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당뇨병성 신증 초기에 칼슘뇨 배출에 있어서 α-Klotho의 역활 규명

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Decreased Renal α-Klotho Expression in Early Diabetic Nephropathy in db/db Mice and its Possible Role in Urinary Calcium Excretion

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Hypercalciuria is one of the early manifestations of diabetic nephropathy (DN). We explored the role of α-Klotho, a protein expressed predominantly in the distal tubules (DTs). α-Klotho is known to up-regulate transient receptor potential vanilloid type 5 (TRPV5) expression, involved in tubular calcium reabsorption. We used db/db mice, a type II diabetes mellitus (DM) model for type 2 DM model. We employed puromycin aminonucleoside (PAN)-induced nephrotic mice and db/m mice for control. PAN mice were used for nephrotic syndrome control and induced by injecting 150 mg/kg PAN intraperitoneally for every 2 weeks. Animals were sacrificed at the age of 15th week. At 15th week, db/db mice and PAN mice developed albuminuria (218±33 μg/day and 68±9 μg/day, respectively), while db/m mice were normoalbuminuric (14±3 μg/day). Urinary calcium excretion (UCa/UCr) significantly increased in db/db mice (0.91±0.09 mg/mg Cr), compared to PAN (0.30±0.02 mg/mg Cr) or db/m mice (0.29±0.03 mg/mg Cr). mRNA and protein expression levels of α-Klotho in the distal tubule were markedly decreased. Urinary klotho concentration (UKL/UCr) was significantly reduced in db/db mice (1.45±0.02 fM/mg Cr) compared to PAN (10.77±3.01 fM/mg Cr) or db/m mice (6.39±0.40 fM/mg Cr). By immunohistochemistry and immunofluorescence staining, we also confirmed reductions of renal α-Klotho, FGF receptor type 1 (FGFR1) and TRPV5 expressions in db/db mice. Thus, renal loss of α-Klotho may affect urinary calcium excretion via inhibition of TRPV5 expression in DTs in early diabetic nephropathy.

Key Words: 고칼슘뇨, α-Klotho, TRPV5
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