Cell-cycle arrest biomarkers: the light at the end of the acute kidney injury tunnel

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For many years, terms such as acute renal failure, acute tubular necrosis and acute kidney disease have been used to identify a group of disorders in which oliguria and an increase in serum creatinine were the final common findings. A more sophisticated and articulated definition of the abrupt decline in renal function was reached when the term acute kidney injury (AKI) started to be applied. Today we are facing a new era in which the possibility of molecular diagnosis of disease implies a careful evaluation of all aspects of a clinical disorder, including organ dysfunction and tissue damage. The impact of this approach is enormous since it may allow early identification of patients subject to damage progression or complete organ dysfunction, ultimately affecting clinical outcomes such as morbidity, mortality and dialysis requirement in the case of the kidney. There is now a common consensus that the development of AKI depends on the condition of the organ (susceptibility) and the intensity of the insult (exposure).

AKI is a complex disorder with important consequences in terms of morbidity and mortality. AKI is also an important concern for healthcare systems since it may represent a path towards chronic kidney disease (CKD) [1]. Clinicians are subject to many challenges when dealing with AKI patients. These challenges include the identification of patients at risk and evaluation of the susceptibility of the kidney to exposures, the need for early recognition of injury/dysfunction of the target organ and monitoring of progression towards severe dysfunction, chronic disease or possible recovery. These challenges are even more pronounced when critical illness is present and other conditions such as sepsis are involved [2]. In this evolving area of research and care, the process of implementation of new biomarkers is becoming crucial. The process of discovery has been conducted by evaluation of several molecules that are expressed in the blood or urine of patients with AKI. In this case, candidate biomarkers have been studied, selecting the most suitable molecules. Furthermore, the pathophysiological plausibility of candidate biomarkers’ involvements in the damage process has been elucidated under experimental and clinical conditions. The subsequent step was validation, where specific molecules have been evaluated prospectively in a cohort of patients to establish their capacity to predict the occurrence of a certain event or even to identify individuals at risk to develop the syndrome. We are far from the times in which one could accept a 60% chance to predict an event. New biomarkers should be capable of offering predictive capabilities >80 or even 90%.

In spite of a growing body of publications, many new biomarkers have not satisfied these requirements and most have
not yet been utilized in clinical settings because of a series of unresolved issues [3]. The first is the lack of specificity of the candidate molecule. The number of false-positive cases associated with the elevation of biomarkers caused by acute and chronic comorbidities in patients without AKI has often been too high. The second is the lack of biomarker sensitivity, particularly at the earliest stages of a disease. The third is the absence of clinically relevant and validated cut-off values that help guide biomarker use to trigger appropriate interventions and changes to patient management. In addition, one major concern has been that once significant damage has occurred, the possibility to modify the clinical course, and especially the recovery phase, was considered minimal or absent, since the process of disease progression or function recovery and tissue repair is complex and dependent on several contingent situations. While a number of patients with AKI recover kidney function, others may inevitably progress towards CKD [4].

Therefore, there is enormous interest in exploring all avenues of research to increase the number of patients in which kidney tissue can be preserved and early detection of the damage/dysfunction may prevent further progression and help in effective recovery and repair. In this case, the adequate biomarker or group of biomarkers might trigger interventions that are likely to benefit the patient. This may be especially true at the earliest stages of stress and injury when it may be possible to prevent further damage and preserve remaining kidney function. Removing potentially injurious exposures such as nephrotoxic drugs or providing protective measures such as careful fluid management, the treating physician may offer the patient the best option for AKI prevention as well as instructions to avoid AKI to CKD progression due to maladaptive repair mechanisms [2].

There is a common consensus that a specific plan should be undertaken to fight AKI and its consequences. A strategic move of the scientific community to prevent, protect, diagnose and cure AKI is definitely needed not only to save many lives from the acute disorder, but also to avoid the evolution into CKD, either by reducing the level of injury or by facilitating healing and recovery of the damaged parenchyma.

These are good perspectives that have been hindered by the lack of reliable methods for early diagnosis of the injury and early identification of patients at risk.

Recently, the US Food and Drug Administration made an important step forward in the battle against AKI and its consequences. The FDA approved use of the NephroCheck test (Astute Medical, San Diego, CA, USA), a rapid test for the quantitative measurement of the cell cycle arrest biomarkers tissue inhibitor of metalloproteinase-2 (TIMP2) and insulin-like growth factor binding protein-7 (IGFBP7) [5]. The combination of the two biomarkers ([TIMP2]-[IGFBP7]) measured by the test seems to be highly predictive of which patients will develop moderate to severe AKI in the next 12–24 h.

Early work in the international multicentre Sapphire study of 728 critically ill patients showed that elevation of the combination of biomarkers measured by the NephroCheck test is specific to AKI (i.e. not caused by other comorbidities such as sepsis or CKD) and provides a strong signal or ‘renal alarm’ to identify when a patient is at imminent risk of developing AKI [6]. These urinary biomarkers are believed to be elevated in response to renal tubule cell stress or early injury associated with the types of exposures known to cause AKI. A primary clinical cut-off value (0.3) for the combination of the two biomarkers was derived from the Sapphire study data and verified in a new cohort of 153 critically ill patients (Opal study) [7]. This cut-off value was selected to have high sensitivity for the primary endpoint of moderate to severe AKI in the next 12 h, with the intent to be used in routine clinical practice to identify patients at high risk for AKI who thus are candidates for kidney-sparing management strategies such as those outlined in the Kidney Disease: Improving Global Outcomes guideline for high-risk patients [2]. A second, high-specificity cut-off value (2.0) was selected and verified to identify the subgroup of patients who are at the highest risk of AKI and who therefore might be appropriate for more active interventions. Both cut-off values (0.3 and 2.0) were subsequently validated in a 23 site study of 408 critically ill patients in the USA (Topaz study) using clinical adjudication to determine the primary endpoint of moderate to severe AKI [8].

The NephroCheck test quantitatively measures the combination of the two cell cycle arrest biomarkers ([TIMP2]-[IGFBP7]) by both point-of-care techniques and other laboratory platforms, thus expanding the availability of the test worldwide [9].

According to a recent publication from the Acute Dialysis Quality Initiative Consensus Group [10], there is a need for early identification of damage or risk of AKI, especially in those patients in which creatinine is still negative but biomarkers are positive. In this sense, NephroCheck may be used alone or in combination with other biomarkers of AKI, as a discriminating test to alert physicians. All these considerations assume that putting the diagnostic clock ahead by 12–24 h compared with the clinical clock can make a difference. We are convinced that this is the case. Early diagnosis or assessment of the risk of injury may not only contribute to identification of the cause of AKI, and hopefully mitigate its effects, but also may help to identify patients in which, due to high susceptibility, even a small exposure may cause severe injury. Even a subclinical (creatinine-negative) injury, which may appear to be negligible, can produce significant parenchymal damage [11]. This may be underestimated due to the presence of a significant renal functional reserve in the kidney and the absence of clinical signs and symptoms [12]. The injury, however, reduces the functioning renal mass and produces a progressive increase in kidney frailty with a remarkable susceptibility to future injuries. This process may be the gateway to CKD.

We must therefore use all the tools we have to raise the level of patient care and escalate the battle against AKI. A reliable, validated and widely available test with a specific cut-off threshold has been requested by clinicians for a long time. A simple urinary biomarker test to screen critically ill patients for the risk of AKI is something that is likely to be a useful new weapon in the battle against AKI. Thus the FDA has taken an important step to provide us with a new tool that is an early alert of which patients are at imminent risk. We...
should take the next step by using this new tool to help us improve the care of our patients.

The new perspective today is that molecules expressed in the process of an injury may be seen as biomarkers of the event but also as a defensive mechanism against the very same event. In the first case (called the dark side by the authors of the paper [13]), cell cycle arrest biomarkers can be identified as molecules that are involved in the pathogenetic mechanisms of the injury. In the second case (the light side), since these molecules seem to protect the tubular cells from progressive damage perpetuated by damaged cell division and multiplication, the protective effect appears evident and molecular detection of the biomarkers may alert the clinician in the very early phase of the process. Furthermore, such molecules could have the function to promote healing and recovery, and their behaviour may become the mirror of a complete, partial or even maladaptive recovery. These molecules could even be considered as therapeutic targets to be antagonized or in some cases supported with synergistic actions or drugs to favour recovery. The biomarker in such circumstances may become not only theragnostic, but it could be considered as a therapeutic molecule to be used in the right time window of the process of injury and recovery.

For these reasons, Kellum et al., in this issue of NDT [13], highlight the possible role of biomarkers as effectors of the dark side of the force or as potential allies in the process of protection and recovery, showing finally the light at the end of the tunnel.

CONFLICT OF INTEREST STATEMENT

C.R. has received speaker honoraria from Astute medical, GE, Asahi Medical, Nipro, FMC, Toray, Biporto, Alere.


REFERENCES


Received for publication: 7.8.2015; Accepted in revised form: 8.8.2015