Effect of Erythropoietin Therapy on Lipogram in Chronic Haemodialysis Patients

Thesis

Submitted for Partial fulfillment of master Degree in Internal Medicine

By

IHAB EL-SAYED GODA

(MB. B.Ch)

Faculty of Medicine- Zagazig University

Supervised by

Prof. Dr. Mohamed Ali Ibrahim

Professor of Internal Medicine and Nephrology
Faculty of Medicine
Ain Shams University

Prof. Dr. Ibrahim Youssef Abdel-Maseh

Professor of Clinical Pathology
Faculty of Medicine
Ain Shams University

Dr. Essam Nour El-Din Afiffy

Lecturer of Internal Medicine and Nephrology
Faculty of Medicine
Ain Shams University

Faculty of Medicine

AIN SHAMS UNIVERSITY

2009

تأثير العلاج بالاريثروبيوتين على دهنيات الدم فى مرضى الفشل الكلوى المزمن الذين يعالجون بالاستصفاء الدموى

رساله مقدمه من

الطبيب/ ايهاب السيد جودة

بكالوريوس الطب والجراحة

كلية الطب – جامعة الزقازيق

توطئة للحصول على درجة الماجستير

في الأمراض الباطنة

تحت إشراف

أ.د. محمد على ابراهيم

استاذ الأمراض الباطنة و امراض الكلى

كلية الطب- جامعة عين شمس

أ.د. ابراهيم يوسف عبد المسيح

استاذ الباثولوجيا الاكلنيكية

كلية الطب- جامعة عين شمس

د. عصام نور الدين عفيفى

مدرس الأمراض الباطنة و امراض الكلى

كلية الطب – جامعة عين شمس

كلية الطب

جامعة عين شمس

2009

ACKNOWLEDGEMENT

*First and forever, thanks to **ALLAH**. I wish to express my deepest appreciation and gratitude to Prof. Dr. **Mohamed Ali Ibrahim**, professor of internal medicine and nephrology, Faculty of Medicine, Ain Shams University, for his continuous encouragement and generous support.*

*I hope to express my deepest gratitude and cordial thanks to Prof. Dr. **Ibrahim Youssef**, Professor of clinical pathology, Faculty of Medicine, Ain Shams University, for his beneficial guidance, valuable remarks, keen supervision and moral support throughout this work.*

*I would like to express my highest gratitude to Dr. **Essam Nour El Din**, lecturer of internal medicine and nephrology, Faculty of Medicine, Ain Shams University, for his constant guidance, encouragement and precious suggestions which helped me greatly to complete this work.*

Finally, I would like to thank all the Staff Members of internal medicine and nephrology department in Zagazig general hospital, and all those who helped me and facilitated the whole procedures to accomplish this work.

List of abbreviation

ABCA1 : ATP binding cassette transporter type 1
ACAT : Acyl-CoA cholesterol acyltransferase
ADMA : Asymmetrical dimethyl arginine
APOA : Apolipoprotein A
APOB : Apolipoprotein B
BP : Blood pressure
CETP : Cholesterol ester transfer protein
CKD : Chronic kidney disease
CM : Chylomicron
CRF : Chronic renal failure
CRP : C-reactive protein
CVD : Cardiovascular disease
DDAH : Dimethylarginine dimethyaminohydrolase
DGAT : Diglycerol acyltransferase
DOAT : Diacylglycerol acyltransferase
EPO : Erythropoietin
EPO-R : Erythropoietin receptor
ESRD : End stage renal disease
FA : Fatty acids
FC : Free cholesterol
GFR : Glomerular filteration rate
HD : Hemodialysis
HDL : High-density lipoprotein
HTL : Hepatic lipase
IDL : Intermediate- density lipoprotein
IL-6 : Interleukin-6
IR : Insulin resistance
LCAT : Lecithin-cholesterol acyltransferase

LDL : Low-density lipoprotein
LMW : Low molecular weight
LPL : Lipoprotein lipase
LRP : Receptor related protein
LVH : Left ventricular hypertrophy
MHPs : Maintenance hemodialysis patients
MI : Myocardial infarction
MIA : Malnutrition-inflamation, atherosclerosis
PL : Phospholipids
PTH : Parathyroid hormone
PWV : Pulse wave velocity
rHuEPO : Recombinant human erythropoietin
RLPs : Remnant lipoprotein paeticles
TC : Total cholesterol
TG : Triglycerides
TNF-a : Tumour necrosis factor-a
VLDL : Very Low-density lipoprotein
TSAT : Transferin saturation

LIST OF FIGURES

LIST OF TABLES

CONTENTS

Page

LIST OF FIGURES

LIST OF TABLES

CONTENTS

Page

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in patients with stage 5 chronic kidney disease (CKD), and the mortality rate in stage 5 CKD is even higher in patients with diabetes. CVD risk reduction includes control of hyperglycemia, dyslipidaemia and blood pressure (BP) **(Mark, 2006)**.

Dyslipidaemia is a consequence of renal disease, wherein hepatic synthesis of lipoproteins is increased and clearance decreased. The resulting lipoprotein phenotype is highly atherogenic and significantly increases the cardiovascular risk of the patients **(Lechleitner, 2000).**

Chronic renal disease is accompanied by characteristic abnormalities of lipid metabolism,which appear as a consequence of renal insufficiency and are reflected in an altered apolipoprotein profile as well as elevated plasma lipid levels. Experimental and clinical studies have suggested a correlation between the progression of renal disease and dyslipidemia. High cholesterol and triglyceride plasma levels have been demonstrated to be independent risk factors for progression of renal disease in humans **(Roberto and Dodesini, 2006)**.

Chronic renal failure (CRF) results in profound lipid disorders, which stem largely from dysregulation of high-density lipoprotein (HDL) and triglyceride-rich lipoprotein metabolism. Specifically, maturation of HDL is impaired and its composition is altered in CRF. In addition, clearance of triglyceride-rich lipoprotein and their atherogenic remnants is impaired, their composition is altered, and their plasma concentrations are elevated in CRF. Impaired maturation of HDL in CRF is primarily due to downregulation of lecithin-cholesterol acyltransferase (LCAT) and, to a

lesser extent, increased plasma cholesterol ester transfer protein (CETP). Triglyceride enrichment of HDL in CRF is primarily due to hepatic lipase deficiency and elevated CETP activity **(Vaziri, 2006)**.

The CRF-induced hypertriglyceridemia, abnormal composition, and impaired clearance of triglyceride-rich lipoproteins and their remnants are primarily due to downregulation of lipoprotein lipase, hepatic lipase, and the very-low-density lipoprotein receptor, as well as, upregulation of hepatic acyl-CoA cholesterol acyltransferase (ACAT). In addition, impaired HDL metabolism contributes to the disturbances of triglyceride-rich lipoprotein metabolism. These abnormalities are compounded by downregulation of apolipoproteins apoA-I, apoA-II, apoC-II in CRF. Together, these abnormalities may contribute to the risk of arteriosclerotic cardiovascular disease and may adversely affect progression of renal disease and energy metabolism in CRF **(Vaziri, 2006)**.

Recombinant human erythropoietin (rHuEPO) a novel and a triumph of modern medicine in the field of nephrology, allowing: avoidance of blood transfusion, reduction in the risk of sensitization, prevention of iron overload and improved exercise tolerance, cognitive capacity, sexual function and quality of life. The treatment of anaemia was deeply transformed **(Juan F. Navarro, 2003)**.

Erythropoietin (EPO) has been used widely for the treatment of anaemia associated with chronic kidney disease and cancer chemotherapy for nearly 20 years. More recently, EPO has been found to interact with its receptor (EPO-R) expressed in a large variety of non-haematopoietic tissues to induce a range of cytoprotective cellular responses, including mitogenesis, angiogenesis, inhibition of apoptosis and promotion of vascular repair through mobilization of endothelial progenitor cells from

bone marrow. EPO may be renoprotective in chronic kidney disease **(Johnson et al., 2006)**.

Three types of recombinant human erythropoietin are currently available: epoetin alfa, epoetin beta and darbepoetin alfa. All, like endogenous counterpart, act as mitosis stimulating factor and differentiating hormone, promoting the production of erythrocytes from precursors of stem cell compartment. Epoetin alfa and epoetin beta are identical in their amino acid and carbohydrate composition to endogenous human erythropoietin. Darbepoetin alfa is a hyperglycosylated derivative of epoetin **(Wilson et al,, 2007; British Medical Association, 2004)**.

EPO treatment of predialysis patients with chronic kidney disease (CKD) significantly increases serum high-density lipoprotein cholesterol (HDL-C) levels, which may represent an important antiatherogenic effect of this hormone **(Siamopoulos et al., 2006)**.

Long-term rHuEPO treatment is associated with an improvement in the lipid profile. So that, the high incidence of cardiovascular disease in hemodialysis (HD) patients might be reduced with rHuEPO therapy **(Kes et al., 2002).**

Long-term rHuEPO treatment seems to positively influence the lipid profile in maintenance haemodialysis patients (MHPs), but an associated increase in food intake may allow a rise in some atherogenic blood lipid fractions. Dietary control in MHPs on rHuEPO therapy may decrease the cardiovascular risk profile **(Allegra et al., 1997)**.

AIM OF THE WORK

Is to study the possible effect of recombinant human erythropoietin (rHuEPO) therapy on lipogram in chronic haemodialysis patients.

SUBJECTS AND METHODS

Patient's selection:

- A group of 15 maintenance haemodialysis patients will be randomly selected from the haemodialysis unit with haemoglobin level below 8 g/dl .
- The patients selected will be studied over 6 months period and the study will be divided into 2 stages :
  1. **Stage 1** (3 months): the patient's anemia will be corrected by non-EPO therapy (e.g: iron therapy) for 3 months.
  2. **Stage 2** (3 months): all patients will be treated with recombinant human erythropoietin (rHuEPO) for 3 months.

The following will be excluded from the study:

1. Diabetic patients.
2. Smokers.
3. Hypertensive patients on ACEI, ARBs, B-blockers.

All patients will be subjected to:

1- Full medical history and detailed clinical examination.

2- Measurement of lipid and haematological parameters 3 times (before and after stage 1 and after stage 2) .

3- Lipid parameters :

- Total cholesterol.
- LDL- cholesterol.
- HDL- cholesterol.