Institutionen för Fysiologi och Farmakologi

Biomarkers of Acute Kidney Injury

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Nanna Svartz föreläsningssal, Karolinska Universitetssjukhuset Solna.

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ABSTRACT

Acute kidney injury (AKI) is a common and potentially fatal complication in critically ill patients. The diagnosis relies on functional markers of decreased glomerular filtration rate (GFR) such as creatinine. Unfortunately, a rise in plasma creatinine lags behind the early structural changes that occur in response to various renal insults. Future treatment of AKI will most certainly be based on early biomarkers of structural damage. In addition, better real-time measures of GFR are needed to be able to monitor the course of the disease. Cystatin C outperforms creatinine as a marker of GFR in stable patients and human neutrophil lipocalin/neutrophil gelatinase-associated lipocalin (HNL/NGAL) has emerged as an early biomarker of AKI since it is readily synthesized by tubular cells following kidney damage. However, HNL/NGAL is also released by neutrophils in response to bacterial infections. Consequently, sepsis may affect HNL/NGAL concentrations in plasma and urine.

The aim of this thesis was to investigate the ability of HNL/NGAL and cystatin C to predict AKI and/or mortality in critically ill patients as well as to assess the impact of sepsis on HNL/NGAL and cystatin C levels in plasma and urine. In addition, we wanted to study the ability of two enzyme-linked immunosorbent assays (ELISAs) to detect HNL/NGAL released in urine from kidney epithelial cells and neutrophils, respectively, during the development of AKI.

Cystatin C predicted long-term mortality independently of AKI severity. Even in patients without AKI, elevated cystatin C was associated with increased mortality. During the first week in the intensive care unit cystatin C gradually increased, in patients both with and without AKI. This increase was similar in septic and non-septic patients. Cystatin C predicted sustained AKI, worsening AKI or death. HNL/NGAL in plasma was not predictive of AKI in patients with septic shock since sepsis *per se* increased plasma levels of HNL/NGAL. Urinary HNL/NGAL was less affected by sepsis and performed well as an AKI predictor. In combination, our two ELISAs effectively distinguished monomeric HNL/NGAL, released from kidney tubular cells, from dimeric HNL/NGAL, mainly released by activated neutrophils, during the development of AKI.

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