

## Synergistic Effects of Leflunomide and Benazepril in Streptozotocin-induced Diabetic Nephropathy

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**Background/Aims:** Leflunomide (LEF) and benazepril have renoprotective effects on diabetic nephropathy (DN) through their anti-inflammatory and anti-fibrotic activities. This study investigated whether combined treatment using LEF and benazepril affords superior protection compared with the respective monotherapies.

**Methods:** Diabetes was induced with streptozotocin (STZ, 65 mg/kg) by intraperitoneal injection in male Wistar rats. Two weeks after STZ injection, diabetic rats were treated daily for 12 weeks with LEF (10mg/kg), benazepril (10 mg/kg), or a combination of LEF and benazepril. Basic parameters (body weight, fasting blood glucose level, and 24 h urinary protein excretion), histopathology, inflammatory (monocyte chemoattractant protein-1 [MCP-1] and Toll-like receptor-2 [TLR-2]) and glomerulosclerotic factors (Transforming growth factor-beta1 [TGF- $\beta$ 1] and connective tissue growth factor [CTGF]), and oxidative stress (8-hydroxy-2'-deoxyguanosine, 8-OHdG) were studied.

**Results:** Benazepril or LEF treatment significantly prevented body weight loss and 24 h urinary protein excretion induced by diabetes; combined treatment with LEF and benazepril further improved these parameters compared with giving each drug alone (all  $p < 0.01$ ). Increased expression of inflammatory (MCP-1 and TLR-2) and glomerulosclerotic (TGF- $\beta$ 1 and CTGF) factors in diabetic rat kidney was reduced by treatment with either LEF or benazepril and was further reduced by the combined administration of the two drugs ( $p < 0.01$ ). These effects were accompanied by suppression of urinary 8-OHdG excretion. There was no significant between-group difference in blood glucose level.

**Conclusion:** LEF treatment lessens DN, and combined treatment with LEF and benazepril provided synergistic effects in preventing DN.

**Key Words:** Leflunomide, Benazepril, Diabetic nephropathy, MCP-1