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## The Potential of Non-Invasive Biochemical Testing Late Post-transplant in Prediction of Declining Kidney Allograft Function

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### Summary

Identification of kidney transplant recipients at risk for allograft failure late posttransplant is an unmet demand. Our aim was to determine the capacity of serum beta-2-microglobulin (2MG), serum and urinary interleukins (IL-2, IL-10 and IL-8) and enzymes ( $\gamma$ -glutamyl transpeptidase, alkaline phosphatase, aspartate aminotransferase [ALT], and N-acetyl- $\beta$ -D-hexosaminidase [NAG]) in the late posttransplant period to predict a deterioration of kidney allograft function. Several non-invasive biomarkers predicted certain (serum 2MG, urinary IL-2 and AST), and rapid (urinary IL-2 and AST) drop of glomerular filtration rate over two years. We are standing on underestimated potential of non-invasive biochemical testing in kidney transplant setting.

### Editorial

Kidney transplantation is a treatment of choice among renal replacement therapies [1]. However, despite excellent 1-year graft survival, many kidney transplant recipients present with chronic allograft dysfunction; thus, the preservation of graft function late posttransplant has become the main task [1]. Risk stratification for deterioration of kidney graft function using non-invasive tests is a prerequisite for individualized care without side effects of invasive procedures [2]. Several recent papers have examined the role of serum creatinine and glomerular filtration rate (GFR) or slope of changes in GFR as predictors of graft survival [2,3].

Additional non-invasive surrogate biomarkers of decline in kidney graft function late posttransplant can allow better understand mechanisms of disease, detect early injuries to the graft, perform differential diagnoses, and stratify the risk of failure to guide therapy [4]. Several classes of biomarkers, including enzymes, interleukins and low-molecular weight proteins showed diagnostic and prognostic significance in diseases of native and transplanted kidneys [5-8].

Recently we have been testing hypothesis that serum 2-microglobulin (2MG), serum and urinary interleukins (IL-2, IL-8 and IL-10) and enzymes ( $\gamma$ -glutamyl transpeptidase, alanine aminotransferase [ALT], alkaline phosphatase, aspartate aminotransferase [AST], and N-acetyl- $\beta$ -D-hexosaminidase [NAG]) at different times (from 1 to 17 years) of late period after kidney transplantation could predict GFR and different patterns of changes in GFR over a period of two years.

We demonstrated the association between serum levels of 2MG and a forthcoming decline in GFR [5]. A single measurement value of serum 2MG was independently associated with lower GFR at enrollment and after 1 and 2 years, as well as with the value of negative slope in GFR and the certain ( $\geq 25\%$  from baseline) drop of GFR. Notably, the negative slope of GFR did not depend on GFR at baseline. The increase of serum 2MG may indicate glomerular diseases, which has recently been recognized as one of the main causes of allograft dysfunction. Meanwhile, only modest correlation between serum 2MG and creatinine suggests that increased 2MG synthesis (ex. due to PTLD, rejection, CMV-infection or nephrotoxicity) might be another reason for the increase of concentration. Thus, high serum 2MG can encourage and guide further diagnostics. Regarding prognostic accuracy of 2MG-testing, we observed that when combined with proteinuria at baseline and experienced acute rejection, serum 2MG demonstrated excellent accuracy in predicting certain decline of GFR after one year. Together with time after transplantation serum 2MG demonstrated good accuracy in forecasting the certain decline of GFR after two years. Wherein, 2MG ensures absolutely important data for the forecasting model. Association of increased 2MG in serum with both low GFR and drop of GFR from baseline suggests that serum 2MG can be a link between low intercept and negative slope of GFR and can be a surrogate for the progression of kidney graft dysfunction.

We also observed that higher urinary levels of AST predicted drop in GFR, irrespective of kidney graft function at baseline [6]. The activity AST in urine negatively correlated with slope values of GFR, and predicted certain drop of GFR after 1 and 2

years of follow up and rapid ( $>5$  mL/min) decline in GFR over 2 years with fair accuracy. Together with time after transplant, urinary AST exhibited good accuracy for predicting certain decline in graft function after 2 years. The mitochondria and cytosol of epithelial cells predominantly of the distal tubules of the nephron are the main source of urinary AST. Therefore, high activity of urinary AST at enrollment could have been a sign of ongoing serious injury to the tubular epithelial cells. Highlighted associations between activities of AST, ALT, NAG, and proteinuria confirm this hypothesis. Our observations are also in line with reports that urinary enzymes more likely reflect the activity of pathologic process in the kidney graft, rather than its function. Our results indicate that high urinary excretion of AST, even under normal graft function, mirrors ongoing graft injury and should guide diagnostic biopsy. Thus, urinary AST represent one of those transplant biomarkers that measured during times of clinical quiescence can predict outcomes. Our results support the theory that progression of kidney allograft dysfunction can be explained only as a sequel of ongoing disease and injury in the graft [9]. AST appears to be better than other urinary enzymes for differentiating recipients who subsequently lose kidney transplant function from those who do not. The measurement of urinary AST is quick and accurate as well as commonly available and cost-effective colorimetric-based assay, which can be readily implemented in clinical laboratories. The enzymes activity in the serum did not correlate with the allograft function. Furthermore, no correlation was found between the activity of all enzymes in the serum and urine, which confirms the literature data on the renal origin of the isoforms of the enzymes in the urine.

We also observed the association between higher urinary levels of IL-2 with declining kidney allograft function (unpublished data). Higher urinary IL-2 concentrations were not only associated with lower GFR at baseline and during two years of follow-up, but also independently predicted a certain drop in GFR after one year of follow-up. With respect to discriminative characteristics the combination of time after transplantation and urinary IL-2 predicted rapid decline in GFR over 2 years with good accuracy. As higher urinary IL-2 concentrations are associated with lower GFR, higher serum creatinine and urea, and higher proteinuria at baseline, we believe that IL-2 plays role in the pathogenesis of late renal allograft dysfunction. Considering activated T-cells as the main source of IL-2 and a certain role of IL-2 in graft pathology we hypothesize that high urinary IL-2 reflects ongoing T-cell-dependent alloimmune response in late post-transplant period, which may lead to decline of GFR in the near future. Our results also indirectly support the feasibility of using anti-IL-2 therapy not only for the induction immunosuppressive therapy, but also for prevention and treatment of acute rejection in post-transplant period [10]. IL-2 provides an accurate and quick measurement by a commonly available cost-efficient ELISA, which can readily be implemented in clinical labs. Another interesting observation is the absence of correlation between different interleukins in serum, and between any interleukin in the serum and its counterpart in

urine. Altogether, our findings allow us to think that urinary interleukins have renal origin and should be regarded as more reliable markers of kidney allograft status.

In summary, we are standing on underestimated potential of non-invasive biochemical testing in kidney transplant setting. Relationship of high 2MG in serum as well as AST and IL-2 in urine with both low GFR and certain drop in GFR might have substantial clinical meaning, since these surrogates are related to suboptimal kidney graft survival [2,3]. Since there are a number of biomarkers that can help to change the approach to therapy, even if they are measured only in the late posttransplant period, we think that late posttransplant tests can provide useful information.

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