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Novel Biomarkers of Acute Kidney Injury in Patients After Hematopoietic Stem Cell and Kidney Transplantation

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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Summary

Acute kidney injury (AKI) and chronic kidney disease (CKD) are common and clinically significant complications following allogeneic hematopoietic stem cell transplantation (allo-HSCT) and solid organ transplantation, including kidney transplantation. Current diagnostic approaches rely primarily on serum creatinine measurements and estimated glomerular filtration rate (eGFR), which limits the early detection of kidney injury. Molecular biomarkers are increasingly recognized as promising tools for identifying subclinical kidney damage, predicting CKD progression, and facilitating personalized management of transplant recipients.

The aim of this dissertation was to evaluate the usefulness of selected biomarkers—proenkephalin A (PENK), uromodulin (UMOD), Dickkopf-3 (DKK3), and urinary retinol-binding protein 4 (RBP4)—in the detection and monitoring of kidney injury and chronic kidney disease in patients following allo-HSCT.

The dissertation is based on three original research articles and one case report. The clinical studies included a total of 80 patients after allo-HSCT and a group of healthy volunteers. The studies focused on the evaluation of selected urinary biomarkers of kidney injury as well as the prevalence of anemia and CKD in the investigated populations. The final publication was a case report emphasizing the importance of kidney biopsy as a diagnostic and prognostic tool in patients after allogeneic hematopoietic stem cell transplantation.

In the original study entitled *"One Novel Urinary Biomarker of Acute Kidney Injury in Patients After Allogeneic Hematopoietic Stem Cell Transplantation"*, urinary RBP4 concentrations were evaluated in patients following allo-HSCT. The results demonstrated that urinary RBP4 levels were significantly higher in transplant recipients than in healthy controls. Moreover, RBP4 concentrations were significantly elevated in patients with stage 3 CKD and showed a positive correlation with serum creatinine and a negative correlation with eGFR. These findings suggest that RBP4 may serve as a sensitive marker of early proximal tubular injury and facilitate the detection of subclinical kidney dysfunction before the development of overt renal failure.

In the original study *"Markers of Kidney Injury: Proenkephalin A and Uromodulin, but Not Dickkopf-3, Are Elevated in Patients After Hematopoietic Stem Cell Transplantation"*, urinary concentrations of PENK, DKK3, and UMOD were analyzed for the first time in patients after allo-HSCT. The study demonstrated significantly higher concentrations of all three biomarkers in transplant recipients compared with healthy controls. PENK showed a significant inverse

correlation with eGFR, supporting its potential role as a sensitive marker of declining glomerular filtration. Particularly noteworthy was the observation of higher PENK levels in patients with eGFR below 60 mL/min/1.73 m², suggesting its ability to identify individuals at risk of CKD progression before conventional laboratory abnormalities become apparent. Although DKK3 concentrations were elevated in the allo-HSCT group, no significant associations were observed between DKK3 and kidney function parameters, indicating limited utility of this biomarker in assessing renal impairment in this population despite its established role in renal fibrosis. Elevated urinary uromodulin levels further confirmed the presence of kidney injury in transplant recipients; however, no significant correlations were found between UMOD and either eGFR or serum creatinine.

The third original article, *"Anemia in Patients After Stem Cell Transplantation and in Kidney Transplant Recipients"*, evaluated the prevalence of anemia in transplant recipients. Among 156 patients after HSCT, anemia was diagnosed in 13% of women and 35% of men. Furthermore, more than half of the women with anemia and 17% of the men fulfilled the diagnostic criteria for CKD. The study demonstrated a significant association between anemia and impaired kidney function. As anemia is a well-established marker of advanced kidney disease, our findings further highlight its prognostic importance in patients following both hematopoietic stem cell transplantation and solid organ transplantation.

The final component of the dissertation is a case report entitled *"Kidney Failure in the Course of Focal Segmental Glomerulosclerosis in a Patient After Allo-HSCT—A Case Study and Review of the Literature"*. The report describes a patient with chronic graft-versus-host disease (cGvHD) who developed nephrotic syndrome secondary to focal segmental glomerulosclerosis (FSGS), ultimately progressing to end-stage kidney disease requiring renal replacement therapy. This case illustrates the complexity of nephrological complications following allo-HSCT and underscores the crucial role of kidney biopsy in establishing the diagnosis, assessing the extent of irreversible renal damage, and guiding therapeutic decision-making.

In conclusion, the findings of this dissertation indicate that traditional markers of kidney function, such as serum creatinine and eGFR, may not adequately reflect the early stages of kidney injury in patients after allogeneic hematopoietic stem cell transplantation. The implementation of novel biomarkers in clinical practice, particularly PENK and RBP4, may contribute to earlier diagnosis of post-transplant nephropathy and support the personalization

of nephroprotective strategies. Based on these results, further studies have been planned to evaluate additional biomarkers of acute kidney injury in transplant populations.