Pioglitazone inhibits in-stent restenosis in atherosclerotic rabbits by targeting transforming growth factor-beta and MCP-1.

OBJECTIVE: Although emerging data from preclinical and clinical studies suggests a reduction of in-stent restenosis with peroxisome proliferator-activated receptor (PPAR)-gamma agonists, the reduction of neointimal growth via anti-inflammatory mechanisms has not been explored. METHODS AND RESULTS: Hypercholesterolemic New Zealand White rabbits (n=45) received bilateral balloon-expandable stents implanted into atherosclerotic iliac arteries. Animals were randomized to oral pioglitazone 3 (low dose) or 10 mg/kg per day (high dose) started on the day of stent implantation; control rabbits received placebo. Tissue harvest was performed 28 days after stenting, and stented segments underwent histology, morphometry, immunostaining for macrophages, and scanning electron microscopy. In selected animals, stented arterial segments were placed in organoid culture for 48 hours, and the conditioned media was assayed for 23 different cytokines. There was a 21% reduction in neointimal area for high-dose pioglitazone treated versus placebo rabbits (P<0.005), which was associated with a significant reduction of neointimal macrophages. Analysis of conditioned media revealed an 82% and 74% reduction in the release of monocyte chemoattractant protein-1 (MCP-1) (P<0.007) and transforming growth factor (TGF)-beta1 (P<0.01),
respectively, in stented segments from animals treated with 10 mg/kg per day pioglitazone versus placebo. CONCLUSIONS: Oral pioglitazone suppresses in-stent neointimal growth by limiting local inflammatory pathways and may be useful as an adjunctive therapy in patients undergoing percutaneous interventions.