Biomarkers of renal disease

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The National Institutes of Health (NIH) Biomarkers Working Group has defined a biological marker (biomarker) as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".

Kidney diseases like acute kidney injury (AKI), chronic kidney disease (CKD), diabetic nephropathy, glomerular disease, cardiorenal syndrome, renal cancer and pre-eclampsia have a high morbidity. Measurement of biomarkers in the blood or urine that detect patients at risk of kidney diseases, or that detect kidney diseases in the earliest stage, may ultimately result in preventive, earlier or more effective treatments for kidney diseases.

AKI occurs in 9% of hospitalised patients and > 35% of critically ill patients. Traditional biomarkers for AKI are serum creatinine, urea and urine output. Serum creatinine, traditionally used in almost all definitions of AKI, is a suboptimal marker following injury. Human neutrophil gelatinase-associated lipocalin (NGAL) is one of the earliest markers in the kidney after ischaemic or nephrotoxic injury and may be detected in the blood and urine of humans with AKI. NGAL values may be affected by pre-existing renal disease and systemic and urinary tract infections.

Cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with CKD. In an ICU setting, a 50% increase in serum cystatin C predicted AKI one to two days before the rise in serum creatinine. NGAL is more sensitive than cystatin C at earlier time points of AKI and both predicted AKI at 12 hours.

Kidney injury molecule-1 (KIM-1) is detectable in the urine after ischaemic or nephrotoxic insults to proximal tubular cells and is highly specific for ischaemic AKI.

N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal brush border enzyme found in proximal tubular cells. NAG levels have been elevated in acute and chronic kidney disease, diabetic nephropathy and hypertensive patients with heart failure.

Liver-type fatty acid binding protein (L-FABP) shows promise as an early, accurate biomarker of AKI.

Interleukin-18 (IL-18), a pro-inflammatory cytokine, has been detected in the urine after acute ischaemic proximal tubular damage.

There is a paucity of sensitive and specific biomarkers for the early prediction of CKD progression. The recent application of innovative technologies such as functional genomics, proteomics, and biofluid profiling has uncovered several new candidates that are emerging as predictive biomarkers of CKD. The most promising among these include urinary proteins such as NGAL, KIM-1, and liver-type fatty acid binding protein. In addition, an improved understanding of the complex pathophysiologic processes underlying CKD progression has also provided discriminatory biomarkers of CKD progression that are being actively evaluated. Candidates included in this category are plasma proteins such as asymmetric dimethylarginine, adiponectin, apolipoprotein A-IV, fibroblast growth factor 23, NGAL, and the natriuretic peptides, as well as urinary NAG.

A recent study showed that the biomarkers homocysteine and aldosterone were significantly

associated with chronic kidney disease incidence, while log-transformed aldosterone, B-type natriuretic peptide and homocysteine were significantly associated with incident microalbuminuria.

Currently, none of these are ready for routine clinical use. Additional large, multi-centre prospective studies are needed to validate the biomarkers, identify thresholds and cut-offs for prediction of CKD progression and adverse events, assess the effects of confounding variables, and establish the ideal assays.

Conclusion

Novel renal biomarkers can be used to evaluate kidney function in a variety of clinical settings; NGAL, L-FABP and cystatin C have superior sensitivity and detect AKI earlier than serum creatinine, enhancing the ability to demonstrate the benefit of kidney-protective strategies.