Nephroprotective Effects of a Novel Long-Acting GLP-1/GIP/GCG Triple Agonist, HM15275, in Preclinical Models of Acute and Chronic Kidney Diseases

799-P

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ABSTRACT

Introduction & Objective: Obesity is associated with the risk of chronic kidney disease (CKD). Recently, potential benefits of incretin drugs on cardio- and renal-related outcomes were demonstrated. The aim of this study is to evaluate whether HM15275, which shows a potent anti-obesity effect with optimized GLP-1/GIP/GCG activity balance, also has a renal protective effect.

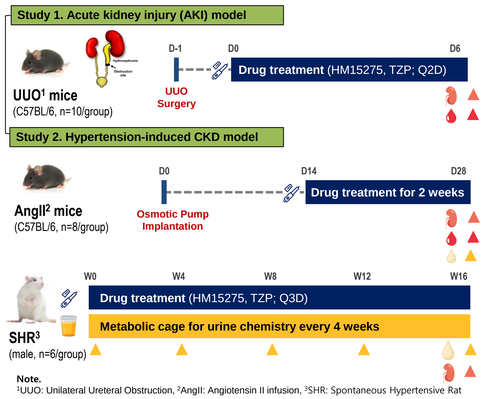
Methods: To investigate therapeutic effect on acute kidney injury, unilateral ureteral obstruction (UUO) mice were administered with HM15275, followed by determining the kidney structure and renal fibrosis. In angiotensin II (Ang II) mice, spontaneously hypertensive rats (SHR), and AMLN mice, renal fibrosis and function were determined after 2 ~ 16 weeks treatment. Human primary podocytes and renal proximal tubular epithelial cells (RPTEC) were used for in vitro mechanistic study. Tirzepatide (TZP) was used as comparative control.

Results: UUO-induced increased pro-col1α1 in the kidney was robustly attenuated by HM15275 (-35.3% vs. TZP; p<0.05). In Ang II mice, HM15275 treatment showed significantly less renal dysfunction (BUN, serum creatinine, and uACR). Similarly, elevated levels of renal pro-col1α1 were significantly attenuated by HM15275 (-40.3% vs. TZP; p<0.01). In SHRs, urinary albumin excretion (-76.5% vs. TZP; p<0.01) and uACR (-72.0% vs. TZP; p<0.01) were significantly improved by HM15275 treatment for 16 weeks. Consistently, improvement of gluomerulosclerosis was observed in AMLN mice. In mechanistic study, suppression of stress-induced apoptosis in podocytes and reduced expression of EMT markers in RPTEC well explain how HM15275 could provide renal protection effects in AKI and CKD models.

Conclusion: HM15275 improved renal damage and fibrosis more effectively than TZP. Considering the observation in podocytes and RPTEC, HM15275 might have direct nephroprotective effects in addition to the improvement of metabolic abnormalities.

METHODS

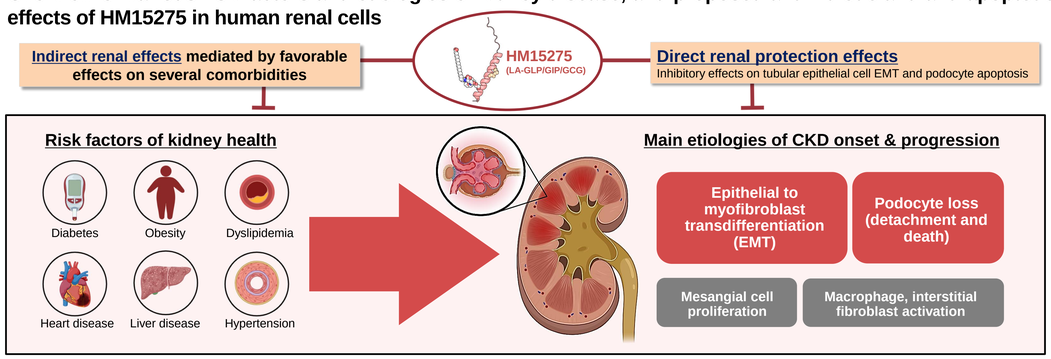
Experimental scheme



- To evaluate therapeutic effect of HM15275 on kidney function and fibrosis, rodent models of AKI [UUO mice, Study 1] and CKD [Ang II mice and SHR, Study 2] were utilized.
- Kidney function parameters were evaluated during and/or after drug treatment, and kidney tissue was analyzed after drug treatment

BACKGROUND

Overview of various risk factors and etiologies of kidney disease, and proposed anti-fibrotic and anti-apoptotic effects of HM15275 in human renal cells

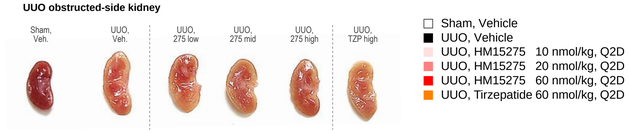


RESULTS

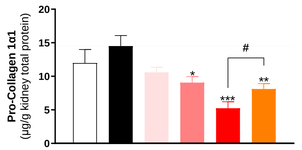
Protective effect against renal damage in acute kidney injury (AKI) model

Figure 1. Effect of HM15275 on renal structure and fibrosis (n=10)

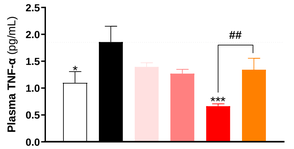
(a) Representative image for kidney in UUO mice



(b) Renal pro-collagen 1α1 level



(c) Plasma TNF-α level



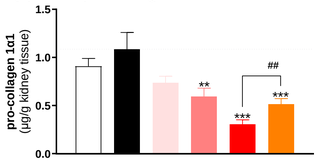
*-***p< 0.05~0.001 *vs.* UUO vehicle by one-way ANOVA, #-##p< 0.05~0.01 by unpaired t-test

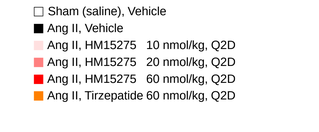
➢ In UUO mice, HM15275 effectively protects from kidney structure damage, fibrosis, and systemic inflammation by UUO, demonstrating therapeutic potential of HM15275 on AKI (more benefits *vs.* tirzepaide)

Protective effects on renal injury by Ang II infusion

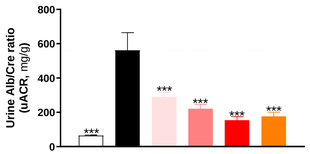
Figure 2. Effect of HM15275 on renal fibrosis and function (n=8)

(a) Renal pro-collagen 1α1 level

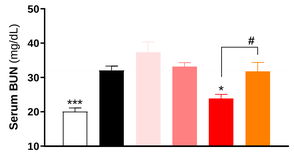




(b) Urine ACR (albumin/creatinine ratio, mg/g)



(c) Serum BUN



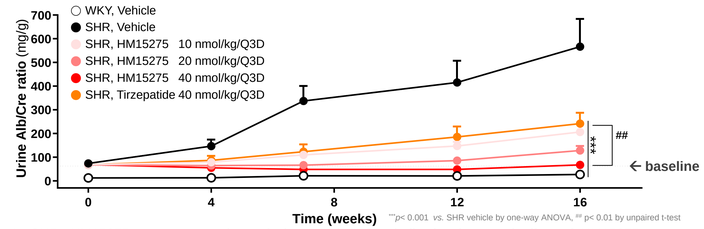
*-***p< 0.05~0.001 *vs.* Ang II vehicle by one-way ANOVA, #-##p< 0.05~0.01 by unpaired t-test

➢ In Ang II mice, HM15275 dose dependently improved markers for kidney fibrosis and function, further demonstrating therapeutic potential of HM15275 on hypertension-induced kidney injury (more benefits *vs.* tirzepaide)

Renal function improvement in progressive kidney disease

Figure 3. Effect of HM15275 on kidney disease progression (n=6)

(a) Urine ACR over time



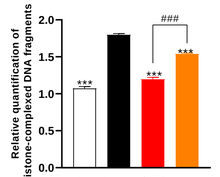
-*p< 0.001 *vs.* SHR vehicle by one-way ANOVA, ## p< 0.01 by unpaired t-test

➢ In SHR, HM15275 treatment continuously improved uACR, indicating improved effect of HM15275 on hypertension-induced kidney disease progression (more benefits *vs.* tirzepaide)

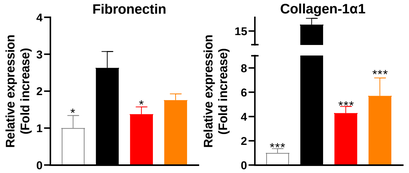
In vitro evidence for direct renal protection of HM15275

Figure 4. Effects of HM15275 on podocyte apoptosis and EMT marker expression

(a) Apoptosis of human podocyte



(b) EMT of human renal proximal tubular epithelial cell



***p<0.001 *vs.* HG+PAN, vehicle by One-way ANOVA, ###p<0.001 by unpaired t-test
*-***p<0.05~0.001 *vs.* TGF-β, vehicle by One-way ANOVA

➢ HM15275 prevented from not only stress-induced human podocyte apoptosis, but also TGF-β induced EMT marker expression in human proximal tubular epithelial cells, elucidating the underlying MoAs on how HM15275 improves renal function and fibrosis (more benefits *vs.* tirzepaide)

CONCLUSIONS

- **In rodent models of AKI and CKD, HM15275 improved renal function and fibrosis, and even greater improvement was observed compared to tirzepatide**
- **In addition to potent BWL (please visit 776-P) and improving metabolic risk factors, HM15275 reduces stress-induced podocyte apoptosis and TGF-β-induced myofibroblast activation, indicating a direct renoprotective effect of HM15275 with more benefits over tirzepatide**
- **Together with improvement effects on heart (please visit 798-P and LB-1872), these results clearly demonstrate the potential benefits of HM15275 for CVRM (cardiovascular-renal metabolic) disease management in addition to obesity management**

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