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Review

The use of cell cycle arrest biomarkers in the early detection of acute kidney injury. Is this the new renal troponin?

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ABSTRACT

Acute kidney injury (AKI) has a high prevalence in critical care patients. Early detection might prevent patients from developing chronic kidney disease and requirement for renal replacement therapy. If we compare AKI with acute coronary syndrome, in which an increase in cardiac troponin may trigger early diagnosis and therapeutic intervention, we could extrapolate a similar technique in patients with early AKI without changes in urinary frequency or serum creatinine. The objective is to identify biomarker-positive, creatinine-negative patients that would allow therapeutic interventions to be initiated before finding changes in serum creatinine, preventing kidney damage. Tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 are cell cycle arrest biomarkers that have demonstrated, in recent clinical trials, to have good sensitivity and specificity for early detection of AKI. Other recent studies have shown that the joint use of these biomarkers with serum creatinine and urine production could improve the prognosis of AKI in critical patients. The application of these biomarkers in clinical practice would enable the early identification of patients at risk of AKI, establishing interventions that would improve the survival of renal function.

El uso de biomarcadores de detección del ciclo celular para el diagnóstico precoz del fracaso renal agudo. ¿La nueva troponina renal?

Palabras clave:
Fracaso renal agudo
Biomarcadores de detección del ciclo celular

RESUMEN

Existe una gran prevalencia del fracaso renal agudo (FRA) en pacientes críticos. La detección temprana prevendría el desarrollo de la enfermedad renal crónica y el requerimiento de terapias renales de sustitución. Si comparamos el FRA con el síndrome coronario agudo, en el que el uso de la troponina cardiaca permite el diagnóstico precoz y su consecuente

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terapia, se podría extrapolar técnica similar en pacientes con FRA temprano sin cambios en la frecuencia urinaria o creatinina sérica. El objetivo sería identificar a pacientes con un biomarcador positivo y la creatinina negativa que permitiera iniciar intervenciones terapéuticas antes de objetivar cambios en la creatinina sérica, previniendo el daño renal. El inhibidor tisular de metaloproteinasa-2 y la proteína de enlace 7 del factor de crecimiento insulínico, son biomarcadores de detención del ciclo celular, que han demostrado, en estudios recientes, tener adecuada sensibilidad y especificidad para la pronta identificación del FRA. Otros estudios recientes han mostrado que el uso conjunto de estos biomarcadores con la creatinina sérica y la producción de orina, pudieran mejorar el pronóstico del FRA en pacientes críticos. La aplicación de estos biomarcadores en la práctica clínica permitiría la identificación precoz de pacientes con riesgo de FRA estableciendo intervenciones que mejorarían la supervivencia de la función renal.

Introduction

There is an increased incidence and prevalence of acute kidney injury (AKI) in the critical care population that influences the probability of survival a complicates comorbidities.[1] Acute kidney injury implies reversible kidney damage that occurs in a particular time period. A distinction should be made between kidney injury and dysfunction. The rise in serum creatinine lags behind changes in glomerular filtration rate and depends on its own generation and steady state. This influences the rate of excretion setting the serum creatinine at a higher value. An important goal in the past few years has been to identify a biomarker sensitive enough to detect kidney injury and at the same time complement or substitute the dependency on serum creatinine and or urine output. If we compare AKI with acute coronary syndrome, in which a increase in troponin may trigger a diagnosis and therapeutic intervention, the diagnosis of AKI could be made in the absence of oliguria or increase creatinine level. The fact that AKI (subclinical) is not clinically determined does not mean that the kidney is intact with normal glomerular filtration rate. Sub clinical AKI may be identified by the isolation of new biomarkers. The goal is to identify a biomarker positive creatinine negative patient that has sustained injury to the kidney but still is in a pre-clinical phase based on serum creatinine. This new approach will identify more conditions causing AKI changing its incidence, prevalence and triggering interventions prior to changes in serum creatinine that will possibly improve renal outcomes. The end result will be to distinguish between renal function loss and AKI with tubular damage. All this will improve the time table for prompt recognition of pre-renal versus non renal causes of renal failure. A practical way to apply this concept will be to established different phases of dysfunction: Phase 1) no AKI with no biomarker detection. Phase 2) AKI with tubular damage and biomarker positive (subclinical AKI). Phase 3) AKI with filtration dysfunction (RIFLE/AKIN/KDIGO positive). Phase 4) with tubular damage, biomarker positive and filtration dysfunction (RIFLE/AKIN/KDIGO positive). These pre injury phases can also be define as acute kidney stress.[2]

Efforts for discovering new biomarkers for AKI have been curtailed by their sensitivity and specificity to identified patients at risk. The multifactorial nature of AKI plays an important part to that effect. A number of clinical trials have evaluated different biomarkers in plasma and urine. Some of these biomarkers (neutrophil-gelatinase-associated lipocalin-NGAL, interleukin-IL, liver-type fatty acid binding protein L-FABP, kidney injury molecule 1-KIM1) have been utilized for early identification AKI with mixed results.[3] More recently, two new cell cycle arrest biomarkers; tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), have been isolated in different multicenter discovery and validation clinical trials and marketed in the U.S. for risk assessment of AKI.[4] These are cell cycle arrest proteins synthesized and secreted in injured renal tubular cells blocking endothelial cell proliferation by kinase activation[5] and affecting the bioavailability of insulin growth factors that participate in tumor suppression and cell senescence.[6] These biomarkers will be able to detect moderate to severe AKI within 24 h. The approval of these novel biomarkers represents a step in the search for a robust and accurate means of early diagnosis of kidney injury. We will review the biology of these biomarkers, enumerate the clinical trials performed to date to identify them and also discuss their applicability in clinical practice.

Biology of cell cycle biomarkers

As previously mentioned, cell cycle division is required for cell proliferation (Fig. 1). Cells respond to injury by repairing while entering and exiting different phases of proliferation assisted by kinases.[7] Exit from the cell cycle in G1 leads to apoptosis.[7] Furthermore, failure to achieve G1 cycle arrest leads to fibrosis through collagen production during the G2 mitotic phase. On the other hand, G1 cell cycle arrest, prevents division of cells with damaged DNA, permitting adequate repair.[8] This is a protective mechanism designed to avoid exposure to stress and injury. If cells become arrested at the G1 or G2 phases for prolonged periods, senescence and fibrosis will ensue.[9] This cell cycle is regulated by different proteins, particularly kinases,