Serum Neutrophil Gelatinase Associated Lipocalin: A New Biomarker in Renal Failure

Thesis

Submitted in partial fulfillment
Of the Master Degree in
Clinical and Chemical Pathology
By

Mona Mohsen Ahmed Abou EL-Ghar

Supervisors

Prof. Dr. Nadida Goher
Professor of Clinical & Chemical Pathology
Faculty of Medicine
Cairo University

Prof. Dr. Naglaa Khloussi
Professor of Clinical & Chemical Pathology
National Research Center

Dr. Reham Ziada
Lecturer of Clinical & Chemical Pathology
Faculty of Medicine
Cairo University

Faculty of Medicine
Cairo University
2008

Abstract

It Was Found That Change in Seurm Creatinine is inadequate for follow up of Kidney damage . This change is delayed of Kidney damage Which leads to need of a new biomarker to monitor Kidney damage Serum Neutrophil Gelatinase Lipocalin is an acute phase reactant which activates nephron formation in embryonic kidney . Its robustly expressed in renal failure . cystatin C concentration correlates negatively with GFR and positively with serum creatinine so it is a very sensitive marker of changes in GFR .

Key Words :

Kidney Failure – Lipocalin Cystatinc.

Acknowledgement

First of all, praise to God the most generous for enabling me to conduct this study.

I would like to thank **Professor Doctor Nadida Goher** for her wise guidance and unusual co-operation throughout the duration of the study. Without her genuine advice and understanding this work would have never been complete.

My deepest gratitude to **Professor Doctor Naglaa Kholoussi**, for her extraordinary co-operation and assistance, whose sincere effort and devotion were a cornerstone to this study.

My appreciation is due to **Doctor Reham Ziada** for her kind and valuable help.

My all appreciation for my father for his outstanding support and love, my mother and sister for their care and devotion.

CONTENTS

LIST of TABLES

LIST of FIGURES

LIST of ABBREVIATIONS

ACE : Angiotensin Converting Enzyme.
ADH : Antidiuretic Hormone.
AKI : Acute Kidney Injury.
ANS : 8-anilino-1-naphthalene sulfonic acid.
ARF : Acute Renal Failure.
BSA : Body Surface Area.
CKD : Chronic Kidney Disease.
COPD : Chronic Obstructive Pulmonary Disease.
Cys C : Cystatin C.
DAUDA : Dimethyl/amino naphthalene sulfonylamino undecanoic acid.
eGFR : Estimated Glomerular Filtration Rate.
ELISA : Enzyme Linked Immunosorbant Assay.
ERF : End Stage Renal Failure.
FABP : Fatty Acid Binding Protein.
GFR : Glomerular Filtration Rate.
HRS : Hepatorenal Syndrome.
JGA : Juxta Glomerular Apparatus.
KDOQI : Kidney Disease Outcome Quality Initiative.
MDRD : Modification of Dietry Renal Disease.
NGAL : Neutrophil Gelatinase Associated Lipocalin.
NKF : National Kidney Foundation.
PTH : Parathyroid Hormone.
RBP : Retinol Binding Protein.
SLE : Systemic Lupus Erythromatosis.
TLR : Toll like Receptors.

Introduction & Aim of the Work

Neutrophil gelatinase-associated lipocalin (NGAL) is an acute phase protein that is rapidly released from neutrophils as well as other cell types upon inflammation and tissue injury ***(Ding et al., 2007)***. It activates nephron formation in the embryonic kidney, is one of the most robustly expressed proteins in the kidney, and its production is rapidly and massively induced in renal failure ***(Mori and Nakao., 2007)***. It functions as an effector molecule of the innate immune system and has an important role in cell homeostasis ***(De-xiu Bu et al., 2006).***

Change in serum creatinine, which is the standard test used to define and monitor the progression of kidney damage, was proven inadequate for a number of reasons, including the fact that it is delayed after kidney injury, which created the need for a new biomarker that would predict and monitor kidney damage ***(Bonventre et al., 2007)***.

Human Cystatin C is produced at a constant rate by all nucleated body cells and is present in all body fluids. Serum Cystatin C concentration correlates negatively with glomerular filtration rate (GFR) and positively with serum creatinine, therefore was recently proposed as a very sensitive marker of changes in GFR ***(Dharrindharka et al., 2002)***.

Serum NGAL significantly correlates with Cystatin C and glomerular filtration rate, and both NGAL and Cystatin C were proven useful for the quantization of kidney damage ***(Mitsnefes et al., 2007)***. NGAL represents a non-invasive biomarker for renal tissue injury that is especially important in subclinical ischemic renal injury and subclinical nephrotoxic damage. It is useful as an early marker that predicts development of severe kidney damage of unknown etiology ***(Zapitelli et al., 2007).***

Hypothesis: Serum NGAL is a specific and sensitive marker for renal damage

Aim of the Work

The aim of the present study is to assess the relationship between serum NGAL and Cystatin C as an estimation of GFR in patients with chronic kidney disease.

Chapter 1: Renal Functions

Review of Literature

Functional Anatomy

The kidneys are paired organs, 11-14 cm in length in adults, 5-6 cm in width and 3-4 cm in depth. They lie retroperitoneal on either side of the vertebral column at the level of Thoracic 12(T_{12}) to Lumbar 3(L_3). The renal parenchyma comprises an outer cortex and an inner medulla.

The Nephron

The functional unit of the kidney is the nephron of which each contains approximately one million. *Each nephron* is made up of a glomerulus, proximal tubule, loop of Henle, distal tubule and collecting duct. Each kidney has been reported to contain between 1 and 1.5 million nephrons, but more recent estimations suggest a wider range ***(Nyengaard et al., 1992***).

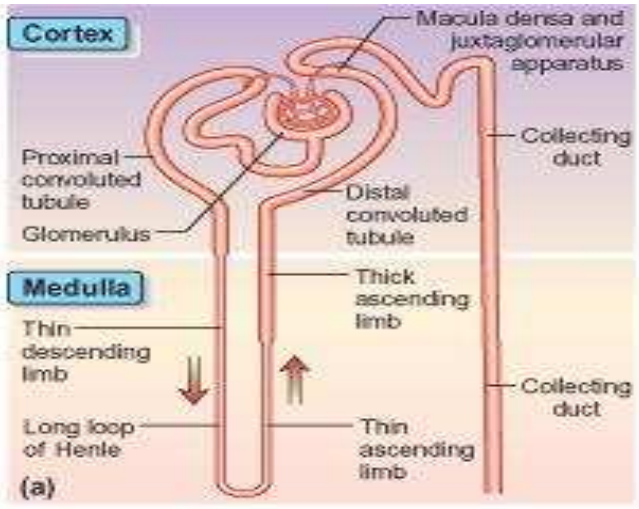

Figure 1: Principal parts of the nephron. The point where the distal tubule is in close proximity to its own glomerulus is called the juxtaglomerular apparatus. This contains the macula densa.

The Glomerulus

The glomerulus comprises four main cell types: (1) Endothelial cells which are fenestrated ; (2) Visceral epithelial cells (podocytes) which support the delicate glomerular basement membrane by means of an extensive trabecular network (foot processes); (3) Parietal epithelial cells which cover the Bowman's capsule; (4) Mesangial cells are believed to be related to macrophages of the reticuloendothelial system and have a phagocytic function and contractile capabilities that can control blood flow and filtration surface area along the glomerular capillaries in response to a host of mediators. Together the endothelial cells, basement membrane and epithelial cells form the filtration barrier or sieve ***(Yagob 2005).***

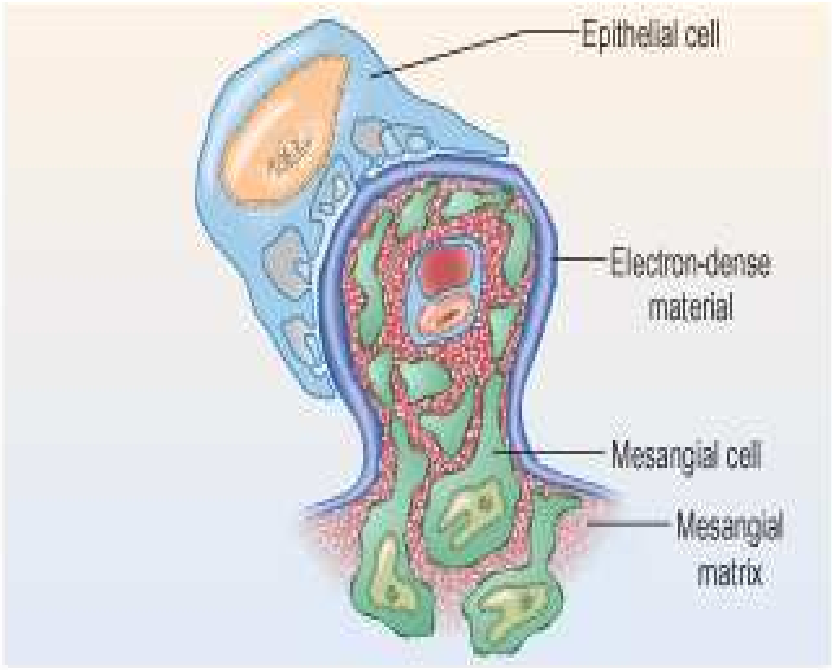

Figure 2: The Glomerulus

The Tubules

The renal tubules are lined by epithelial cells, which are cubical except in the thin limb of the loop of Henle where they are flat. Proximal tubular cells differ from other cells of the system as they have a luminal brush border. The cortical portion of the collecting ducts contains two cell types with namely principal cells and intercalated cells. Fibroblast-like cells in the renal cortical interstitium have been identified and shown to produce erythropoietin in response to hypoxia (***Breyer, 2002***).

JuxtaGlomerular Appartus

Where the ascending loop of Henle passes very close to the Bowman's capsule of its own nephron, the cells of the tubule and the afferent arteriole show regional specialization. The tubule forms the macula densa and the arteriolar cells are filled with granules (containing renin) and innervated with sympathetic nerve fibres. This area is called the juxtaglomerular apparatus(JGA).The JGA plays an important part in maintaining systemic blood pressure through the regulation of the circulating intravascular blood volume and sodium concentration ***(Michael et al., 2006).***

Blood Supply

Arterial blood is supplied to the kidneys via the renal arteries, which branch off the abdominal aorta, and venous blood is conveyed to the inferior vena cava via the renal veins. Approximately 25% of humans possess dual or multiple renal arteries on one or both sides (***Kon and Baylis, 1997***). Adult kidneys receive approximately 25%of cardiac output: however in the newborn infant it is 5% only reaching adult proportions by the end of the first year of life ***(Seldin et al., 1992)***.