

# **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

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

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**List of Abbreviations (Cont...)**

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

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**List of Abbreviations** (Cont...)

<b>RAS</b> .....	Renin-angiotensin system
<b>RAS</b> .....	Renin–angiotensin system
<b>RCT</b> .....	Randomized controlled trial
<b>RRT</b> .....	Renal replacement therapy
<b>SHARP</b> .....	Study of Heart and Renal Protection
<b>SLE</b> .....	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 insufficiency 12%), chronic diseases (20%) and unexplained (24%) (*Karuna et al., 2011*). A normocytic normochromic anemia usually accompanies progressive 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 (*Guenther 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 Zariwsky, 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:

**C**hronic 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