URINARY LEVELS OF KIM-1 AND NGAL DO NOT CORRELATE WITH THE EXTENSION OF RENAL PARENCHYMAL DAMAGE

Sancho-Martínez SM [1,2,3] , Prieto-García L [1,2,3] , Blanco-Gozalo V [1,2,3] , Quiros-Luis Y [1,2,3], López-Novoa JM [1,2,3] , López-Hernández FJ [1,2,3]

[1]Translational Research on Renal and Cardiovascular Diseases (TRECARD), Department of Physiology and Pharmacology, University of Salamanca, Salamanca, Spain.[2]Instituto de Estudios de Ciencias de la Salud de Castilla y León (IECSCYL), Research Unit, University Hospital of Salamanca, Salamanca, Spain. [3]Salamanca Institute for Biomedical Research (IBSAL), University Hospital of Salamanca, Salamanca, Spain.

Introduction

Internationally recognized acute kidney injury (AKI) stratification scales (i.e. RIFLE, AKIN, KDIGO) are based on the plasma levels of creatinine, a late and indirect proxy of glomerular filtration rate. However, extensive renal damage must occur before plasma creatinine becomes altered, and even substantial damage can run without elevations in this parameter. This gave recently rise to the concept of "sub-clinical AKI", which has been linked to adverse clinical outcomes. A new generation of biomarkers has arisen in the last two decades, whose level in different bodily samples (including blood and urine) become elevated in association with renal damage, independently from, and even in the absence of, creatinine levels. Two of these markers have gained special attention in the field of AKI, namely neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). Although their expression is increased in damaged kidneys, no relation has been stablished between the degree of damage and their presence in biological samples.

Aims

In this study we aimed at studying the relation between renal damage and urinary levels of NGAL and KIM-1.

Methods/ experimental design

Different forms of AKI were induced in Wistar rats, including nephrotoxic AKI (cisplatin, gentamicin, uranyl nitrate and others), ischemic AKI (unilateral nephrectomy plus temporary renal artery clamping in the remaining kidney), drug-induced pre-renal AKI. Untreated rats were used as control. Renal function was monitored through plasma creatinine and urea, and proteinuria. At necropsy, renal specimens were processed for histological studies. Hematoxylin-eosin- stained renal slices were evaluated with a damage score. The urinary level of NGAL and KIM-1 was measured by Western blot. Plots of total, cortical and corticomedullary damage score marks versus biomarker levels were obtained, and correlation and regression analysis performed with all data irrespectively of the cause of AKI.

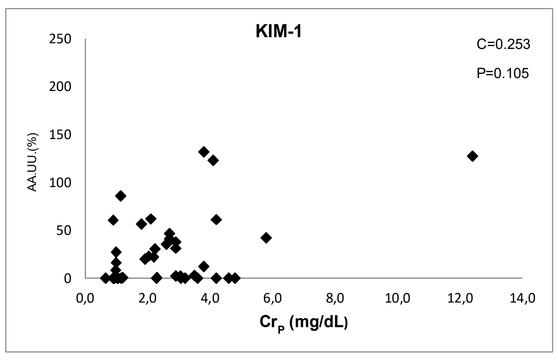
Results

No statistical relationship was found between any histological scoring and the level of any of the two biomarkers, nor on histological damage and plasma creatinine levels. Spearman analysis reveals low p values for all correlations tested.

Results

Plasma Creatinine groups (Crp mg/dL)	
1-1.5	Low damage
1.5-3.5	Moderate damage
> 3.5	High damage

n=42



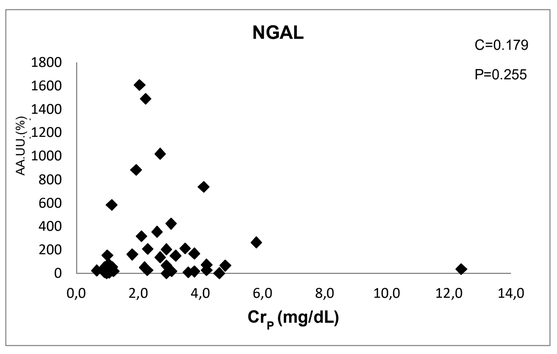


Figure 1: Representation of the functional damage comparison (based on the Cr_p value, mg / dL) and the level of excreted biomarker. Correlation analysis of Spearman.P: p-value, C: correlation coefficient. A value of P> 0.05 indicates absence of correlation between the pairs of variables compared. A value of P <0.05 and positive C indicate that as one of the variables increases, the other one also does it and, conversely if it is negative.

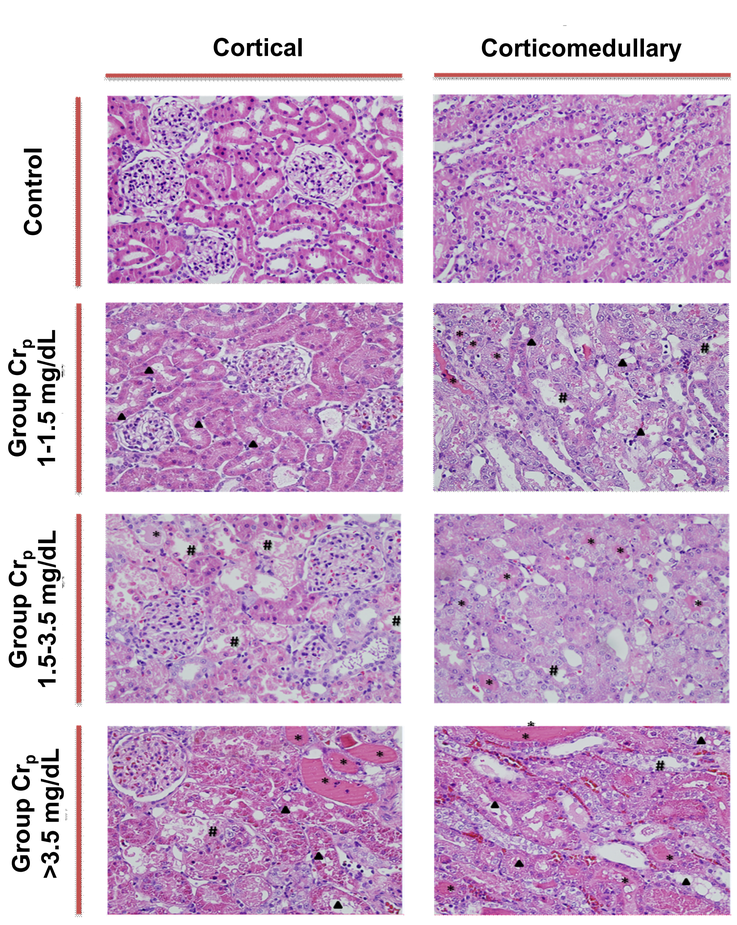


Figure 2: Representative images (original x200 magnification) of renal sections stained with hematoxylin and eosin from kidneys of animals of each of the three plasma creatinine (Cr_p) ranges analyzed. The * symbolize hyaline cylinders or casts, the triangles indicate phenomena of vacuolization, the # represent epithelialization and tubular necrosis.

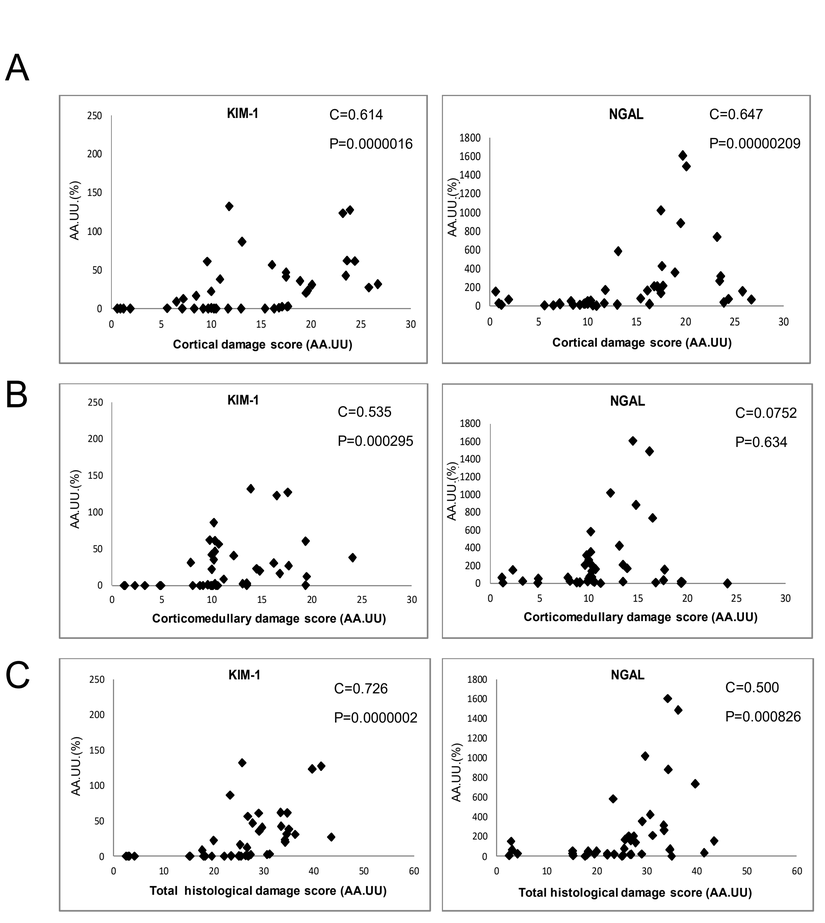


Figure 3: Comparative representation of cortical (A), corticomedullary (B) and total (C) histological damage and level of excreted biomarker (KIM-1 and NGAL). Correlation analysis of Spearman.P: p-value, C: correlation coefficient. A value of P> 0.05 indicates absence of correlation between the pairs of variables compared. A value of P <0.05 and positive C indicate that as one of the variables increases, the other one also does it and, conversely if it is negative.

Conclusions

Our results demonstrate that, in rats, neither KIM-1 nor NGAL inform in absolute terms on the underlying degree of renal damage. More research is needed to unravel the true pathophysiological meaning of each biomarker in each biological sample to reach a more accurate and personalised diagnosis.

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