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Urinary Metabolomics Reveals Guanidinoacetic Acid as a Predictor of eGFR Decline in Borderline Rejection After Kidney Transplantation

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Objectives : Borderline rejection (BDR) in kidney transplant (KT) recipients presents a clinical challenge due to the absence of standardized guidelines and uncertainty regarding long-term graft outcomes. Identifying biomarkers predictive of kidney function decline could improve risk stratification and guide treatment decisions in this population.
Methods : We analyzed 117 urine samples from 79 KT recipients undergoing protocol biopsy, profiling 61 metabolites, via in vitro diagnostic research nuclear magnetic resonance (IVDr NMR) spectroscopy. Among them, 51 had BDR and were classified based on ≥30% estimated glomerular filtration rate (eGFR) decline or graft failure during follow-up. Subgroups were compared with the no rejection (NR, n = 61) and T cell-mediated rejection (TCR, n = 5) groups. Ranked ANCOVA was performed to compare metabolic profiles across groups. Area under the curve (AUC) and survival analyses were also conducted to assess the predictive value of metabolites for kidney function decline.
Results : Guanidinoacetic acid (GAA) was identified as a predictive marker of eGFR decline in BDR subgroups, with significantly lower levels in the decline group than in the stable group ($p = 0.02$). While no significant difference was observed between eGFR stable and NR groups, GAA levels in decline group were significantly lower than in both the stable and NR groups. Incorporating GAA into multivariate models improved risk stratification for eGFR decline, increasing the AUC from 0.719 to 0.778. Survival analysis further demonstrated that lower GAA levels were associated with a higher risk of kidney function decline ($p < 0.001$). Additionally, in BDR patients who received steroid treatment, GAA levels showed an increasing trend post-treatment, though not statistically significant (fold change: 2.04, $p = 0.48$).
Conclusions : This study identifies GAA as a potential urinary biomarker for predicting eGFR decline in KT recipients with BDR. Further research is needed to explore GAA the role of GAA metabolism and its therapeutic potential.