Study of serum hepcidin in Hereditary hemolytic anemias

Thesis

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قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

(البقرة٣٢)

Dedicated To:

My Father & My Mother

Maged Abdel-Rahman Mohamed

Sanaa Mohamed Ali

My Wife & My Sons

Dr. Nermeen Salah

Omar & Ali

And my brother

Dr. Mohamed Maged

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Heart to heart talk

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Abstract

Study of serum hepcidin in hereditary hemolytic anemias

(Key words): Hereditary haemolytic anemias, Thalassemia, hepcidin, iron overload disorders.

Thalassemia, the most common genetic disorder in Egypt, is a major health problem with an estimated carrier rate of 5.3%-9%. Registered cases in large centers in Egypt in September 2007 were 9912 cases, and in Cairo University hematology clinic were 2597 cases. Hepcidin, a 25 amino-acid peptide hormone synthesized in the liver is the key regulator of iron homeostasis. We measured the level of hepcidin in congenital chronic hemolytic anemias including sickle cell anemia, hereditary spherocytosis, thalassemia syndromes. This study revealed the decrease of hepcidin level in all congenital chronic hemolytic anemias in comparison to control. The use of hepcidin as an adjuvant therapy with oral iron chelators is important as it has a vital role in combating hemosidrosis.

LIST OF ABBREVIATIONS

ACD	: Anemia of chronic disease
AML	: Acute myleogenous leukemia
ATCUN	: Amino terminal Cu and Ni binding
BMD	: Bone mineral density
BMP	: Bone morphogenetic protein
CFU-E	: Colony-forming unit-erythroid
CHr	: Reticulocyte hemoglobin content
CKD	: Chronic kidney disease
CV	: Coefficient of variance
CVAD	: Central vascular access devices
DFO	: Desferrioxamine
DFP	: Deferiprone
DMT1	: Divalent metal transporter 1
DNA	: Deoxy ribonucleic acid
EPO	: Erythropoietin
ESAs	: Erythropoiesis-stimulating agents
FE (2+)	: Ferrous
FE (3+)	: Ferric
FID	: Functional iron deficiency
FPN1	: Ferroportin-1
HAMP	: Hepcidin antimicrobial peptide
HAART	: Highly Active Anti-Retroviral Therapy
HB	: Hemoglobin
HCP	: Heme-carrier protein

HCV : Hepatitis C virus

HFE : Haemochromatosis gene

HH : Hereditary Haemochromatosis

HIF : Hypoxia-inducible transcription factor

HII : Hepatic iron index

HJV : Haemojuvelin

HO : Heme oxygenase

HS : Hereditary shperocytosis

HSCT : Hematopoietic stem cell transplantation

ID : Iron deficiency

IDA : Iron deficiency anemia

IFN : Interferon

IFU : Instructions for use

IL : Interleukin

IRE/IRP System : Iron responsive element/Iron regulatory protein

IRIDA : Iron refractory iron-deficiency anemia

LEAP : Liver-expressed antimicrobial peptide

LIC : Liver iron concentration

LPS : Lipopolysaccharide

MCV : Mean corpuscular volume

MCHC : Mean corpuscular hemoglobin concentration

MDS : Myelodysplastic syndromes

MS : Mass spectrometry

OD : Optical denisty

OPG : Osteoprotegrin

OsM : Oncostatins M

RA : Renal anemia

RA : Rheumatoid arthritis

RBC : Red blood cell

RES : Reticuloendothelial system

RGM : Repulsive Guidance Molecule

rHuEPO : Recombinant human erythropoietin

RIA : Radioimmunoassay

SELDI-TOF MS : Surface-enhanced laserdesorption/ ionization time- of-flight mass spectrometry

SCD : Sickle cell disease

SQUID : Superconducting quantum-interference device

TI : Thalassemia intermedia

TM : Thalassemia major

TMPRSS6 : Transmembrane serine protease- 6

TNF : Tumour necrosis factor

TR : Transferrin receptor

TS : Transferrin saturation

VHL : Von Hippel–Lindau

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INTRODUCTION AND AIM OF THE WORK

Thalassemia is the most common genetic disorder in Egypt; it composes a major health problem with an estimated carrier rate of 5.3-9%. Registered cases in large centers in Egypt September 2007 were 9912 cases, and in Cairo University hematology clinic were alone 2597 cases **(El-Beshlawy et al., 2007)**. Patients with thalassemia major requiring regular blood transfusions accumulate iron that is toxic to the heart, liver, and endocrine systems **(El-Beshlawy et al., 2008)**.

Complications secondary to iron overload should essentially be prevented as the treatment is difficult and often lifelong. Endocrinopathies secondary to ironoverload include hypogonadism, hypothyroidism, diabetes mellitus and hypoparathyroidism. Most of these occur towards the end of second decade of life and often require lifelong replacement therapy. Iron related cardiac disorders vary from rhythm disturbances to chronic heart failure. The latter being the chief cause of death in young adults with thalassemia major. They need inotropic and anti-arrhythmic medications **(Agarwal, 2009)**.

Park et al., (2001) discovered Hepcidin, a 25 amino-acid peptide hormone synthesized in the liver, and described it as a key regulator of iron homeostasis. **Pigeon et al., (2001)** found that the expression of hepcidin mRNA in the mouse liver was increased in setting of iron overload. In **2005, Ganz** explained that downstream effect of hepcidin is to inhibit intestinal iron absorption, recycling of iron from the reticuloendothelial system, and mobilization of iron from hepatic stores. On the molecular level, this is achieved by hepcidin binding to, and inducing internalization of the cellular iron exporter ferroportin **(Nemeth**