Serum matrix metalloproteinases MMP-2 and MMP-9 and tissue inhibitors of metalloproteinases TIMP-1 and TIMP-2 in patients with acute kidney injury

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Introduction:

Acute kidney injury (AKI) is a common renal disease with a prevalence of 10 to 30% in patients in critical care units. The course of the illness is highly variable, ranging from a transient disease associated with full recovery of renal function to a disease requiring dialysis and intensive care management. Matrix metalloproteinases (MMP) are members of the metzincin superfamily of zinc-based proteinases. MMPs mediate both degradation of extracellular matrix components and cell proliferation and facilitate leukocyte function cells. Matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs) play important roles in the pathophysiology of renal diseases. Connections with matrix accumulation, inflammation, stress, or endothelial dysfunction are probable. However, their clinical significance in acute kidney injury (AKI) is unknown.

Aim:

To assess whether serum levels of MMPs, TIMPs are changed in AKI patients, we measured serum levels of MMP-2, MMP-9, TIMP-1, and TIMP-2 in acute kidney injury and compared these to predialysis chronic kidney disease and healthy control subjects.

Methods:

The studied groups were categorized as follows: 41 patients with AKI at the inception of renal replacement therapy [mean age 58 ± 17 years, 23 M, 18 F], 29 patients starting dialysis defined as CKD 5 [mean age 57 ± 12 years, 17 M, 12 F] , and 10 healthy controls[mean age 50 ± 5 years, 6 M, 4 F].

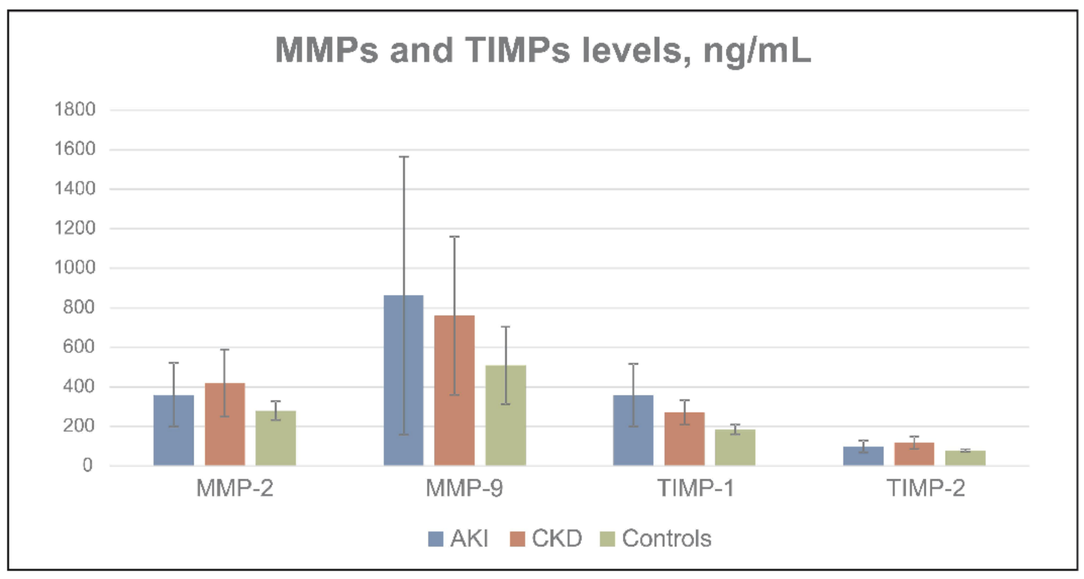
MMP-2, MMP-9, TIMP-1, TIMP-2 were assessed using enzyme linked immunosorbent assay (ELISA, R & D Systems). Results are expressed in nanograms per millilitre.

Routine biochemical parameters were measured using standard methods.

Statistics: Statistical analyses were performed using Statistics Toolbox™ MATLAB® software (The MathWorks™, Inc., Natick, Massachusetts, USA) - t-tests, ANOVA, and Spearmen correlation test was used for continuous variables. All results were considered statistically significant at $p < 0.05$.

Results:

Levels of MMP-2, MMP-9, TIMP-1, TIMP-2 in patients with acute kidney injury, chronic kidney disease stage 5, and controls



Parameter	AKI	CKD	Controls	p (t-test)
MMP-2 (ng/mL)	360±161	420±170	279±47	0.008 (AKI vs cont.) 0.001 (CKD vs cont.)
MMP-9 (ng/mL)	862±703	760±400	508±195	0.007 (AKI vs cont.) 0.01 (CKD vs cont.)
TIMP-1 (ng/mL)	358±158	271±62	185±24	< 0.001 (AKI vs cont.) 0.005 (AKI vs CKD) < 0.001 (CKD vs cont.)
TIMP-2 (ng/mL)	99±30	117±31	79±6	< 0.001 (AKI vs cont) 0.02 (AKI vs CKD) < 0.001 (CKD vs cont)

Compared with controls, the MMP-2, MMP-9 levels were higher in AKI patients. TIMP-1 levels were elevated in AKI in comparison with CKD 5 and controls. TIMP-2 concentrations were higher in AKI versus controls, but were lower compared with CKD 5.

In AKI group, MMP-2 levels were correlated with TIMP-2 ($r = 0.8$; $p = 0.0001$), proteinuria ($r = 0.4$; $p = 0.004$), and were inversely correlated with MMP-9 ($r = -0.4$; $p = 0.001$), and orosomucoid ($r = -0.36$; $p = 0.02$).

MMP-9 positively correlated with number of leucocytes ($r = 0.4$; $p = 0.01$), and inversely with TIMP-2 ($r = -0.3$; $p = 0.03$), proteinuria ($r = -0.3$; $p = 0.04$).

TIMP-1 correlated with C reactive protein ($r = 0.6$, $p = 0.0001$), and negatively with prealbumin ($r = -0.6$, $p = 0.0001$), glomerular filtration rate ($r = -0.4$, $p = 0.001$).

TIMP-2 correlated with proteinuria ($r = 0.5$; $p = 0.001$) and negatively correlated with orosomucoid ($r = -0.5$, $p = 0.0001$).

Conclusions:

These data indicate that circulating MMP-2, MMP-9, TIMP-1 and TIMP-2 are increased in patients with acute kidney injury. The value of circulating TIMP-1 and TIMP-2 may be useful for differentiating between AKI and CKD5. Future studies may delineate whether the above studied biomarkers are also markers of disease activity and severity as well as predictors of outcome in AKI.

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