Streszczenie w języku angielskim

Proenkephalin in chronic kidney disease

Previous studies aiming to identify novel biomarkers of acute kidney injury (AKI) have highlighted the potential clinical utility of proenkephalin 119–159 (Proenkephalin, PENK) as a promising indicator of kidney function and a predictor of AKI. In various populations, such as patients with sepsis or acute heart failure, proenkephalin has demonstrated superior accuracy in the early detection of AKI compared to traditional markers of kidney function such as serum creatinine (SCr). Proenkephalin exhibits high affinity for delta opioid receptors, which were shown to have highest expression in the kidney. Although its exact role in the kidney remains unknown, it has been suggested that proenkephalin may promote natriuresis and diuresis, either via receptor binding or by inhibiting the release of antidiuretic hormone. Given its low molecular weight, proenkephalin is presumed to be freely filtered through the glomerulus. Also, no extrarenal elimination mechanism have been identified to date. Furthermore, unlike enkephalins, proenkephalin has a longer half-life and remains stable after collection, which makes it a promising surrogate marker of glomerular filtration rate (GFR).

Previous studies have shown a negative correlation between proenkephalin levels and GFR in patients with both stable kidney function and acute injury. Proenkephalin has been shown not only to improve the early AKI detection but also correlate with AKI severity. Moreover, in the AKI setting, high proenkephalin levels has been shown to predict adverse clinical outcomes, such as the need for kidney replacement therapy (KRT), persistent renal dysfunction or mortality. The rise of proenkephalin concentrations in the setting of kidney dysfunction might reflect impaired clearance, upregulation of proenkephalin production or a combination of both mechanisms.

While numerous studies have explored proenkephalins value as a functional and predictive biomarker in patients with preserved kidney function, limited data are available on its role in chronic kidney disease (CKD), especially in advanced stages. Given that patients with CKD are particularly susceptible to acute-on-chronic kidney injury AKI, validation of PENK in this high-risk group is essential. Moreover, it remains unclear how end-stage kidney disease (ESKD) and kidney replacement therapy influence PENK levels and whether this molecule is effectively cleared during dialysis.

This dissertation comprises a series of thematically consistent studies aimed at evaluating the diagnostic performance of proenkephalin as a biomarker of renal function in patients with CKD, including those with ESKD receiving dialysis therapy.

In the original research ("Proenkephalin Levels and Its Determinants in Patients with End-Stage Kidney Disease Treated with Hemodialysis and Peritoneal Dialysis") we evaluated proenkephalin concentrations for the first time in patients undergoing either hemodialysis or peritoneal dialysis. The study examined correlations between proenkephalin levels and selected clinical and biochemical parameters as well as analyzed how hemodialysis affects its serum concentrations. Notably, no association were found between proenkephalin and renal function indicators such as serum creatinine, urea, or residual urine output. Furthermore, proenkephalin levels were found to be significantly higher after hemodialysis than before, suggesting that the molecule may not be effectively removed across hemodialysis membranes. The rise in concentration may result from fluid removal during treatment which exceeds the elimination of the peptide itself. These findings were consistent with the observation that patients treated with low-flux dialyzers, which are less efficient in removing middle-molecular-weight moleculesm, had higher proenkephalin levels. Altogether, these results raise into question the reliability of proenkephalin as a functional biomarker in the setting of AKI, particularly in patients requiring dialysis, where continuous renal function monitoring is crucial.

In the review article ("Proenkephalin (PENK): a functional biomarker in chronic kidney diseases – hope or just a new bystander?"), we provide an overview of proenkephalin as a renal function biomarker and disscuss its potential role in detecting AKI in patients with CKD. Based on available data, the diagnostic value of proenkephalins seems to be reduced in subjects with CKD, especially regarding AKI prediction. The review also summarizes current evidence on proenkephalin in patients receiving kidney replacement therapy and highlights the need for further research, given the inconsistencies in data regarding its removal by dialysis.

In conclusion, the available data may undermine the usefulness of proenkephalin as a functional marker of kidney function in CKD and ESKD, especially in patients undergoing hemodialysis. Further studies are warranted to assess the utility of proenkephalin as an indicator of kidney dysfunction in various clinical populations, including patients receiving dialysis and those with comorbidities. Future research should also aim to determine the mechanisms of proenkephalin elimination via the kidneys and dialysis membranes.