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Plasma cyclo(His-Pro) levels can be used as potential biomarker of disease severity in Chronic Kidney Injury

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Objectives: Cyclic(His-Pro) (CHP) is an endogenous cyclic dipeptide that has antioxidative, anti-inflammatory effect via Nuclear factor erythroid 2-related factor (Nrf2) pathway. Endogenous CHP is distributed in the central nervous system (CNS), gastrointestinal tract, blood, semen and prostate in humans. The objective of study is to evaluate the effect of CHP in kidneys.

Methods: In this study, we performed analysis using plasma samples and kidney tissues of patients who were diagnosed chronic kidney disease. Plasma CHP concentrations were measured by using liquid chromatography with mass spectrometry/mass spectrometry (LC-MS/MS) And We performed immunohistochemistry staining of Nrf2, a pathway that activated by CHP. As in vitro model, primary cultured human tubular epithelial were induced apoptosis with TGFβ- and hydrogen peroxide (H_2O_2).

Results: Plasma CHP level and tissue expression of Nrf2 were associated with renal functions. Patients were divided into three groups: (CKD stage 1,2/ CKD stage 3/CKD stage 4,5) Significant differences of plasma CHP concentration and tissue expression of Nrf2 were observed between each group. Higher plasma CHP concentration was measured in samples of progressed CKD patient (0.77±0.30/ 1.43±0.75/ 2.48±1.2, ng/ml, $p<0.0001$). In contrast, tissue expression of Nrf2 decreased as the CKD progression (16.78±6.64/ 9.05±4.38/ 5.85±2.98, % Area, $p<0.0001$). In H_2O_2 induction model, CHP treated group displayed increased Nrf2 mRNA level (H_2O_2 Vs CHP treated group, $P=0.014$) and decreased apoptosis (H_2O_2 Vs CHP treated group, $P=0.0067$). In TGFβ induction model, CHP treatment is associated with decreased fibronectin (TGFβ vs CHP, 17.88±2.66 vs 5.57±2.12, fold, $P<0.0001$) and increased cell junctional marker, E-cadherin. (0.60±0.11 vs 1.82±0.20, fold, $P=0.0010$)

Conclusions: The plasma CHP concentration and tissue expression of Nrf2 reflects the kidney function. And exogenous CHP treatment showed protective effect on kidney cells. Considering these results, increasing endogenous plasma CHP following CKD progression may be compensatory response to enhance the Nrf2 pathway.