AMELIORATION OF PODOCYTE INJURY BY AN ORAL ADSORBENT AST-120 IN METABOLIC SYNDROME/DIABETES RATS : POSSIBLE ASSOCIATION WITH REDUCTION OF PROTEINURIA AND ALBUMINURIA

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OBJECTIVES

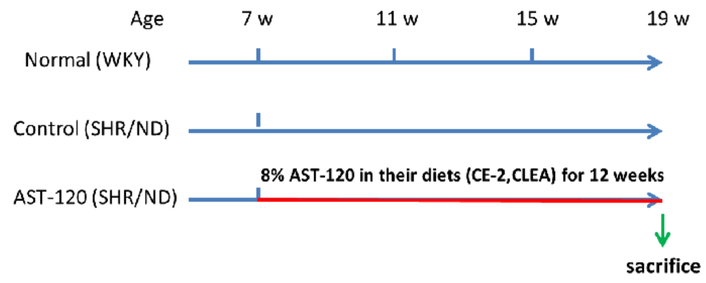
- Metabolic syndrome is known to be an important risk factor involved in the development of diabetic nephropathy.
  Diabetes Care. 2008; 31(12):2357-61
- AST-120 is an oral carbon adsorbent consisting of porous carbon particles.
- It has been used clinically for treatment of chronic kidney disease (CKD) patients to slow the progression of CKD
  Nephron Clin Pract. 2007; 105(3):c99–c107
- There is little evidence that AST-120 should be prescribed for subjects with early stage overt diabetic nephropathy.

Therefore, we investigated whether AST-120 has an effect on the early stage of nephropathy using SHR/NDmc-cp (SHR/ND), a rat model of metabolic syndrome/ type 2 diabetes.

METHODS

Effect of treatment with AST-120 in SHR/ND

Seven-week-old male SHR/ND (n=10) rats were divided into two groups (n=5 each) : AST-120 group and control group. AST-120 group was administered AST-120 with a diet containing 8% for 4 or 12 weeks. Wistar-Kyoto (n=5) rats were used as a normal.



Oxidative stress

The urinary 8-OHdG excretion was measured by ELISA.

Podocyte injury

Podocyte foot process width (FPW) was measured by Transmission Electron Microscopy

$$FPW = \pi/4 \times \frac{\Sigma \text{ GBM length}}{\Sigma \text{ foot process}}$$

Kidney International 2004; 66, 1901-06

Metabolomic analysis

Serum samples of three groups at 8 weeks after administration of AST-120 were analyzed by capillary electrophoresis mass spectrometry with time-of-flight (CE-TOFMS) and applied CE-TOFMS data to principal component analysis (PCA).
To validate these metabolites for the markers, we measured the serum levels of them by selected reaction monitoring method of LC/ESI-MS/MS.

RESULTS

Tabele1. Biochemical parameters in Normal and Control groups at 19 weeks of age.

	Body weight (g)	Dietary intake (g/day)	*Systolic BP (mmHg)*	T-cho (mg/dL)	TG (mg/dL)	HbA1c (%)
Normal	410±6.1	18.8±0.4	*134.9±3.6*	80.4 ± 0.8	56.2±5.5	4.0±0.1
Control	564±7.1***	27.5±0.4***	*189.9±5.0****	101.6 ± 3.9***	753±38.5***	5.3±0.04***

Mean ± SE. *** p < 0.001 versus Normal.

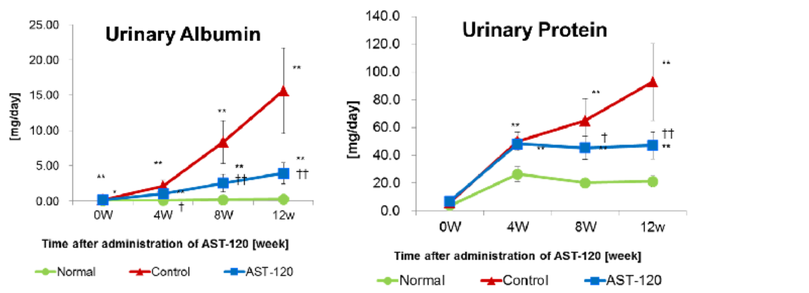


Fig. 1 Excretions of albumin and protein in the urine of Normal, Control and AST-120 groups.
Mean ± SD, n=5 * p < 0.05, ** p < 0.01 versus Normal. †p < 0.05 , †† p < 0.01 versus Control

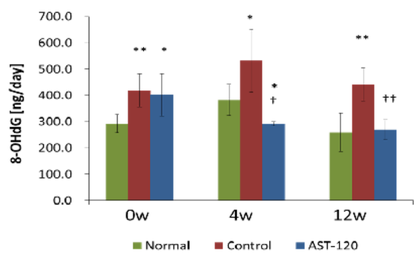


Fig.2 Urinary 8-hydroxy-2'-deoxyguanosine (8-OhdG) excretion of 3 Groups.
Mean ± SD, n=5 , * p < 0.05, ** p < 0.01 versus Normal. †p < 0.05 , †† p < 0.01 versus Control

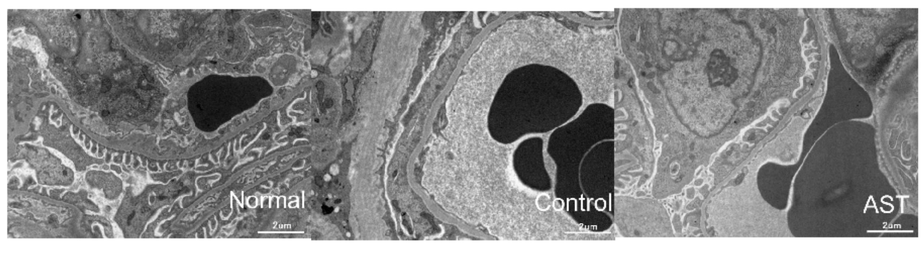


Fig. 3 Representative electron microscopy images

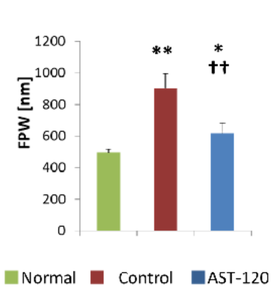


Fig. 4 podocyte foot process width (FPW) of 3 Groups
Mean ± SD, n=5 , ** p < 0.01, * p < 0.05 vs. Normal, †† p < 0.01 versus Control

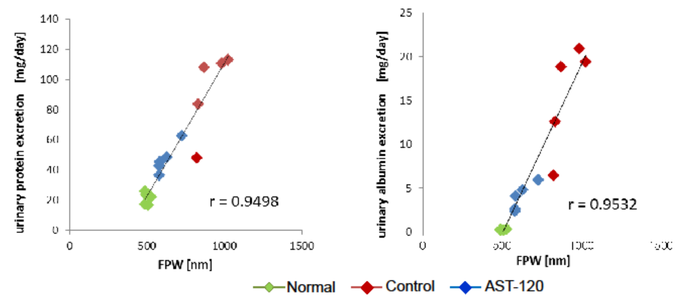


Fig. 5 Correlation between FPW and the levels of urinary protein excretion and urinary albumin excretion

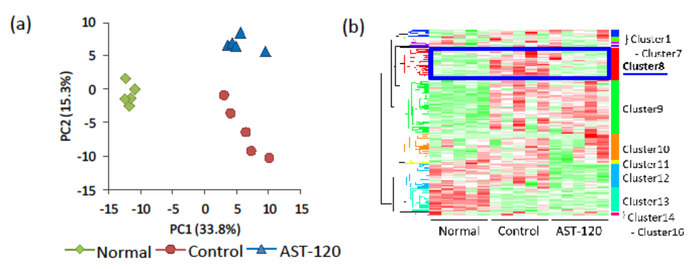


Fig. 6 The difference in the serum metabolites among three groups.
(a) PCA score plot of the CE-TOFMS data of serum samples.
(b) Hierarchical clustering showing patterns of metabolites.
Red and green indicate high and low concentration of metabolites, respectively.

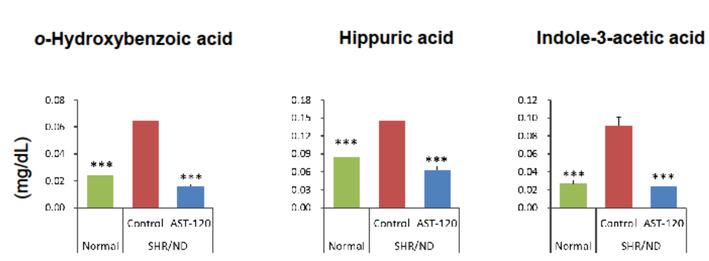


Fig. 7 Serum levels of *o*-hydroxybenzoic acid, hippuric acid and indole-3-acetic acid in 3 groups.
Mean ± SE, *** p < 0.001 versus Control.

AST-120-administered SHR/ND rats showed significantly lower levels of urinary protein excretion, urinary albumin excretion (Fig.1), urinary 8-OHdG excretion (Fig.2) and the FPW (Fig.4) as compared with SHR/ND rats.

The FPW was significantly correlated with the levels of urinary protein excretion (r = 0.9498) and urinary albumin excretion (r = 0.9532) (Fig.5).

PCA score plot showed clear separation among three groups (Fig.6).
We could detect 40 metabolites, such as o-hydroxybenzoic acid, hippuric acid and indole-3-acetic acid, which accumulated in the serum of SHR/ND rats, and of which serum levels were reduced by administration of AST-120 (Fig.6, 7).

CONCLUSIONS

The amelioration of podocyte injury by AST-120 may contribute to the reduction of proteinuria and albuminuria.
It indicates that the administration of AST-120 at an early stage of diabetic nephropathy has a protective effect on the disease progression.

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I) Diabetes. I2) Clinical studies.
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