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Neutrophil gelatinase-associated lipocalin: a novel biomarker for the early diagnosis of acute kidney injury in the Emergency Department

A. DI GRANDE, C. GIUFFRIDA[+], G. CARPINTERI[++], G. NARBONE, G. PIRRONE, A. DI MAURO, S. CALANDRA[+], P. NOTO[++], C. LE MOLI, B. ALONGI, F. NIGRO

U.O.C. di Medicina e Chirurgia d'Accettazione e d'Urgenza, Azienda Ospedaliera Elia, Caltanissetta (Italy)
[+]U.O.C. di Medicina e Chirurgia d'Accettazione e d'Urgenza, Azienda Ospedaliera Piemonte, Messina (Italy)
[++]U.O.C. di Medicina e Chirurgia d'Accettazione e d'Urgenza, Azienda Ospedaliera Vittorio Emanuele, Ferrarotto, S. Bambino, Catania (Italy)

Abstract. – Acute kidney injury (AKI) is a common medical problem among critical patients. In current clinical practice, AKI is diagnosed by measuring serum creatinine concentration, which is an unreliable and delayed marker of the deterioration of kidney function. Its rise occurs when a significant amount of renal function has been lost. Many are the factors able to modify physiological levels, such as age, gender, ethnicity, dietary protein intake, muscle mass or metabolism, hydration status and drugs.

Definitely, creatinine, as well as blood urea nitrogen (BUN) or urine markers of kidney injury (fractional excretion of sodium, urinary concentrating ability, casts), do not directly reflect cell injury, but rather the delayed functional consequences of the damage.

Due to the lack of sensitive and specific biomarkers, the identification of early stages of AKI has been impossible but, recently, neutrophil gelatinase-associated lipocalin (NGAL) is emerging as a novel biomarker of AKI from several etiologies, such as cardiac surgery, contrast nephropathy, kidney transplantation and sepsis.

This protein, produced in a number of human tissues and particularly in the distal nephron, has siderophore-chelating property and acts as an iron-trasporting shuttle.

NGAL increases in both serum and urine 48 hours before the rise of creatinine, and shows a strong correlation with change in creatinine concentrations.

An early diagnosis of AKI allows the early institution of therapeutic measures for the protection of renal function and improves the prognosis.

This possibility is particularly important in the Emergency Department for the treatment of critical patients with potential nefrotoxic therapies.

Use of NGAL as early marker of AKI in the Emergency Department is discussed.

Key Words:

Lipocalin, Neutrophil gelatinase-associated lipocalin, NGAL, Acute kidney injury, AKI.

Introduction

Acute kidney injury (AKI) is a clinical problem with an estimated incidence of 7% in hospitalized patients[1]. In Intensive Care Unit (ICU) the prevalence of patients with AKI requiring hemodialysis is approximately 6% with an associated mortality of 60%[2].

Generally defined as an abrupt and sustained decrease in kidney function, this condition is better identified using the "Risk-Injury-Failure-Loss and End stage kidney classification" (RIFLE), issued from a process of formal evidence, appraisal and expert opinion.

The RIFLE, based on either serum creatinine rise or urine output reduction, defines accurately the level of AKI and the associated risk of mortality[3-5].

Measure of serum creatinine or BUN concentration, as well as urine markers of kidney injury, do not allow the identification of early stages of AKI, impairing the possibility to start a suitable therapy in a timely manner[6].

Recently, a lipocalin produced in the distal nephron, namely NGAL, is emerging as a novel biomarker of AKI.

Corresponding Author: Aulo Di Grande, MD; e-mail: adigrande@yahoo.it

NGAL increases in both serum and urine approximately 24 hours before the rise of creatinine, and shows a strong correlation with change in creatinine concentrations[7].

An early diagnosis of AKI allows the early institution of therapeutic measures for the protection of renal function and improves the prognosis.

Availability of a sensitive and specific biomarker of AKI is particularly important in critical patients, often lacking in anamnestic data, and treated with potential nefrotoxic therapies.

Discussion

Lipocalins are a family of more than 20 proteins able of binding to a wide variety of molecules[8]. NGAL, also known as lipocalin 2, uterocalin, siderocalin or neu-related lipocalin, is a member of this family, first isolated in human neutrophils[9].

Expressed in a number of human tissues including gastro-intestinal, respiratory and urinary tracts, NGAL shows siderophore-chelating property and acts as a component of immunity to exogenous bacterial and fungal infections depleting the intracellular iron stores of the micro-organisms.

Since iron is an essential nutrient for micro-organisms but is strongly bound to host proteins in mammals, bacteria and many fungal organisms must compete with these proteins for the iron and have evolved specific iron chelators (siderophores) in response to iron deficiency.

Thus, inhibition of the iron acquisition process by scavenging microbial siderophores is a powerful mechanism in the defence against microbial infections[10,11].

Enhancement in systemic and tissue NGAL expression has been well documented in many conditions characterized by infection or inflammation, including diverticulitis, appendicitis, inflammatory bowel disease or urinary tract infection but, in clinical practice, interest is particularly focused on AKI.

Strong evidences support a close correlation between AKI from diverse etiologies (contrast nephropathy, kidney transplantation, cardiac surgery, preeclampsia, sepsis) and the increase in plasma and urinary levels of NGAL[12-18].

Patients with established AKI have a greater than 10-fold increase in plasma NGAL concentration or more than a 100-fold increase in urine NGAL concentration when compared to normal controls, and kidney biopsies in these subjects show intense accumulation of immuno-reactive NGAL in 50% of the cortical tubules[19].

NGAL is emerging now as a new sensitive and reliable biomarker extremely useful in the early phase of AKI, condition that measuring of serum creatinine does not detect.

Serum creatinine increases late in case of kidney injury when a variable amount of kidney function has already been lost, and, as well as BUN or urine markers of kidney injury (fractional excretion of sodium, urinary concentrating ability, casts), do not directly reflect cell injury, but rather the delayed functional consequences of the damage[6].

Furthermore, creatinine serum concentrations may be affected by age, gender, ethnicity, dietary protein intake, hydration status, drugs and may remain within the reference range despite marked renal impairment in patients with low muscle mass[20,21].

Rise in serum NGAL occurs 48 hours before creatinine and several studies have demonstrated a strong direct correlation with change in creatinine concentrations[22].

Diagnosing AKI in its early stages is important in term of prevention of tissue damage and can significantly reduce mortality in non-complicated cases[23].

A such opportunity is particularly useful in critical patients of the Emergency Department, often lacking in anamnestic data and treated in aggressive manner.

An early marker of AKI may warn the emergency physician of a subclinical renal impairment, preventing potentially harmful interventions (administration of nephrotoxic drugs or contrast media) and providing an adequate renal replacement therapy promptly.

Moreover, it is reported that a single Emergency Department measurement of NGAL helps to distinguish AKI from chronic kidney disease or prerenal azotemia, and predict in patient outcomes[24].

Due to the need to trigger an immediate intervention in critical patients, standardized point-of-care devices for a quantitative measurement of NGAL in approximately 15 minutes are currently undergoing large-scale validation[25].

Further comparative researches among other different novel biomarkers, particularly cystatin C or interleukin-18, are required to established

their potential value, singly or in combination, compared to NGAL, and it is entirely possible that different panels of biomarkers will be required to increase sensitivity and specificity in the early diagnosis of AKI[26,27].

Conclusion

"Time is kidney" and the usefulness of markers of kidney injury (NGAL), rather than markers of kidney function (creatinine), is emerging increasingly.

In an Emergency Department and in any different critical care setting, the identification of early stages of AKI brings a new hope for a timely institution of measure for renal prevention and protection.

The risk of missed therapeutic opportunity has stimulated an ongoing and intensive evaluation of a variety of alternative biomarkers of AKI, and NGAL seems to be a sensitive and specific tool with significant potential for early diagnosis.

In an Emergency Department and in any different critical care setting, the identification of early stages of AKI brings a new hope for a timely institution of measure for renal prevention and protection.

Future studies are required to validate this marker for a routine clinical use.

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