Impact of Serum Hepcidin and Inflammatory Markers on Resistance to Recombinant Human Erythropoietin Therapy in Hemodialysis Patients

Thesis

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Nahla Raafat Aboul-Fetouh

Contents

List of Abbreviations

Abbrev.	Full-term
ACD	: Anemia of chronic disease
ACE	: Angiotenosin converting enzyme
ACEI	: Angiotenosin converting enzyme inhibitor
AI	: Anemia of chronic inflammation
ALK2	:Activing like kinase 2
ALK3	:Activing like kinase 3
ANOVA	: Analysis of variance
anti-IL-6R	: Anti-IL-6 receptor antibody
ARBs	: Angiotensin receptor blockers
BFU-E	: Burst-forming unit-erythroid
BMI	: Body mass index
BMP	: Bone morphogenetic proteins
BMPR	: Bone morphogenetic proteins receptor
bp	: Base pair
CFU-E	: Colony-forming unit-erythroid
CFU-G/M	: Colony-forming unit-granulocyte/macrophage
CKD	: Chronic kidney disease
CRP	: C-reactive protein
EBPG	:European Best Practice Guidlines
EDTA	: Ethylenediaminetetraacetic acid
ELISA	: Enzyme-linked immunosorbent assay
EPO	: Erythropoietin
EPOR	: EPO receptor
ERI	: Erythropoietin resistance index

ESAs : Erythropoiesis-stimulating agents
ESRD : End stage renal disease
GDF15 : Growth differentiation factor 15
GFR : Glomerular filtration rate
Hb : Hemoglobin
HCT : Hematocrit
HD : Hemodialysis
HH :Hereditary hemochromatosis
HJV :Hemojuvelin
HsCRP : High sensitivity C-reactive protein
HSCs : Hematopoietic stem cells
IL1 : Interleukin 1
Il6 : Interleukin 6
IV : Intravenous
KDOQI :Kidney Disease Outcome Quality initiatives
LEAP-1 : Liver-expressed antimicrobial peptide
LPS : Lipopolysaccharide
mAb : Monoclonal antibody
MCD : Multicentric Castleman's Disease
MPP : Multipotent progenitors
mRNA : Messenrger ribonucleotide acid
RBC : Red blood cell
RE : Reticuloendothelial
RES **:** Reticuloendothelial system
rhEPO : Recombinant human erythropoietin
RNAi : RNA interference
shRNA : Short hairpin RNA
SMAD **:** Sma and Mad,Mothers against decapentaplegic

STAT-3 :signal transducer and activator of transcription 3
TfR :Transferrin receptor
TIBC :Total iron binding capacity
TMPRSS6 : transmembrane protease serine 6
TSAT : Transferrin saturation
UV : Ultraviolet

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ABSTRACT

Anemia and Resistance to to recombinant human erythropoietin (rhEPO) therapy are common common complications in Hemodialysis (HD) Patients . Here, we investigated how Hepcidin could influence anemia ,rhEPO resistance and the plasma levels of inflammatory markers which are interleukin 6 (IL6), high sensitivity c reactive protein (hsCRP). This study was conducted on 60 patients on maintenance hemodialysis presented to Ain Shams University Hospitals. They were 38 males & 22 females with mean age(48.83±13.89). Patients' group was further divided into responders and non responders to treatment of rhEPO according to hemoglobin (Hb) level and erythropoietin resistance index (ERI). Also the studyincluded 40 healthy subjects of matched age and sex as a control group. They were 21 males and 19 females with mean ages (48.03±10.33). We measured hepcidin ,il6,hsCRP for all the subjects,and ERI was calculated for the patients group only.There was a statistically significant difference between patients' and controlgroup were patients' group had higher levels of hepcidin,IL6,hsCRP and lower Hb level. There was a statistically significant difference between responders and non responders patients' group where the non responders group had higher levels of hepcidin,IL6,hsCRP andERI,and lower Hb levels. A positive correlation was found between hepcidin with IL6 and hsCRP,with a negative correlation with Hb level. Data demonstrated that hepcidin plays a major role in anemia of HD patients and it affects the levels of inflammatory markers and the degree of resistance to rhEPO treatment.

KEYWORDS: Hepcidin, anemia, hemodialysis, IL-6, hsCRP erythropoietin resistance index.

Introduction

Chronic kidney disease (CKD) is a prevalent, worldwide condition ***(O'Mara, 2008).*** It is recognized as an important public health issue because of the increasing prevalence and associations with morbidity and mortality ***(Rebholz et al., 2015).***

End stage renal disease (ESRD) is the final stage of CKD ***(Lew et al., 2016)***, it refers to patients exhibiting glomerular filtration rate (GFR) <15ml/min/1.73m^2) ***(Staples et al., 2009),*** and/or those treated by dialysis ≥3 months irrespective of the filtration rate levels ***(Rim et al., 2016).***

Many kinds of metabolic changes may accompany chronic kidney failure either caused by the kidney disease itself or due to dialysis treatment ***(Cibulka and Racek, 2007).***

Diabetes and arterial hypertension represent the leading causes of ESRD, although infections and genetic or autoimmune disorders may also result in advanced kidney failure ***(Staples et al., 2009).***

Its increasing incidence in combination with population aging, age-associated comorbidities and greater access to care, resulted in the explosion of the number of dialysis patients during the past decade ***(Williams et al., 2012).***