, compliance with DFO (A criterion used in patient assignment to either group in the present work) may possibly be influenced by socioeconomic background (discussed below) which

obviously is a major determinant of life style and dietary habits; it may accordingly be assumed that different life style and dietary habits may possibly affect final lipid pattern seen in both study groups.

Due to the multiple factors influencing lipid profile in thalassemia, including even the type of thalassemia itself [4], it was necessary to neutralize the confounding effects of such factors by adopting the study design used in the present work; although the presence of IOL in one group may arguably bias the results. However, previous studies in TM and TI [1, 4] have generally showed lack of correlation of serum lipids (Except LDL-C) with IOL (as indicated by ferritin levels); therefore any such concerns of IOL biasing the results are possibly overestimated.

We could not find any previous work of a similar study design, i.e., comparing TM patients on DFO to those not taking DFO. The existence of the latter category of patients maybe attributed to many social, economic and even geographic factors affecting accessibility of chelation therapy in our study locality. Thalassemia Center in Mosul is the only center available to TM patients in the northern region; long distance and strict requirements of continued and prolonged DFO therapy leave many patients discouraged to strictly comply with treatment [25], consistently, a previous study [11] reported their patients not being appropriately chelated due to distance, social and economic reasons. In the same context, over 90 % patients worldwide cannot afford the cost of adequate DFO dosage, especially in the developing world [15, 25, 26]. Compliance in most patients is poor [25]; in fact, compliance with long-term DFO therapy declines as supervision of this regimen becomes increasingly the responsibility of the patients [27]. All these factors may

contribute to the existence of a category of TM patients who do not take DFO therapy.

In conclusion, DFO therapy in TM patients appears to have a favorable effect on lipid profile, and may possibly be protective against cardiovascular disease and CHD; whether this favorable effect is due to chelation therapy alone or due to multiple factors affecting lipid profile in TM; further studies are required to elucidate this issue.

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