SERUM LEVEL OF HEPCIDIN IN DIABETIC AND NON DIABETIC CHRONIC KIDNEY DISEASE STAGE 5 AND ITS APPLICATION IN ANEMIA

Thesis

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List of Abbreviations

ACE..... Angiotensin-converting enzyme
ACEI..... Angiotensin converting enzyme inhibitor
ACE-I ..... Angiotensin-converting enzyme inhibitor
AER..... Albumin excretion rate
ALERT..... Assessment of Lescol in Renal Transplant
ARAS..... Atherosclerotic renal artery stenosis
ARB..... Angiotensin receptor blocker
ARB..... Angiotensin receptor blocker
ARF..... Acute renal failure
AUA ..... American Urological Association
AVOID ..... Aliskiren in the Evaluation of Proteinuria in Diabetes
BGS..... British Geriatrics Society
BMD ..... Bone mineral density
BSA ..... Body surface area
CARE ..... Cholesterol and Recurrent Events
CARI..... Caring for Australians with Renal Impairment
CHD..... Coronary heart disease
CHOIR..... Correction of Hemoglobin and Outcomes in Renal Insufficiency (Study)
CKD..... Chronic kidney disease
CKD..... Chronic kidney disease
Cr..... Creatinine
CREATE ..... Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin (Trial)
CT..... Computed tomography
CVD ..... Cardiovascular disease
CVD ..... Cardiovascular disease
DAIS ..... Diabetes Atherosclerosis Intervention Study
DCCT ..... The Diabetes Control and Complications Trial
DKD..... Diabetic kidney disease
DM ..... Diabetes mellitus
EDIC..... Epidemiology of Diabetes Interventions and Complications

List of Abbreviations (Cont…)

eGFR..... Estimated glomerular filtration rate
EPO..... Erythropoietin
ERF..... Established renal failure
ESA..... Erythropoiesis stimulating agent
ESRD..... End-stage renal disease
FDA..... Food and Drug Administration
GFR..... Glomerular filtration rate
GFR..... Glomerular filtration rate
Hb..... Hemoglobin
HbA1c..... Hemoglobin A1c
HDL-C..... High-density lipoprotein cholesterol
Hep..... Hepcidin
HOPE..... Heart Outcomes Prevention Evaluation Study
HOT..... Hypertension optimal treatment
HPS..... Heart Protection Study
hs-CRP..... High sensitive C-reactive protein
K/DOQI..... Kidney Disease Outcomes Quality Initiative
KDIGO..... Kidney Disease: Improving Global Outcomes
KDIGO..... Kidney Disease: Improving Global Outcomes
KDOQI..... Kidney Disease Outcomes Quality Initiative
MDRD..... Modification of diet in renal disease
MR..... Magnetic resonance
NCCAM..... National Center for Complementary and Alternative Medicine
NHANES..... National Health and Nutrition Examination Survey
NHANES..... National Health And Nutrition Examination Survey
NHS..... National Health Service
NICE..... National Institute for Health and Clinical Excellence
NIHCE..... National Institutes of Health and Clinical Excellence
NKF..... National Kidney Federation
NKF..... National Kidney Foundation
NSAID..... Non-steroidal anti-inflammatory drug
NSF..... National service framework

List of Abbreviations (Cont…)

RAS..... Renin-angiotensin system
RAS..... Renin–angiotensin system
RCT..... Randomized controlled trial
RRT..... Renal replacement therapy
SHARP..... Study of Heart and Renal Protection
SLE..... Systemic lupus erythematosus

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INTRODUCTION

CKD is defined as the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (GFR) that persists for more than 3 months ***(KDOQI, 2006).***

The 2002 guidelines for definition and classification of this disease represented an important shift towards its recognition as a worldwide public health problem that should be managed in its early stages by general internists. Disease and management are classified according to stages of disease severity, which are assessed from glomerular filtration rate (GFR), and albuminuria, and clinical diagnosis (cause and pathology) ***(Levey AS, 2011).***

Anemia is a major complication of chronic kidney disease (CKD) ***(Tsubakihara et al., 2010).*** Anemia occurs when there is a reduction in one or more of the major red blood cell measurements; hemoglobin concentration, hematocrit, or red blood cell counts ***(Robert et al., 2008).*** The World Health Organization (WHO) defines anemia as a hemoglobin concentration lower than 13.0 g/dL in men and postmenopausal women and lower than 12.0 g/dL in other women ***(NIHCE, 2008).*** Etiology of anemia is frequently difficult to determine even after extensive investigations including bone marrow examinations. It is reported as nutritional (34%),

renal insufficiency12%), chronic diseases (20%) and unexplained (24%) ***(Karuna et al., 2011).*** A normocytic normochromic anemia usually accompanies progressive of anemia of chronic kidney Disease (CKD) ***(Besarab et al., 2000),*** and the overall prevalence of CKD-associated Anemia is approximately 50% ***(McClellan et al., 2004).*** Although anemia may be diagnosed in patients at any stage of CKD, there is a strong correlation between the prevalence of anemia and the severity of CKD ***(Guenter et al., 2005).*** Treatment of CKD-associated anemia has been dramatically advanced by the introduction of recombinant human erythropoietin (EPO).However; CKD-associated anemia can be resistant to EPO treatment. In addition to EPO deficiency, inflammatory effects of the primary disease, inflammatory effects of its complications and of its treatments, and iron-restricted erythropoiesis could be involved in this pathogenesis ***(Ganz et al., 2007).***

Hepcidin, a small peptide produced by the liver, is a recently discovered central mediator of iron homeostasis via regulation of ferroportin, hepcidin inhibits intestinal iron absorption and iron release from macrophages and hepatocytes ***(Young and Zaritasky, 2009).***

Hepcidin, a 25-amino acid peptide primarily produced in the liver, is thought to be the central regulator of body iron metabolism ***(Kemna et al., 2008).*** Hepcidin controls the plasma iron concentration by inhibiting iron export by ferroportin from enterocytes and macrophages ***(Nemeth et al., 2004).*** Therefore,

increased Hepcidin production leads to a decrease in plasma iron concentrations and to iron-restricted erythropoietin ***(Ganz et al., 2007).***

Hepcidin expression is induced by iron loading ***(Pigeon et al., 2001)*** and by inflammation ***(Nemeth et al., 2004)*** and is suppressed by erythropoietic activity ***(Pak et al., 2006).***

Studies of humans with chronic infections and severe inflammatory disease have shown markedly increased levels of Hepcidin, strongly suggesting that elevated Hepcidin levels play a key role in the anemia of inflammation and reticuloendothelial blockade ***(Nemeth et al., 2004).***

AIM OF THE STUDY

The aim of the present study is to spot the light on the use of serum level of Hepcidin as biochemical marker in Chronic Kidney Disease patients and to compare its level in diabetic and non diabetic Chronic Kidney Disease patients' stage 5 before hemodialysis.

CHRONIC KIDNEY DISEASE

Introduction:

Chronic kidney disease (CKD) is a worldwide public health problem. It is recognized as a common condition that is associated with an increased risk of cardiovascular disease and chronic renal failure (CRF) ***(Matsushita, 2010).***

Chronic kidney disease (CKD) is recognized as a major health problem affecting approximately 13% of the US population**.** In the United States, the incidence and prevalence of kidney failure are rising, the outcomes are poor, and the costs are high. The number of persons with kidney failure who are treated with dialysis and transplantation is projected to increase from 340 000 in 1999 to 651 000 in 2010 ***(NKF/ KDOQI, 2012).***

Chronic kidney disease (CKD) epidemiologic wave is a worldwide health issue associated with high morbidity, mortality and rising health-care costs. Approximately 20 million patients in the USA have CKD, and this number is estimated to reach 30 million by 2010. This is mainly the result of ageing as well as increasing frequency of type 2 diabetes mellitus, hypertension and metabolic syndrome in the general population ***(Levey et al., 2007).*** Patients with CKD are more likely to die than to progress to end-stage renal disease (ESRD) and cardiovascular disease (CVD) accounts for a large proportion of these deaths. This increased