KSN SEOUL, KOREA 2023
April 27(Thu) - 30(Sun), 2023
Coex, Seoul, Korea

Abstract Type : Oral
Abstract Submission No. : 1144

Effect of KS101 on albuminuria in a diabetic mouse model (db/db mice)

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Objectives: A decrease in klotho is associated with chronic kidney disease (CKD) progression, and supplementation of klotho improves CKD progression in an animal model. KS101 is a novel compound developed as a drug candidate that increases klotho expression. We investigated whether KS101 may reduce albuminuria and improve CKD progression in db/db mice.

Methods: We fed a high-protein diet (HPD) to db/db mice. KS101 was administered by oral gavage once daily according to the following concentrations: 2, 10, and 50mg/kg for 12 weeks. We tested urine albumin creatinine ratio (ACR) at 4, 8, and 12 weeks of KS101 administration. Blood sugar was tested in a prandial meal weekly. We sacrificed the whole mice at 12 weeks after KS101 administration. We checked serum levels of blood urea nitrogen (BUN) and klotho. We confirmed the expression of klotho, alpha-SMA, and fibronectin by immunohistochemistry (IHC) or western blotting.

Results: ACR decreased on KS101 50mg/kg administered for 8 weeks, compared to the control. The elevated BUN in db/db mice decreased by KS101, which showed a dose dependency. The expression of klotho increased in the kidney and serum of KS101-treated mice, confirmed by IHC and western blot in a dose-dependent manner. In vehicle-treated db/db mice, mesangial expansion was remarkable, and KS101 decreased this change dose-dependently. The expression of a-SMA decreased in the KS101-treated group, compared to the control, but there was no difference according to the concentration of KS101. Expression of fibronectin reduced in KS101 50mg/kg-treated compared to the control group.

Conclusions: We found that KS101 decreased CKD progression by modulating BUN, ACR, and klotho expression in db/db mice. KS101 also improved kidney fibrosis and mesangial expansion. Therefore, KS101 may be a candidate for the therapeutic drug in diabetic kidney disease.

Figure1. Klotho and Fibronectin expression in db/db