Hepcidin as a Biomarker for Iron Status in Chronic Kidney Disease

Thesis
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Dedication

This work is dedicated to my Mother who inspired me and taught me the way to perform my goals. Thanks to my husband that I think without his support, this work would not appear.

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List of Abbreviations

A1C	glycosylated hemoglobin
AIDS	Acquired Immune Deficiency Disease
AA	Aplastic anemia
AcSDKP	N-acetyl-seryl-aspartyl-lysyl-proline
ADP	adenosine diphosphate
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ATP	Adenosine triphosphate
Aza	Azathioprine
BMI	Body mass index
BCAA	Branched Chain Amino Acid
BFU-e	Burst Forming Undifferentiated Erythroid
BBB	Blood brain barrier
BUN	Blood Urea Nitrogen
BMP	Bone morphogenic protein
CdCl2	Cadmium chloride
CHF	Congestive Heart Failure
CRF	Chronic Renal Failure
CKD	Chronic Kidney Disease
cAMP	cyclic adenosine monophosphate
CAPD	Continuous Ambulatory Peritoneal Dialysis
CRP	C-reactive protein
CsA	Ciclosporin A
CHr	Reticulocyte Hb Content
Ctl	Cytotoxic t lymphocyte
CVD	Cardiovascular disease

CPD	Continuous Peritoneal Dialysis
DM	Diabetes mellitus
Dcytb	Duodenal cytochrome b
DHF	Dihydroxyfumarate
DEXA	Dual Energy X-ray Absorbometry
DFO	Desferroxamine
DMT1	divalent metal transporter 1
DMS	Dialysis Malnutrition Score
DPO-α	darbepoetin-α
DRIVE study	Dialysis Patients Response To IV Iron With Elevated Ferritin
ESA	Erthropoiesis stimulating agent
ESRD	End Stage Renal Disease
EBV	Epstein-Barr virus
EPO	Erythropoietin
Fe	Iron
FPG	Fasting plasma glucose
FFM	Fat Free Mass
FM	Fat Mass
GI	Gastrointestinal
G-CSF	Granulocytes- Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyltransferase
GH	Growth Hormone
HCT	Hematocrit
HD	Hemodialysis
Hb	Hemoglobin
HCV	Hepatitis C virus

HDL	High-density lipoprotein
IDDM	Insulin dependent diabetes mellitus
IFN	Interferon
IFG	Impaired fasting glucose
Ig	Immunoglobulin
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
IL	Interleukin
IGF	Insulin Growth Factor
INF	Interferon
ISAT	Iron Saturation Ratio
IDA	Iron deficiency anemia
IMP	Integrin-mobilferrin pathway
IPSS	International prognostic scoring system
IRE	Iron regulatory elements
IRIDA	Iron refractory iron deficiency anemia
IRP	Iron regulatory peptide
LDL	Low density lipoprotein
KFT	Kidney function test
LFT	Liver function test
MIA	Malnutrition –Inflammation Atherosclerosis
MHD	Maintenance Hemodialysis
Mmf	Mycophenolate mofetil
Mg/mo	Milligram/Month
MICS	Malnutrition –Inflammation Complex Syndrome
MIS	Malnutrition Inflammation Score
MN	Malnutrition
NIDDM	Non-insulin-dependent diabetes mellitus

NHANES	National Health And Nutritional Examination Survey
nHuEPO	Recombinant Human Erythropoietin
NKF/KDOQI	National Kidney Foundation /Kidney Disease Outcome and Quality Initiative
NO	Nitric Oxide
nPNA	Normalized Protein Nitrogen Appearance
PCR	Protein Catabolic Rate
PD	Peritoneal Dialysis
PEM	Protein Energy Malnutrition
PHRC	Percentage Of Hypochromic Red Blood Cells
PNA	Protein Equivalent To Total Nitrogen Appearance
PTH	Parathyroid hormone
RBCs	Red Blood Cells
RE	Reticuloendothelial
REE	Resting Energy Expendition
RES	Reticuloendothelial system
SBW	Standard Body Weight
SGA	Subjective Global Assessment
SQUID	Super Conducting Quantum Interference Device
Stfr	Soluble Transferring Receptor
TIBC	Total Iron Binding Capacity
TNF	Tumor Necrosis Factor
TSAT	Transferrin Saturation
UBW	Usual Body Weight
USF1	Upstream stimulatory factor-1
UTR	Untranslated region
VEGF	Vascular endothelial cell growth factor
WHO	World Health Organization

WPSS	WHO prognostic scoring system
ZnPP	Erythrocyte Zinc Protoporphyrin

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Introduction

INTRODUCTION

Anemia is a severe complication of chronic kidney disease (CKD) that is seen in more than 80% of patients with impaired renal function (***Kalantar, 2003***).

Anemia has also been implicated in the development of congestive heart failure and left ventricular hypertrophy. If left untreated, anemia may cause death (***Macdougall …, 2002***).

Although there are many mechanisms involved in the pathogenesis of anemia of renal disease, the primary cause is the inadequate production of erythropoietin by the damaged kidneys (***Stenvinkel …, 2001***).

Erythropoietin is produced in the peritubular cells of the kidney and is the major hormone involved in the production of red blood cells (erythropoiesis). When erythropoietin levels are low, an inadequate number of oxygen-carrying red blood cells are produced (***Chonchol …., 2008***).

Adequate iron stores are essential for achieving maximum benefit from erythropoietic agents, such as recombinant human erythropoietin (EPO) or darbepoetinalfa. Decreased iron stores or decreased availability of iron are the most common reasons for resistance to the effect of these agents (***Kalantar, 2006***).

Recombinant erythropoietin (rhEPO) has transformed anemia therapyin patients with chronic kidney disease (CKD). However, rhEPOresistance, often associated with iron deficiency and inflammation,remains a challenging problem. Current availableiron indices do not reliably identify iron-restricted erythropoiesis,often a sequel of inflammation, or those patients who wouldlikely benefit from parenteral iron therapy. Toaddress these issues, it is crucial to understand the molecularmechanisms that link inflammation, iron balance, and erythropoiesis (***Singh , 2007***).

Hepcidin, an acute phase reactant protein produced in the liver,is a recently discovered key regulator of iron homeostasis.Hepcidin inhibits intestinal iron absorption and iron releasefrom macrophages and hepatocytes. Because hepcidin productionis increased by inflammation, and high hepcidin concentrationslimit iron availability for erythropoiesis, hepcidin likelyplays a major role in the anemia of inflammation and rhEPO resistance (***Singh AK, 2007***).

Because of its renal elimination and regulation by inflammation, it is possible that progressive renal insufficiency leads to altered hepcidin metabolism, subsequently affecting enteric absorption of iron and the availability of iron stores (***Ganz T, 2007***).