Evaluation of Lipocalin in diagnosing acute kidney injury in Egypt

Thesis submitted in partial fulfillment of master degree of internal medicine

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Abstract

Acute kidney injury (AKI) is a major clinical problem with a rising incidence and high mortality rate.
Since creatinine detects injury after more than 50% of renal function be lost & serum creatinine does not accurately depict kidney function until a steady state has been reached.
So lipocalin present an early detector of kidney function & predict outcome of kidney state.

Our results showed statistically significant differences of mean lipocalin levels in the studied groups. From these results, it was concluded that serum & urinary lipocalin can be accepted as diagnostic predictors of the degree acute kidney injury as an ELISA test for the injury

Key words:

- Lipocalin.
- NGAL (Neutrophil Gelatinase Associated Lipocalin).
- Acute renal failure.
- MDRD (modified diet in Renal Diseases).

Contents

List of abbreviations

γGT	Gamma Glutamyl Transferase.
µL	Micro Liter.
ACEIs	angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome
ADQI	Acute Dialysis Quality Initiative
AKI	Acute kidney injury
AKP	Alkaline Phosphatase.
ANA	Anti Nuclear Antibodies.
ANCA	Anti–neutrophil cytoplasmic antibody
ANOVA	Analysis Of Variance.
Anti-GBM	Anti–glomerular basement membrane
ARBs	angiotensin receptor blockers
ARF	Acute renal failure
AUC	Area Under the Curve.
BPH	benign prostatic hypertrophy
BUN	blood urea nitrogen
C	Control.
C&G	Cockcroft-Gault equations
CPB	Cardiopulmonary bypass
cvs	cardiovascular stroke
DIC	Disseminated intravascular coagulopathy
ELISA	Enzyme Linked Immuno- Sorbent Assay.
FE_{Na}	Fractional excretion of Na
GFR	Glomerular Filtration Rate.

GGT	Gamma Glutamyl Transferase.
HAV	Hepatitis A Virus.
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus.
HCV	Hepatitis C Virus.
HIV	Human Immunodeficiency Virus .
HTN	Hypertension
HUS	Hemolytic Uremic Syndrome
IFN	Interferon.
IgG	Immunoglobulin G.
IgM	Immunoglobulin M.
IL	Interleukin.
IV	Intra Venous.
IVU	Intravenous urography
JVP/CVP	Jugular venous pressure/Central venous pressure
KDa	Kilo Dalton.
MAG3 scan	Mercapto Acetyl Tri Glycine scan
MDRD	Modification of Diet in Renal Disease
mL	Milliliter.
mm	Millimeter.
NPV	Negative Predictive Value.
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSTEMI	Non ST segment Elevation Myocardial Infarction
PC	Prothrombin Concentration.
PCR	Polymerase Chain Reaction.
PLT	Platelets.

PMNL	Polymorph Nuclear Leucocyte.
PPV	Positive Predictive Value.
PT	Prothrombin Time.
RIFLE	Risk, Injury, Failure, Loss, End Stage Kidney Disease
ROC	Receiver Operator Characteristic.
SD	Standard Deviation.
SLE	Systemic Lupus Erythromatosis
SIRS	Systemic Inflammatory Response Syndrome
Std	Standard.
T. Bilirubin	Total Bilirubin
TTP	Thrombotic Thrombocytopenic purpura
U/L	Unit/Liter.
UO	Urine Output
US	United States.
WBCs	White Blood Cells.
WHO	World Health Organization.

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Introduction:

Acute kidney injury (AKI) is a major clinical problem with a rising incidence and high mortality rate.**(Uchino et al.,2006)**

Acute renal injury (AKI) secondary to ischemic injury remains a common and potentially a risk in patient admitted to ICU. **(Devarajan 2007)**

Hospital-acquired ARF complicates up to 4% of hospital admissions, and as many as 20-40% of ICU admissions. The mortality of ARF has not changed appreciably in the past fifty years, holding steady at 50% (and as high as 70% in the ICU setting). **(Devarajan 2007)**

Early diagnosis of acute kidney injury (AKI) is often problematic, due to the lack of suitable early biomarkers of renal damage and kidney function.

Serum creatinine is an inadequate marker for AKI

First, more than 50% of renal function must be lost before an elevation in serum creatinine is detected. Second, serum creatinine does not accurately depict kidney function until a steady state has been reached, which may require several days. **(Kingshuk Das et al., 2005).**

Wide interrogation strategy was used to identify renal genes that are induced very early after renal ischemia, whose protein products might serve as novel biomarkers for AKI.

Neutrophil Gelatinase-Associated Lipocalin**(NGAL**) might represent an early, sensitive, non-invasive biomarker for acute renal injury and urinary NGAL might serve as an early marker for ischaemic renal injury.

Seven genes that are upregulated >10-fold were identified, one of which (*Cyr61*) has recently been reported to be induced after renal ischemia. **(Jaya et al., 2007).**

Unexpectedly, the induction of the other six transcripts was novel to the ARF field. **(Han et al 2002).**

The origin of NGAL from tubule cells was confirmed in cultured human proximal tubule cells subjected to ischemic injury.

Aim of work:

Identification of urinary and serum concentration of uNGAL in ICU patient.

We assessed the ability of uNGAL to predict AKI development and severity in critically ill patient.

Comparing value of uNGAL with serum creatinine & GFR in critically ill patient in ICU. **(Nickolas et al., 2008).**

So we evaluate the utility of uNGALto predict persistant AKI & progression of AKI to higher RIFLE. **(Zappitelli et al., 2007).**

Introduction:

Acute renal failure (ARF) or acute kidney injury (AKI), as it is now referred to in the literature, is defined as an abrupt or rapid decline in renal filtration function. This condition is usually marked by a rise in serum creatinine concentration or azotemia (a rise in blood urea nitrogen [BUN] concentration). However, immediately after a kidney injury, BUN or creatinine levels may be normal, and the only sign of a kidney injury may be decreased urine production. A rise in the creatinine level can result from medications (eg, cimetidine, trimethoprim) that inhibit the kidney's tubular secretion. A rise in the BUN level can occur without renal injury, such as in GI or mucosal bleeding, steroid use, or protein loading, so a careful inventory must be taken before determining if a kidney injury is present**. (Bellomo et al., 2004).**

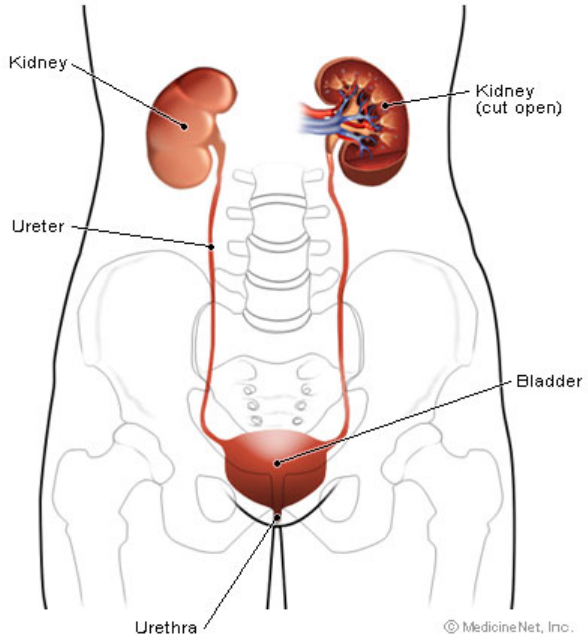

Figure 1: anatomy of kidney, ureters & urinary bladder

ACUTE RENAL FAILURE

Background

Until recently, a systematic definition of acute renal failure (ARF) was lacking, which led to significant confusion both clinically and in the medical literature. The Acute Dialysis Quality Initiative (ADQI) group published the RIFLE classification of ARF, based on changes from the patient's baseline either in serum creatinine level or glomerular filtration rate (GFR) or urine output (UO).

The RIFLE classification of ARF is as follows: **(Bellomo et al., 2004).**

- Risk (**R**) - Increase in serum creatinine level 1.5 fold or decrease in glomerular filtration rate (GFR) by 25%, or urine output(UO) <0.5 mL/kg/h for 6 hours.
- Injury (**I**) - Increase in serum creatinine level 2.0 folds or decrease in glomerular filtration rate (GFR) by 50%, or urine output(UO) <0.5 mL/kg/h for 12 hours.
- Failure (**F**) - Increase in serum creatinine level 3.0 folds, decrease in glomerular filtration rate (GFR) by 75%, or serum creatinine level $\geq$4 mg/dL with acute increase of >0.5 mg/dL; urine output(UO) <0.3 mL/kg/h for 24 hours, or anuria for 12 hours.
- Loss (**L**) - Persistent ARF, complete loss of kidney function >4 weeks.
- End-stage kidney disease (**E**) - Loss of kidney function >3 months.

Since baseline serum creatinine level and GFRs may not be readily available the consensus committee recommends the use of the Modification of Diet in Renal Disease (MDRD) equation (**Bagshaw et al., 2007**) to estimate the patients GFR/1.73 mm based upon: serum creatinine level, age, gender, and race. The proportional decrease in GFR should be calculated from 75 mL/min per 1.73 mm **(Uchino et al., 2005),** the agreed upon lower limit of normal.

ARF is a common entity in the Emergency Department. Emergency physicians play a critical role in recognizing early ARF, preventing iatrogenic injury, and reversing the course of ARF. **(Ostermann M et al., 2007).**

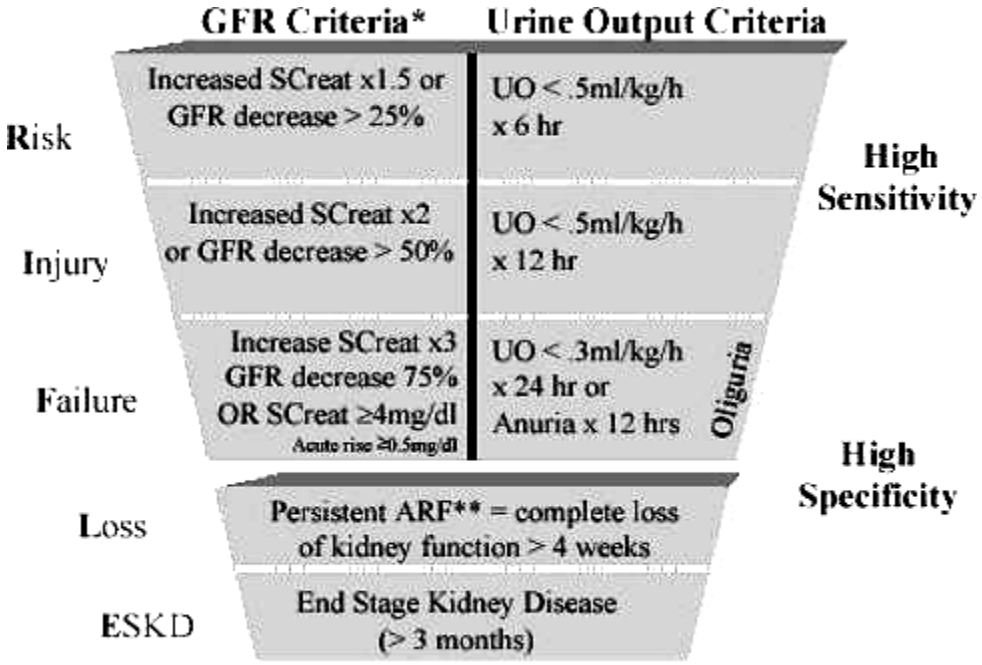

figure 2: The RIFLE classification of ARF is as follows: **(Bellomo et al., 2004).**