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Review

Biomarkers in acute kidney injury: Evidence or paradigm?☆

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ABSTRACT

Acute kidney injury in the critically ill represents an independent risk factor of morbidity and mortality in the short and long terms, with significant economic impacts in terms of public health costs. Currently its diagnosis is still based on the presence of oliguria and/or a gradual increase in serum creatinine, which make the diagnosis a delayed event and to detriment of the so-called 'therapeutic window'. The appearance of new biomarkers of acute kidney injury could potentially improve this situation, contributing to the detection of 'subclinical acute kidney injury', which could allow the precocious employment of multiple treatment strategies in order to preserve kidney function. However these new biomarkers display sensitive features that may threaten their full capacity of action, which focus specifically on their additional contribution in the early approach of the situation, given the lack of specific validated treatments for acute kidney injury. This review aims to analyze the strengths and weaknesses of these new tools in the early management of acute kidney injury.

Biomarcadores en la lesión renal aguda: ¿ paradigma o evidencia?

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RESUMEN

La lesión renal aguda en los pacientes críticos representa un factor de riesgo independiente de la morbilidad y la mortalidad a corto y a largo plazo, con un tremendo impacto económico en cuanto a los costes en salud pública. Por el momento, el diagnóstico de la lesión renal aguda sigue basándose en la presencia de oliguria o en un aumento gradual de la creatinina sérica, hecho que retrasa el diagnóstico, en detrimento de la llamada «ventana terapéutica». La aparición de nuevos biomarcadores de lesión renal aguda podría mejorar esta situación y

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contribuir a la detección de la «lesión renal aguda subclínica», lo que permitiría el uso precoz de múltiples estrategias de tratamiento con el objetivo de preservar la funcionalidad renal. No obstante, los nuevos biomarcadores presentan características que podrían vulnerar su capacidad de acción, centrada concretamente en aportar un valor añadido al abordaje precoz de la enfermedad, dada la falta de tratamientos específicos validados para la lesión renal aguda. Esta revisión tiene como objetivo analizar los puntos fuertes y débiles de esta nueva herramienta para el diagnóstico temprano de la lesión renal aguda.

Introduction

In the article "Dissent, Dogmatism and Belief Polarization",[1] published in The Journal of Philosophy, Thomas Kelly refers to a phenomenon called "belief polarization" by which exposure to the same evidence, far from bringing those who have different opinions closer, usually makes the disagreement between them become more pronounced: we are more demanding with anything that contradicts our belief and more permissive with what favors our own point of view.

This phenomenon may partly explain our acceptance or rejection of the use of new biomarkers in the diagnosis of acute kidney injury (AKI).

In 2005, the American Society of Nephrology Renal Research Report (ASNRRR) assigned the highest research priority to the discovery and standardization of new AKI biomarkers.[2]

AKI in critically ill patients is an independent risk factor that increases morbidity and mortality in the short and long term, with a tremendous financial impact in terms of health costs.[3] AKI is also a gateway to chronic kidney disease (CKD).[4] It is noteworthy that, after an AKI episode, 7.8 of every 100 patients/year develop CKD and 4.9 per 100 patients/year will develop advanced chronic kidney disease.[5]

There has been numerous preventive or curative strategies for AKI that have been either ineffective or insufficiently validated to be routinely recommended.[4]

The most important risk factor for AKI is the pre-existing CKD, which increases its risk up to 10 times.[6,7,8]

Some processes, such as endothelial dysfunction,[9] myocardial remodeling,[10] epigenetic factors[11] and increased oxidative stress,[12] are factors that could explain the increased risk of morbidity and mortality that persists long after the AKI episode.

Another reason that may explain the negative outcome of AKI patients is the late recognition of kidney injury leading to delayed interventions.

We must bear in mind that the diagnosis of AKI is based on indirect markers of kidney damage, that are not very sensitive or specific, to the detriment of the so-called "therapeutic window".[4]

In this context, there are various limitations of serum creatinine (sCr): sCr comes into play as a functional marker when more than 50% of the glomerular filtration rate has been lost and is only useful after a stationary state has been reached. The latter may differ over time, sometimes up to 48 h, especially in patients in intensive care units (ICU).[12] On the other hand, the excretion of creatinine does not depend on the load filtered solely by the glomeruli, but also on that secreted by the kidney tubules, which normally varies from 5 to 20% of total excretion, and may increase to 50% as a compensatory mechanism when the glomerular filtration rate (GFR) decreases.[13] Also, even if there were genuinely a fall in GFR, the sCr might not increase or increase late as a result of recruitment of the renal functional reserve; also the sCr could be "diluted" as a result of a profuse positive balance, which is frequently observed after resuscitation maneuvers, especially in patients in the ICU.[14] Finally, the eGFR seems to overestimate renal function in patients admitted to ICU during a long period of time. This was well demonstrated in a secondary analysis of the EPANIC study, in which 757 patients participated and which showed that a reduction in production of sCr positively correlated with the length of stay in the ICU, probably due to loss of muscle mass.[15]

The other parameter of AKI is oliguria, which is neither sensitive nor specific, since it could occur as a result of a kidney injury, but may also reflect an adaptive physiological response to either intracellular dehydration or hypovolemia.[16] Only a small proportion of oliguric patients in the ICU have in fact a sustained fall in GFR which is reflected in an increase in sCr.[16] Similarly, Mandelbaum et al.[17] showed that only pronounced (<0.3 mL/kg/h) or prolonged (>12 h) episodes of oliguria were associated with the need to start renal replacement therapy (RRT) or with increased hospital mortality.

The most recent biomarkers promise: to identify early patients at risk of AKI; to diagnose AKI earlier than with other conventional tests; to indicate the need to initiate RRT and also predict the risk for progression to CKD.[18,19] The objective is to accomplish more timely interventions the more favorable outcomes in patients with AKI. The availability of these new biomarkers and the evaluation of simultaneous combinations of functional and tissue damage biomarkers may help stratify patients into 4 subgroups: no change in biomarkers, only changes in functional biomarkers, only changes in biomarkers of tissue injury, or changes in the 2, functional and injury biomarkers (Fig. 1).

This new approach allows the identification of a new category of patients with AKI, called "Subclinical AKI", represented by an increase in markers of tissue injury without a simultaneous reduction of kidney function. Based on this new conceptual framework, a modification of the KDIGO criteria recommend the incorporation of kidney injury markers, to sCr, GFR and diuresis (Fig. 2).[20]