Arterial Stiffness and Endothelial Function in Patients with β-Thalassemia Major

Thesis submitted in partial fulfillment of the Master Degree in Cardiology

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2011

تصلب الشرايين ومدى تأثر الخلايا المبطنة لجدار الوعاء الدموي فى مرضى أنيميا البحرالأبيض المتوسط

رسالة

توطئة للحصول على درجة الماجستير في

أمراض القلب والأوعية الدموية

مقدمة من

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The thalassemias are heterogeneous group of genetic disorders of hemoglobin synthesis, all of which result from a reduced rate of production of one or more ofthe globin chains of hemoglobin. This basic defect results in imbalanced globin chain synthesis, which is the hallmark of all forms of thalassemia.

In β-thalassemia, the severity of the pathophysiology depends on the level of β-globin chain deficiency, which leads to an excess of α-globin chains**.**Consequently, thalassemic RBCs are hypochromic and microcytic and have a shorter half-life, leading to anemia.

Thalassemia major is characterized by chronic ineffective erythropoiesis and anemia as its primary problems. These, in turn, produce physiologic adaptations in the cardiovascular system as well as pathologic/iatrogenic processes such as iron overload, splenectomy, nutritional deficiencies, chronic oxidative stress, and lung disease.

Patients with thalassemia develop iron overload through increased iron absorption and transfusional therapy. Iron is toxic to all the endocrine glands that support the heart. Insulin resistance and frank diabetes are relatively common. Hyperglycemia and insulin resistance are powerful oxidative stressors to the heart, worsening the effects of iron overload. Proper insulin sensitivity is

Acknowledgment

First and before anything , I thank GOD for helping me to finish this work..

I would like to express my sincere gratitude to **Professor Dr. Ramzy Hamed El-Mawardy** the Professor of Cardiology, Ain Shams University, firstly for giving me the honor to be his student and work under his supervision..

Never to forget those whom effort was a corner stone to complete this work, **Professor Dr. Sameh Emil Sadek** the Professor of Cardiology, Military medical academy for his great help and assistance**.**

Many great thanks for **Dr. Mohamed Abd El Zaher Abd Allah** lecturers of cardiology, Ain Shams University, whom great support and careful supervision was behind the progress of this work.

Also i would like to thank my wife for her support and encorgement

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List of Abbreviations

Abb.	Meaning
ECs	Endothelial Cells.
NO	Nitric Oxide.
EDRF	Endothelium-Derived Relaxing Factor.
ADP	Adenosine Diphosphate.
ATP	Adenosine Triphosphate.
NOS	Nitric Oxide Synthase.
EDHF	Endothelium-Derived Hyperpolarizing Factor.
ET-1	Endothelin-1.
sICAM-1	Soluble Intercellular Adhesion Molecule-1.
VMCA-1	Vascular cell adhesion molecule_1.
MCTP-1	Monocyte chemotractant protein-1.
CVD	Cardiovascular Disease.
TNF-α	Tumor Necrosis Factor-.
IL-6	Interleukin-6.
FMD	Flow-mediated vasodilation.
eNOS	Endothelial nitric oxide synthase.
LDL	Low-Density Lipoprotein.
L-NMMA	NG-monomethyl-L-arginine
PWF	Pulse-Wave Velocity.
EDD	End-Diastolic Diameter.
ESD	End-Systolic Diameter.
FS	Fractional Shortening.
FMD	Flow-Mediated Dilation.

Protocol

Introduction

Iron overload in patients with ß-thalassemia major may result in systolic and diastolic dysfunction of the left ventricle. ***(Kremastinos et al, 1993)***. Although myocardial parenchymal damage occurs secondary to iron overload, atherogenic vascular complications have also been described in ß-thalassemia patients, which has been attributed to an increase in lipid peroxidation products ***(Livera et al,1998)***.

Increased iron stores have been implicated in the association with increased risk of cardiovascular events***.(Roest et al,1999)*** . However, epidemiological evidence for such association is inconsistent ***(Cortia et al 1997).***

Furthermore, the role of iron in promotion of lipid peroxidation and development of atherogenesis-related pathologies remains controversial ***(Gillum RF, 1997)***. Nonetheless, recent studies shown that iron chelation with desferrioxamine in adults with coronary artery disease improves endothelium-dependent vasodilation suggest that iron contributes to impaired nitric oxide function in atherosclerosis ***(Duffy et al., 2001)***.

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In patients with ß -thalassemia major, despite desferrioxamine therapy, their body iron load remains significantly higher than normal. Indeed, in vitro studies have shown disturbances of human vascular endothelial cell function when the cell culture is incubated with thalassemic serum***. (Butthep et al,1997).***

Vascular endothelial function in patients with β-thalassemia major in vivo hence may be similarly impaired but nonetheless has not been studied previously. Integrity of endothelia function is of particular relevance in these patients in light of the important role of endothelium in regulation of vascular tone and the propensity of these patients to develop cardiac failure ***(Joannides et al., 1997)***.

Arterial stiffness is an important mechanical property, because it is related to vascular impedance and in turn to the afterload that is presented to the left ventricle.Its value in risk stratification has recently been shown in patients with hypertension. ***(Blacher et al,1999).***

Aim of work

In the present study, we will determine the effect of iron over load in patients with ß-thalassemia major as regard :

- Endothelial function.
- Arterial stiffness.
- Left ventricular function.

Methods and Patients

- **Patients**

The study will include 40 patients they will be divided into 2 groups **:**

- **Group I:**

Include 30 thalassemia patients . Left ventricular (LV) mass and function will be assessed echocardiographically. Carotid artery stiffness will be assessed by stiffness index . Brachial artery endothelial function will be assessed by vascular response to reactive hyperemia (flow-mediated dilation [FMD]).

- **Group II:**

Include 10 healthy subjects matched for age and sex will be recruited as controls.

- **Inclusion Criteria :**
  - Thalassemic patients receiving monthly blood transfusion.
  - Male and female.
  - Patients age range (12-20)

Exclusion Criteria :

These patients will be excluded from the study :

- Smokers .
- Patients with heart failure.
- Systemic hypertention .
- Diabetes mellitus .
- Thyroid dysfunction.
- Parathyroid dysfunction .

Methods:

Patients included in the study will be subjected to the following:

- A full history will be taken from the patients .
- Complete cardiological examination will be done.
- Body weight and height will be measured.
- Venous blood sample withdrawn from all subjects for measurement of serum hemoglobin and serum ferritin level.

- Echocardiographic Examination

Transthoracic echocardiography will be performed .Standard parasternal short-axis view at just below the tips of mitral valve leaflets will be used to derive the M-mode measurement of LV systolic and