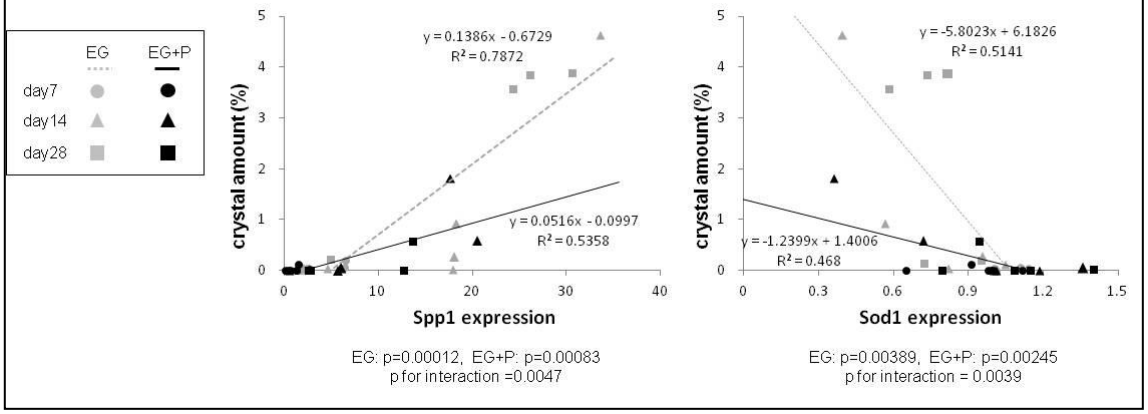
Pioglitazone: A Peroxisome Proliferator-Activated Receptor Gamma Agonist, Prevents Kidney Stone Formation via Antioxidative and Anti-inflammatory Effects

Introduction and Objective: Kidney stone disease has characteristics similar to metabolic syndrome (Mets), involving inflammation and oxidative stress. Molecular biological therapy targeting the formation of kidney stone disease has not yet been developed, although these therapy using statins and peroxisome proliferator-activated receptor gamma (PPARγ) agonists has been used for Mets, including diabetes mellitus, hyperlipidemia, and atherosclerosis, which appears to be related to kidney stone disease. Pioglitazone (PGZ), a PPARγ agonist, has anti-inflammatory and antioxidative effects. We evaluated the *in vivo* efficacy of PGZ for prevention of kidney stone formation, and to investigate gene expression related to inflammation and oxidative stress in a hyperoxaluric rat model.
Materials and Methods: We divided Sprague-Dawley rats into a control group, a 1% ethylene glycol (EG) group, and a 1% EG and 10 mg/kg PGZ (EG+P) group. Blood and 24-h urine samples and kidney sections were collected on days 7, 14, and 28. We examined crystal formation using Pizzolato staining and polarized light optical microscopy. We also evaluated cell injury, apoptosis, and oxidative stress with *N*-acetyl-β-glucosaminidase, 8-hydroxydeoxyguanosine, and TUNEL assay. Expression of stone- and inflammation-related genes was examined by immunohistochemistry and quantitative reverse transcriptase polymerase chain reaction.
Results: Kidney crystal formation was significantly lower in the EG+P than in the EG group. Cell injury, apoptosis, and oxidative stress markedly reduced after PGZ administration. Expression of osteopontin and ED1 for pro-inflammatory macrophages was lower in the EG+P than in the EG group, whereas that of ED2 for anti-inflammatory macrophages was the same in both groups. Linear regression

Figure



analysis showed a significant change in the correlation coefficient with PGZ treatment between Spp1 and Sod1 expressions and the amount of crystals (Figure).
Conclusions: PGZ suppressed kidney crystal formation through its renal tubular cell protection and antioxidative and anti-inflammatory effects, and may be a novel preventive agent for kidney stone disease.