

# **OXIDIZED LDL ANTIBODIES (OLDLAB) IN THALASSEMIC PATIENT**

*Thesis*

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*Dedication*

To:

**My Dear Parents**  
*Who gave me too much*  
*And received too little*

*Dina*



بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ

وَأَنْزَلَ اللّٰهُ عَلَيْكَ  
الْكِتَابَ وَالْحِكْمَةَ  
وَعَلَّمَكَ مَا لَمْ  
تَكُن تَعْلَمُ وَكَانَ  
فَضْلُ اللّٰهِ عَلَيْكَ  
عَظِیْمًا

صدق الله العظيم

سورة النساء آية (١١٢)

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## *LIST OF ABBREVIATIONS*

<b>Abbrev.</b>	<b>Full term</b>
<b>ACAT</b>	Acyl-CoA:cholesterol acyltransferase
<b>AHSP</b>	Alpha hemoglobin stabilizing proteins
<b>APS</b>	Antiphospholipid syndrome
<b>ATIII</b>	Anti thrombin III
<b>ATP</b>	Adenosine triphosphate
<b>BCG</b>	Bacillus calmette Guerin
<b>BM</b>	Bone marrow
<b>BMI</b>	Body mass index
<b>BMT</b>	Bone marrow transplantation
<b>βTM</b>	Beta thalassemia major
<b>CBC</b>	Complete blood count
<b>CIM</b>	Carotid intema thickness
<b>CM</b>	Chylomicrons
<b>CMR</b>	Cardiac magnetic resonance imaging
<b>CVD</b>	Cardiovascular disease
<b>CVS</b>	Chroinic villous sampling
<b>DFO</b>	Desferoxamine
<b>DFT</b>	Tridentate desferrithiocin
<b>DM</b>	Diabetes mellitus
<b>EPO</b>	Erythropoietin
<b>FFA</b>	Free fatty acids
<b>GH-IGF-1</b>	Growth hormone insulin like growth factor-1
<b>GSH</b>	Reduced Glutathione
<b>HB</b>	Hemoglobin
<b>HBED</b>	Hydroxybenzyl-ethylene diamine-diacetic acid
<b>HBF</b>	Hemoglobin F
<b>HBV</b>	Hepatitis B virus
<b>HCV</b>	Hepatitis C virus
<b>HDL</b>	High density lipoprotein

## *LIST OF ABBREVIATIONS* (CONT...)

<b>Abbrev.</b>	<b>Full term</b>
<b>HIC</b>	Hepatic iron concentration
<b>HIV</b>	Human immunodeficiency virus
<b>HLA</b>	Human leucocyte antigen
<b>HPO</b>	Bidentate hydroxypyridinones
<b>ICL 670</b>	Deferasirox
<b>IFN</b>	Interferon
<b>IgA</b>	Immunoglobulin A
<b>IGF</b>	Insulin like growth factor
<b>IgG</b>	Immunoglobulin G
<b>IgM</b>	Immunoglobulin M
<b>IVIG</b>	Intravenous immunoglobulin
<b>L1</b>	Deferiprone
<b>LDH</b>	Lactate dehydrogenase
<b>LDL</b>	Low density lipoprotein
<b>LIC</b>	Liver iron concentration
<b>LOX</b>	Lactin like oxidized LDL
<b>LPI</b>	Labile Plasma Iron
<b>LV</b>	Left ventricle
<b>LVEF</b>	The left ventricular ejection fraction
<b>m RNA</b>	Messenger RNA
<b>MRI</b>	Magnetic resonance imaging
<b>NTBI</b>	Non-transferrin bound iron
<b>OxLDL Ab</b>	Oxidized LDL antibody
<b>PCR</b>	Polymerase chain reaction
<b>PH</b>	Pulmonary hypertension

## *LIST OF ABBREVIATIONS* (CONT...)

<b>Abbrev.</b>	<b>Full term</b>
<b>PIH</b>	Pyridoxal Isonicotilloyl Hydrazone
<b>PUFs</b>	Polyunsaturated fatty acids
<b>PVR</b>	Pulmonary venous return
<b>RBCs</b>	Red blood cells
<b>RDW</b>	Red blood cell distribution width
<b>ROS</b>	Reactive oxygen species
<b>s.TFR</b>	Serum transferrin receptor
<b>SD</b>	Standard deviation
<b>SPL</b>	Splicing mutation
<b>T4</b>	Thyroxin hormone
<b>TBARs</b>	Thiobarbituric Acid Reactive Substances
<b>TC</b>	Total cholesterol
<b>TG</b>	Triglyceride
<b>Th1</b>	Type 1 of T helper cells
<b>Th2</b>	Type 2 of T helper cells
<b>TI</b>	Thalassemia intermedia
<b>TM</b>	Thalassemia major
<b>TNF</b>	Tumor necrosis factor
<b>VLDL</b>	Very low density lipoprotein
<b>HSM</b>	Hepatosplenomegaly

## INTRODUCTION

**T**halassemia is a genetic disorders in globin chain production. In individuals with  $\beta$ -thalassemia, there is either a complete absence of  $\beta$ -globin production ( $\beta^{\circ}$ -thalassemia) or a partial reduction ( $\beta^{+-}$  thalassemia (*Debaun and Vichinisky, 2007*).

Beta thalassemia usually become symptomatic as severe hemolytic anemia during 2<sup>nd</sup> 6 month of life, regular blood transfusion are necessary in these patients to prevent cardiac decompensation caused by anemia (*Eldor et al., 2002*).

Conventional management of  $\beta$ -thalassaemia major requires regular blood transfusions. This leads to excess iron accumulation, initially in the reticuloendothelial system and subsequently in all parenchymal organs, mainly heart, pituitary gland, pancreas and gonads, resulting in serious and sometimes fatal clinical complications (*Afroditi and Vassilios, 2006*).

Transfusions are given on regular basis to maintain hemoglobin level above 10g / dl, which prevents progressive marrow expansion and cosmetic problems associated with facial bone changes and minimize cardiac dilation and osteoprosis (*Wonke et al., 2001*).

The major cause of morbidity and mortality in patients with beta thalassemia major is iron overload associated with chronic blood transfusion therapy, which can lead to iron deposition and damage to the heart, liver and endocrine organs and other organ failure. Iron toxicity is the leading cause of death in beta thalassemia major patients (*Wood et al., 2005*).

Vascular dysfunction with increased arterial stiffness and endothelial dysfunction has been demonstrated in patients with beta-thalassemia major (*Cheung et al., 2002*). Endothelial dysfunction as well as arterial stiffening is an important precursor for atherosclerosis (*Davignon and Ganz, 2004*), studies have also suggested a link between iron load and risk of atherosclerosis (*Timothy et al., 2007*).

Thalassemic (TM) patients are subjected to peroxidative tissue injury because of continuous blood transfusions. It has been documented that circulating LDL from TM patients show marked oxidative modification that could represent an event leading to atherogenesis (*Brizzi et al., 2002*).

In recent years increasing evidence suggests that the oxidative modification of low-density lipoprotein (LDL) is the key step in the sequence of events leading to atherogenesis-related vascular alterations, so modified LDL are internalized in monocyte-derived macrophages through cell surface scavenger receptors, an event that leads to foam