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Detection of chronic allograft nephropathy (CAN) other than calcineurin inhibitor toxicity by serum and urine biomarkers in stable kidney transplant patients

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Background

In kidney transplantation, biomarkers have been proposed to detecting acute kidney injury [1, 2] and even as tools for avoiding invasive biopsy of kidneys [3]. No experience is published with stable kidney transplant patients.

Patients and Methods

We prospectively investigated all patients with stable kidney transplant function in our outpatient office. Patients with transplant glomerulopathy and antibody mediated rejection were excluded.

Standard immunosuppression was prednisolone and mycophenolate. In addition, 32 patients had calcineurin inhibitors (CNIs) either cyclosporine (n = 11), or tacrolimus (n = 21), and 7 cases were on rapamycin due to creeping creatinine or skin carcinoma.

Between July 2011 and March 2012 a set of 8 biomarkers were simultaneously measured in urine and serum. Commercial assays were used for urinary KIM-1 (normal < 5.3 ng/ml), MCP-1 (normal < 410 pg/ml), Cyr-61, NGAL (normal < 350 ng/ml), L-FABP, Fetuin-A , IL-18 and RBP4 (normal < 0.5 mg/l) and for serum KIM-1, MCP-1, Cyr-61, L-FABP , Fetuin-A, NGAL (normal < 400 ng/ml), and RBP4 (normal < 75 mg/l).

Urinary excretion of protein and biomarkers was standardized for differences in urine volume by the urinary creatinine ratio. Sensitivity and specificity were analyzed by the area under the receiver-operating characteristic curve ROC.

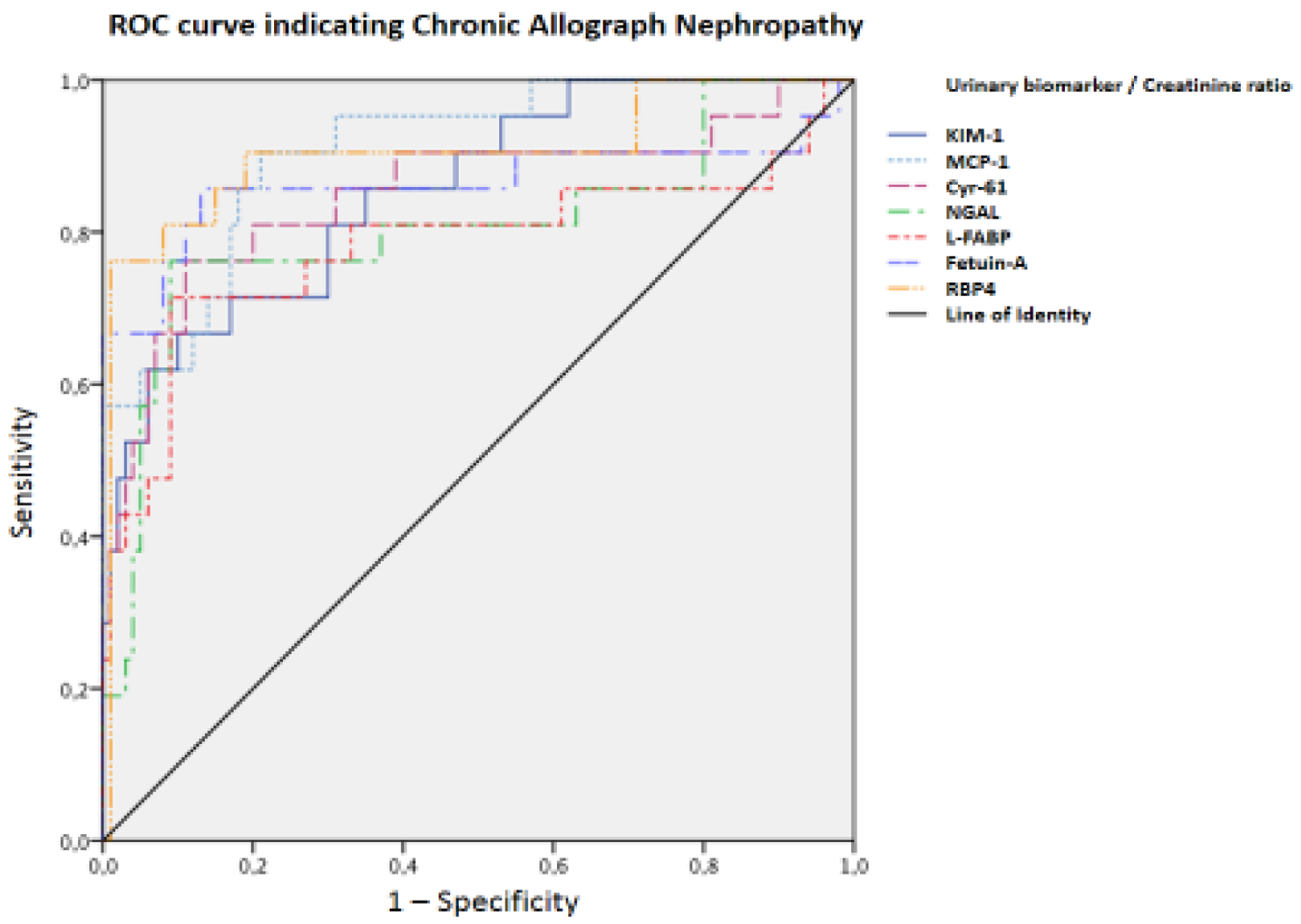

Figure 1 Receiver operating characteristic ROC curves for 7 investigated urinary biomarkers in stable kidney transplant patients. The ROC area was significant with $p < 0.01$ for all 7 biomarkers indicating chronic allograft nephropathy.

Results

A total of 39 patients were enrolled, 11 women and 28 men with a mean age of 55 years (SD 14). Time since transplantation was 5.3 years (SD 5.8). Mean serum creatinine was 192 mcmol/l (SD 124) with estimated GFR of 40 ml/min (SD 16) and urinary protein excretion of 1.0 g/day (SD 0.9). All biomarkers in urine and serum increased with kidney dysfunction and were significantly correlated to the serum creatinine and to the urinary protein to creatinine ratio. The mean eGFR was significantly worse in patients on rapamycin as compared to those on CNIs (28 vs 42 ml/min, $p < 0.01$). Contrasting to our expectations but in agreement with the skeptics in literature [4], the area under the ROC curve was not indicative for CNI use and < 0.37 for all urinary biomarkers while < 0.33 for all serum biomarkers.

However, chronic allograft nephropathy (CAN) with interstitial fibrosis and tubular atrophy (IFTA) was found by transplant biopsy of 7 patients. The area under the Receiver Operating Characteristc curve indicating CAN was significant and highest with an ROC area of 0.91 for urinary MCP-1 (95%CI: 0.84-0.97, $p < 0.01$) and 0.91 for urinary RBP4 (95%CI: 0.81-0.99, $p < 0.01$). But ROC was also significant for serum KIM-1 with 0.84 (95%CI: 0.76-0.92, $p < 0.01$) and serum NGAL with 0.77, respectively (95%CI: 0.64-0.89, $p < 0.01$).

Conclusion

- Urinary and serum biomarkers were elevated in patients with kidney transplant dysfunction.
- Biomarkers did not allow to distinguish CNI toxicity.
- Urinary MCP-1 and RBP4 might help to early diagnose CAN with interstitial fibrosis and tubular atrophy.

Disclosure

The authors declare no conflict of interest.

Literature

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