Novel biomarkers in acute kidney injury: the role of L-FABP, CYR61, TIMP-2, IGFBP-7, PENK e KIM-1 in the diagnosis of kidney dysfunction etiology and their predictive role of structural renal damage severity

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Background: Acute kidney injury (AKI) is a very common life-threatening disease. Early diagnosis is the cornerstone for limiting the progression and chronicity of renal damage and reducing mortality. Estimating the glomerular flow velocity is the most used method to evaluate renal function. However, detecting new circulating molecules has taken hold for the early identification of kidney damage. To investigate the correlation between the urinary and serum biomarker concentrations and renal dysfunction, we studied a cohort of patients with AKI, accounting for aetiology. **Aims**: Our study aimed to find an association between some new circulating markers of renal injury and the pathogenic mechanism of acute kidney failure. In particular, we have evaluated the possible association between the urinary and serum concentrations of LFABP, CYR61, TIMP2, IGFBP7, PENK, and KIM-1 and AKI's prerenal or intrinsic pathogenesis. The secondary aims of the study were (i) evaluating the possible association between the urinary or serum concentrations of the markers with the severity of the acute kidney injury by the estimation of the variation between the serum creatinine at the admission compared with the basal values reported on the previous documentation exhibited; (ii) identifying the prognostic role of these markers and evaluating their association with the range of variation of the creatinine at discharge versus the values at admission.

Methods: In this cross-sectional, observational trial, 57 patients with acute kidney disease were consecutively enrolled and underwent a complete medical history to evaluate comorbidities, physical examination, and routine blood tests after eight hours of fasting; urinary and serum concentrations L-FABP, CYR61, TIMP-2, IGFBP-7, and PENK E KIM-1 were obtained in all patients.

Results: Urinary TIMP2, NGAL, and IGFBP7 and serum PENK values were higher in patients with AKI compared with the control group, with statistical significance. Moreover, higher concentrations of FABP1, Cyr61, TIMP-2, NGAL, IGFB7, and TIMP-2 X IGFBP-7 were found in patients with renal AKI compared with prerenal aetiology. A significant association between the urinary values of FABP1 and TIMP-2 and the serum concentrations of KIM-1 (p= 0,0001) with the variation of the creatinine values from the baseline to the values at the enrollment was found. Furthermore, a statistically significant association was found between KIM-1 and the creatinine variation at the discharge compared with the admission values.

Discussion: In this trial, we evaluated the serum and urinary concentrations of some novel biomarkers of acute kidney injury in a cohort of 57 patients diagnosed with acute renal failure, divided on the aetiology. With the primary aim of finding an association between these markers and the aetiology of the kidney injury, we demonstrated a statistically significant association between the concentrations of FABP1, Cyr61, TIMP-2, NGAL, IGFB7, and TIMP-2 X IGFBP-7 and the intrinsic aetiology of the AKI. Evaluating these "early diagnostic" biomarkers could help identify the underlying physiopathologic mechanism of the renal injury: considering the role of IGFBP-7 and TIMP2 in the cellular cycle and, in particular, in the mechanisms of cellular death, it is clear how the expression of these biomarkers is increased after a direct injury to the renal cells rather than prerenal injury: the levels of IGFBP7 persisted statistically associated with the AKI's aetiology after the multinomial regression, as not affected by other variables. Furthermore, our study has found an association between some of these biomarkers and creatinine variations. In particular, urinary FABP1, TIMP2, and serum KIM-1 levels were associated with a higher variation between the creatinine values at admission compared with the basal values, supporting a possible role of these proteins in defining the severity of renal injury. Moreover, KIM-1 concentrations were proportionally associated with the change of the creatinine values during the hospitalization, with a higher KIM-1 value as much as a higher reduction of the creatinine at recovery compared with admission: we confirm the protective role of KIM-1 in the worsening of renal dysfunction, but the constitutive expression of this protein on the tubule results in gradual fibrosis and progression towards chronic nephropathy. Considering the protective role of KIM-1, the increased values of KIM-1 may be related to a higher probability of recovery from renal dysfunction. Finally, in our study, we confirm the diagnostic role of some of these molecules. In particular, we have found that urinary values of TIMP2, NGAL, and IGFB7 and serum concentrations of PENK were statistically higher in patients with AKI compared to controls. Our study provides further evidence concerning the possible use of these novel biomarkers of AKI in clinical practice. Given their diagnostic and predictive role, these molecules could be used to identify the population at risk for the development of AKI and to identify renal injury early, even before the increase in serum creatinine or cystatin C values.