学 位 論 文 の 要 旨

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学　位　論　文　名　From Cross-section to Prognosis: Risk Factors for Renal Function Deterioration in Primary Hyperparathyroidism

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論 文 内 容 の 要 旨

INTRODUCTION

Primary hyperparathyroidism (pHPT) is a common endocrine disorder caused by the autonomous and excessive secretion of parathyroid hormone (PTH), resulting in hypercalcemia, bone fragility, and kidney injury. Progression of chronic kidney disease (CKD) leads to end-stage kidney disease (ESKD) and increases the risk of cardiovascular disease and death. Patients with pHPT frequently develop renal complications; however, the factors associated with a decline in estimated glomerular filtration rate (eGFR) have not been fully investigated. This study aimed to identify the factors associated with reduced eGFR at diagnosis (cross-sectional analysis) and the determinants of longitudinal eGFR decline among patients with follow-up data (longitudinal analysis).

MATERIALS AND METHODS

Of 100 patients diagnosed with pHPT at Shimane University Hospital between 2012 and 2022, 89 were included. Eleven patients were excluded due to age under 40, medications affecting calcium metabolism, or baseline eGFR ≤30 mL/min/1.73 m². The study protocol was approved by the Research Ethics Committee of Shimane University. Diagnosis was based on elevated corrected serum calcium and non-suppressed intact PTH levels. The percent tubular reabsorption of phosphate (%TRP) was calculated using 24-hour urine samples. eGFR was calculated using coefficients modified for the Japanese population.

For the cross-sectional analysis (N=89), reduced renal function was defined as eGFR < 60 mL/min/1.73 m² at diagnosis. For the longitudinal analysis, the eGFR slope (mL/min/1.73 m² per year) was evaluated in 47 patients with follow-up exceeding 1 year. A rapid decline was

defined as an eGFR slope of a decrease of more than 3 mL/min/1.73 m² per year. Statistical analyses were performed using SPSS; multivariable logistic regression analysis was executed to adjust for clinical confounders.

RESULTS AND DISCUSSION

Cross-Sectional Analysis at Diagnosis

Compared with the normal renal function group (eGFR ≥ 60 mL/min/1.73 m^2, $N = 70$), the reduced renal function group (eGFR < 60 mL/min/1.73 m^2, $N = 19$) had higher age and uric acid levels, and lower diastolic blood pressure, daily urinary calcium excretion, and %TRP. Simple regression analysis showed that eGFR was negatively correlated with age and serum uric acid, and positively correlated with urinary pH, urinary calcium, urinary calcium-to-creatinine ratio, and %TRP. Multiple regression analysis showed that eGFR was positively correlated with %TRP ($r = 0.539$, $p < 0.001$) and U-pH ($r = 0.165$, $p = 0.045$). In logistic regression analysis using renal function decline as the dependent variable, a low %TRP was associated with reduced renal function.

Longitudinal Analysis of eGFR Slope

In the longitudinal cohort (N=47), the mean annual rate of eGFR decline was -2.7 ± 2.5 mL/min/1.73 m². Both simple and multiple regression analyses showed a significant positive correlation between eGFR and HbA1c levels. Patients with rapidly declining eGFR (N=21) had significantly higher baseline serum chloride and 25-hydroxyvitamin D concentrations and lower HbA1c concentrations compared to patients without rapidly declining eGFR (N=26). Logistic regression analysis showed that A high chloride level was associated with a faster decline in eGFR (OR 1.520). These results remained significant even after adjusting for age, sex, BMI, intact PTH, %TRP, HbA1c, DBP, urinary calcium, phosphorus, urine protein, PTX status, and 25(OH)D.

Discussion

In this study, cross-sectional analysis demonstrated that %TRP was associated with impaired renal function at the time of pHPT diagnosis. Furthermore, among patients with follow-up, higher serum chloride levels were associated with a faster annual decline in eGFR. These findings suggest that the %TRP and serum chloride levels at diagnosis are important factors associated with renal dysfunction in patients with pHPT.

Lower %TRP values were independently associated with reduced renal function at the time of pHPT diagnosis. Decreased phosphate reabsorption in pHPT is caused by the action of

PTH and FGF23 on the renal proximal tubules. Reduced phosphate reabsorption may diminish the glycolytic flux in proximal tubular cells, thereby increasing cellular vulnerability. Furthermore, increased urinary phosphate excretion has been implicated as a driver of renal damage, leading to calcium-phosphate crystal deposition within the renal tubules, tubular atrophy, and interstitial fibrosis. Therefore, a decrease in baseline %TRP may be a very useful marker for tubular dysfunction and ongoing renal impairment.

Longitudinally, serum chloride levels were significantly higher in the group with an annual eGFR decline of ≥3 mL/min/1.73 m² compared with the group with a decline of <3 mL/min/1.73 m². Hyperchloremia increases the NaCl load delivered to the macula densa and enhances tubuloglomerular feedback, leading to afferent arteriolar vasoconstriction. This findings suggests that elevated chloride levels contribute to renal injury by reducing glomerular perfusion, indicating that the pronounced effect of PTH on renal tubules in pHPT may contribute to future deterioration of renal function. This study has several limitations. First, the cross-sectional design precludes causal interpretation. Second, the study included only patients evaluated at Shimane University Hospital, resulting in a relatively small sample size. Finally, we did not measure some parameters, including FGF23 and renal tubular injury markers such as L-FABP and NGAL, and not all parameters were assessed in every subject.

CONCLUSION

Reduced eGFR at pHPT diagnosis was associated with lower %TRP, whereas a faster annual eGFR decline was associated with higher serum chloride levels.