

Hypocholesterolaemia in Thalassaemia – Pathogenesis, Implications and Clinical Effects

Paolo Ricchi,¹ Massimiliano Ammirabile² and Aurelio Maggio³

1. Assistant, Department of Oncohaematology, Microcythaemia Centre 'A Mastrobuoni', Antonio Cardarelli Hospital; 2. Fellow, Department of Oncohaematology, Microcythaemia Centre 'A Mastrobuoni', Antonio Cardarelli Hospital; 3. Director, Division of Haematology II, Villa Sofia-Cervello Hospital

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Abstract

In this review, the role of hypocholesterolaemia as a potential source of several clinical features of patients affected by thalassaemia is assessed. The primary focus is on the extent of the phenomenon among different forms of thalassaemia in order to highlight the particularly reduced level in patients with thalassaemia intermedia. In addition, we explore how the reduced levels of cholesterol could influence the atherogenic process and many typical clinical features of patients affected by thalassaemia.

Keywords

Hypocholesterolaemia, thalassaemia, atherogenesis, endocrinopathy

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Correspondence: Paolo Ricchi, UOC Microcitemia, Azienda Ospedaliera di Rilievo Nazionale 'A Cardarelli', Via A Cardarelli 9, 80131 Naples, Italy.
E: paolo.ricchi@ospedalecardarelli.it

Free cholesterol is a constituent of cell membranes. Apart from nucleus-free erythrocytes, all cells of the human body are able to synthesise cholesterol *de novo*. More than 100 enzymatic processes are involved in the complete biosynthesis of cholesterol, which is a complex and energy-consuming process.

For this reason, several tissues prefer to assume cholesterol from plasma lipoproteins rather than from their own intracellular synthesis. Cholesterol devoted to plasma lipoprotein is synthesised in the liver and in the distal part of the small intestine.¹ Chylomicron remnants are the vehicle of cholesterol intake from the diet to the liver. The hepatic cholesterol pools originating from chylomicron remnants and *de novo* synthesised cholesterol are combined and excreted as very-low-density lipoprotein (VLDL). Low-density lipoprotein (LDL), the ultimate catabolic product of VLDL, is the main source of cholesterol for human tissue, especially those with high cell turnover.²

Total cholesterol (TC) consists largely of the cholesterol in LDL particles (LDL cholesterol) plus the cholesterol in high-density lipoprotein particles (HDL cholesterol).

Cholesterol is not only a fundamental element of cell membranes but also the principal precursor for steroid and sexual hormone biosynthesis. Furthermore, cholesterol, through its intermediary products such as farnesyl diphosphate and geranylgeranyl diphosphate, is involved in the regulation of ras-protein intracellular signal transduction.¹

Hypercholesterolaemia in Thalassaemia

A large body of evidence from prospective and retrospective studies has clearly shown that patients affected by thalassaemia have reduced levels of TC with respect to healthy age- and sex-matched controls.^{3–10}

Hypocholesterolaemia has been reported in all phenotypes of β -thalassaemia and has also been described in various haematological disorders associated with high erythropoietic activity.^{11–14} *Table 1* shows cholesterol levels found in different reports exploring lipid profiles in young and adult patients affected by all phenotypes of thalassaemia.

The majority of these studies have evaluated cholesterol level in young patients with severe thalassaemia (thalassaemia major and intermedia). As shown in *Table 1*, low levels of plasma cholesterol are evident among all ages of patients with thalassaemia major and intermedia.

Almost all studies agree with the observation that of all the forms of thalassaemia, thalassaemia intermedia patients show the most marked alterations in lipid profile. Conversely, no studies have identified a cholesterol cut-off value that could clearly distinguish patients with thalassaemia intermedia from those affected by thalassaemia major.

Furthermore, hypocholesterolaemia is only one aspect in the more complex alteration of lipid profile involving LDL and HDL level observed in all thalassaemia patients. In fact, most of the above-mentioned studies reported that thalassaemia patients also have lower HDL and LDL levels than those observed in control patients. Many of these studies have also tried to identify within-patient factors correlating with cholesterol level;^{4,8,9} data analysis of most reported studies failed to show any influence on cholesterol level of age, sex, liver injury, haemoglobin, ferritin levels and the presence or absence of the spleen. However, in the study by Ricchi et al.,⁸ a lack of effect of single genotypes on cholesterol levels in thalassaemia major and intermedia patients was also reported.

Pathogenesis

The pathogenetic mechanism for hypocholesterolaemia was investigated in an interesting study conducted using a model of artificial microemulsion termed LDE (a cholesterol-rich microemulsion), whose composition resembled that of LDL.

It was demonstrated that LDL clearance, the mechanism that removes LDL from the circulation, was enhanced in heterozygous β -thalassaemia patients.¹⁵

However, despite the fact that hypocholesterolaemia in thalassaemia was first described many years ago, there is no definitive explanation for the mechanism underlying this clinical condition in severe forms of thalassaemia. Two main pathogenetic mechanisms have been proposed: the presence of enhanced cholesterol consumption required for cell membrane formation,^{16–18} and the presence of a hyperplastic and overactive reticuloendothelial system, which may be responsible for an increased uptake of LDL.^{19,20}

The first ‘mechanism’ seems to be the more complete and would also explain the difference always reported in cholesterol level among patients with thalassaemia intermedia and major. In fact, in the studies by Ricchi⁸ and by Hartman⁹ it was clearly demonstrated that patients with thalassaemia intermedia have both lower cholesterol and lower haemoglobin (Hb) levels than patients with thalassaemia major. In both studies, patients were accurately selected by eliminating biases (severe liver disorders, hyperthyroidism, fat malabsorption and other factors that could *per se* modify cholesterol levels).

In the study by Ricchi et al.,⁸ it was clearly indicated that pre-transfusional Hb level was considered, which represents the lowest peak of Hb for chronically transfused patients who usually remain at higher values until their next transfusion.

According to current guidelines, patients with thalassaemia major have pre-transfusional Hb ranging from 9.5 to 10g/dl, with the aim being to reduce erythroid marrow activity.²¹ These data may strongly support the hypothesis that the consistently high Hb levels in chronically transfused patients (with thalassaemia major) may mean that this group of patients can sustain a more complete degree of marrow suppression with respect to that present in thalassaemia intermedia patients.

Therefore, in patients with thalassaemia intermedia, a particularly accelerated erythropoiesis and enhanced cholesterol consumption for red cell membrane formation could be responsible for the lower levels of cholesterolaemia. In support of this hypothesis, several clinical and biochemical observations indicate a marked erythropoietic marrow expansion in patients with thalassaemia intermedia.^{22,23}

In fact, such patients, in the absence of surgery, pregnancy or concomitant illnesses, usually do not receive blood transfusions. Consistent with this situation, levels of circulating soluble transferrin receptor, the best estimate of total erythropoiesis in the absence of iron deficiency,²⁴ were found to be lower in patients with thalassaemia major than in patients with thalassaemia intermedia.^{25,26} Interestingly, in the study by Ricchi et al.,⁸ patients with severe forms of thalassaemia intermedia had particularly low levels of cholesterol.⁸ Finally, in a study evaluating hypocholesterolaemia

Table 1: Plasma Cholesterol Values from Thalassaemic Patients

		TM	TI	T Minor
Hartman	n	47	9	
	TC (mg/dl)	106±23	74±24	
	Age (years)	11±4.2 (4–19)	10.3±5.1 (4–20)	
Ricchi	n	55	30	
	TC (mg/dl)	110.9±20.7	96.1±18.8	
	Age (years)	35 (22–40)	32 (20–39)	
Livrea	n		35	
	TC (mg/dl)		107.7±19.8*	
	Age (years)		32±14 (10–60)	
Amendola	n		23	
	TC (mg/dl)		117.3±30.3	
	Age (years)		29±12	
Goldfarb	n	39	27	23
	TC (mg/dl)	118.6±25.2*	104.3±30.2*	150.8±41.1*
	Age (years)	23.1±7.6	16±7.3	
Faizeh	n	30		
	TC (mg/dl)	119.1±37.7		
	Age (years)	8.8±4.05 (1.5–16)		

*Actual cholesterol values were reported as mmol/l. The following formula was used to convert data into mg/dl: mmol/l ÷ 0,0258.
n = number of patients; TC = total cholesterol; TM = thalassaemia major; TI = thalassaemia intermedia; T Minor = thalassaemia minor.

among thalassaemia intermedia patients, a significant inverse correlation was found between cholesterol level and soluble transferrin receptor.²⁷

Further studies are needed to better elucidate the relationship between Hb and cholesterol level and other parameters of erythropoietic activity, such as soluble transferrin receptor, reticulocyte count and extramedullary erythropoiesis in patients affected by thalassaemia.

Implications and Clinical Effects

Despite the fact that hypocholesterolaemia was first described many years ago, its impact on the atherogenic process in patients with severe thalassaemia has been very rarely addressed. While a lower incidence of atherosclerosis-related disease and hypertension has been reported in thalassaemia trait carriers,^{28,29} no study has yet fully evaluated the prevalence of atherosclerotic disease in patients with thalassaemia major and intermedia, or assessed whether the reduced level of cholesterol really protects thalassaemic patients from the development of atherogenesis.

The most frequent cause of death in patients with thalassaemia major is heart disease related to myocardial iron overload, which is responsible for more than half of all deaths as assessed by recent studies of survival.

Due to the introduction of more effective chelation therapy, the mean life expectancy of patients with thalassaemia major is increasing, and cardiac mortality caused by iron accumulation in the heart is decreasing. On the other hand, in the non-thalassaemic adult population, blood levels of total cholesterol are widely used to predict ischaemic heart disease, and treatment with statin, which lowers LDL cholesterol, substantially reduces the incidence of ischaemic heart disease.

However, in recent years increasing evidence has suggested that not only LDL level but also oxidative alteration of LDL are the key steps in

the series of events leading to atherogenesis-related vascular modifications.³⁰⁻³² Modified LDL is internalised in monocyte-derived macrophages through cell surface scavenger receptors, an event that leads to foam cell arrangement. Infiltration and deposition of these cells in the arterial wall are considered the initiating steps in the development of atherosclerotic plaque.

In β -thalassaemia, qualitative modification of LDL status has also been observed; in fact, alteration of iron homeostasis, interactions between damaged erythrocytes and LDL,^{33,34} depletion of antioxidant defences^{19,20} and a reduction in the size of HDL particles³⁵ might endorse oxidative damage to circulating LDL.

On the other hand, large increases in iron concentration are seen in human atherosclerotic lesions in comparison with levels in healthy arterial tissue.³⁶ A further complicating element is that hepcidin, a peptide involved in iron homeostasis and that endorses retention of iron within the plaque,³⁷⁻³⁹ in patients with severe thalassaemia has a strong inverse relationship with both erythropoietin and soluble transferrin receptor, markers of erythropoietic activity.²⁵ Thus, as hepcidin is elevated in thalassaemia major patients as a consequence of the transfusional regimen, it could be responsible for a particularly increased atherogenic process in this population.

Accordingly, in a report from a Turkish group increased abdominal aortic stiffness was found in young patients with thalassaemia major that correlated with body iron stores.⁴⁰

Thus, in thalassaemia patients the atherogenic process could be enhanced in part by the increased iron stores and the induced oxidative status, and in part counterbalanced by the reduced level of cholesterol; however, the final balance probably promotes increased arterial disease.

Furthermore, macrophage accumulation of iron induced by hepcidin could be responsible for the differences seen between patients with thalassaemia intermedia and those with thalassaemia major, in the sense that patients with thalassaemia major, as a consequence of the increased levels of hepcidin, could have a greater propensity to develop cardiovascular atherosclerosis.

Due to the improving survival of thalassaemic patients, more studies are needed to evaluate precisely the prevalence of atherosclerotic disease in adult patients with thalassaemia intermedia and major. To this end, magnetic-resonance-based T_2^* measurement has recently been demonstrated to be a good tool to evaluate and quantify not only heart and liver iron accumulation but also iron deposition in atherosclerotic plaque.⁴¹

In conclusion, patients with severe thalassaemia, notwithstanding their low levels of cholesterol with respect to age- and sex-matched controls³⁻¹⁰ owing to the described pathogenetic mechanism, should be particularly prone to developing atherosclerotic plaque and its clinical consequences.

The potential role of hypocholesterolaemia in the pathogenesis of some clinical aspects of thalassaemia have been rarely discussed. These include alterations in endocrine function, increased susceptibility to infections and vascular complications such as thrombophilia, which affect thalassaemia major and intermedia patients in a different manner.⁴²

Traditionally, most clinical features and complications of endocrinopathies have been essentially linked to iron overload, which disrupts hormonal secretion, resulting in hypoparathyroidism, hypogonadism and hypothyroidism.⁴³ In thalassaemia major patients, the main risk factors associated with endocrine complications were recently found to be high serum ferritin levels, poor compliance with desferioxamine (DFO) therapy, early onset of transfusion therapy (only for hypogonadism) and splenectomy (only for hypothyroidism).⁴⁴

Furthermore, in a study evaluating cortisol and adrenocorticotrophic hormone response to surgical stress (splenectomy) in thalassaemia major patients, a decreased adrenal reserve with increased pre-operative adrenocorticotrophic hormone (ACTH) concentrations was found in thalassaemic patients.⁴⁵

However, cholesterol is the main precursor to steroid biosynthesis in adrenal and sexual glands, and experimental studies suggest that HDL is the favourite resource in the adrenal gland for steroid biosynthesis.⁴⁶ There are no studies investigating whether such low cholesterol and HDL levels might contribute to adrenal and sexual insufficiency, particularly in thalassaemia intermedia patients.⁴⁷

Hypocholesterolaemia, independently of its putative role in determining adrenal insufficiency, may also contribute to further amplify susceptibility to infection in thalassaemic patients. Reduced levels of cholesterol may *per se* limit immune function: lipids, in particular HDL, have been found to bind and neutralise lipopolysaccharides (LPS) and endotoxins.⁴⁸⁻⁵⁰

In the non-thalassaemic population there is an increasing body of evidence that hypocholesterolaemia is associated with nosocomial infections and that hypocholesterolaemia is a risk factor for mortality in hospitalised patients.⁵¹⁻⁵⁷ It is therefore possible that hypocholesterolaemia could be in part responsible for the unfavourable outcome of severe infection and sepsis in thalassaemia patients. Randomised clinical studies evaluating the impact of administration of lipoprotein to septic thalassaemic patients are mandatory.

Finally, coagulation abnormalities are often described in β -thalassaemia. In particular, a thrombophilic status characterised by elevated levels of endothelial adhesion protein (intercellular cell adhesion molecule-1 [ICAM-1], endothelial leukocyte adhesion molecule-1 [ELAM-1], vascular cell adhesion molecule 1 [VCAM-1], von Willebrand factor and thrombomodulin) has been well documented, suggesting that endothelial activation may be involved in vascular occlusion.⁵⁸ On the other hand, in the non-thalassaemic population there is evidence that HDL can also control the fibrinolytic pathway and platelet function directly; in fact, HDL may affect platelet function through interfacing with the glycoprotein IIb-IIIa complex, thus competing with the binding of fibrinogen to platelets and resulting in inhibition of platelet aggregation.⁵⁹ No study has yet evaluated whether hypocholesterolaemia further supports the well recognised procoagulant status of thalassaemic patients.

Conclusion

Hypocholesterolaemia in the absence of a cholesterol metabolism genetic disorder⁶⁰ is a constant clinical feature of patients with severe thalassaemia. The pathophysiology of hypocholesterolaemia in severe forms of thalassaemia should be clarified by studies investigating

cholesterol metabolism and balance. However, being presumably related to erythropoietic cell division, hypocholesterolaemia is most prevalent in patients with thalassaemia intermedia, where it may be a marker of disease severity but does not correlate with age, sex, liver injury, Hb level and iron overload in thalassaemic patients. Such reduced levels of cholesterol cannot protect thalassaemic patients from the development of atherosclerotic disease because of the well-recognised role of iron accumulation in the pathogenesis of the atherogenic process; in this context, iron chelation could be a useful tool to modify their risk of atherosclerosis.

Conversely, such low levels of cholesterol in thalassaemic patients seem to reflect the inability of the organism to balance the increased cholesterol requirement for red cell membrane formation; thus, it is conceivable that the availability of cholesterol, ordinarily used in steroid hormone synthesis to control infection and to control hypercoagulability, could be at least in part reduced.

Additional studies are required to establish whether hypocholesterolaemia promotes complications of thalassaemia and whether cholesterol supplementation can be recommended for the management of thalassaemia intermedia. ■



Paolo Ricchi is an Assistant in the Department of Oncohaematology in the Microcythaemia Centre 'A Mastrobuoni', Antonio Cardarelli Hospital in Naples. His research interests include antineoplastic combined chemotherapy protocols, combined modality therapy, chemoprevention, thalassaemia and haemoglobinopathies.



Massimiliano Ammirabile is a Fellow in the Department of Oncohaematology in the Microcythaemia Centre 'A Mastrobuoni', Antonio Cardarelli Hospital in Naples. His main research fields include haemochromatosis, thalassaemia and haemoglobinopathies, erythrocytosis, cholesterolaemia in thalassaemic patients, haemostasis and thrombosis and genetic and biomolecular resources.



Aurelio Maggio is Director of the Division of Haematology II at Villa Sofia-Cervello Hospital in Palermo. He has extensive experience in biomedical research involving areas of medical genetics, haematology and gene therapy. Dr Maggio is a Professor at the Haematology Post-graduate School of the University of Palermo and is actively involved with professional thalassaemia and haemoglobinopathy organisations.

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