Evaluating anti-inflammatory efficacy of pioglitazone in a rabbit model of atherosclerosis with multimodality imaging

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Introduction: Inflammation is a major contributor to atherosclerotic plaque instability and rupture.[1] Pioglitazone, a PPAR-γ agonist, has been shown to delay atherosclerosis progression in mouse models and increase cardiovascular disease survival rates in high-risk human populations.[2] Pioglitazone displays positive effects through its anti-inflammatory properties, promotion of reversal cholesterol transport, and lipoprotein profile influence.[2] In this study we used a multimodal imaging approach including dynamic contrast enhanced (DCE) MRI and F18 fluorodeoxyglucose (FDG) PET/CT to monitor inflammatory changes of plaque in an atherosclerotic rabbit model[3] during and after pioglitazone treatment. Histological analysis of matched aortic sections validated imaging results in order to accurately evaluate therapeutic efficacy.

Methods: Atherosclerosis was induced in 13 New Zealand White (NZW) rabbits with high cholesterol diet and abdominal aortic double balloon injury. Rabbits underwent baseline DCE-MRI, multicontrast (T1, T2, and PD) MRI, and FDG PET/CT 4 weeks following second balloon injury (plaque age = 4 months). Animals were then divided into a control (n=7) and treatment group (n=6). Both groups maintained a high cholesterol diet and the treatment group received 10 mg/kg pioglitazone admixed to diet. DCE-MRI, multicontrast MRI, and FDG PET/CT were again performed after one and three months (*Figure 1, 2)*. DCE-MRI images were analyzed by calculating the area under the signal intensity versus time curve (AUC) of the contrast agent uptake in atherosclerotic plaque. PET/CT images were analyzed by calculating the standard uptake value (SUV) of F18 FDG in aortic sections directly inferior to the left renal bifurcation (0-5 cm) three hours after injection. Both groups were sacrificed after three months and immuno-histochemistry was performed on a 5 cm length of abdominal aorta using macrophage specific RAM11 and ApoB specific MB47 antibodies.

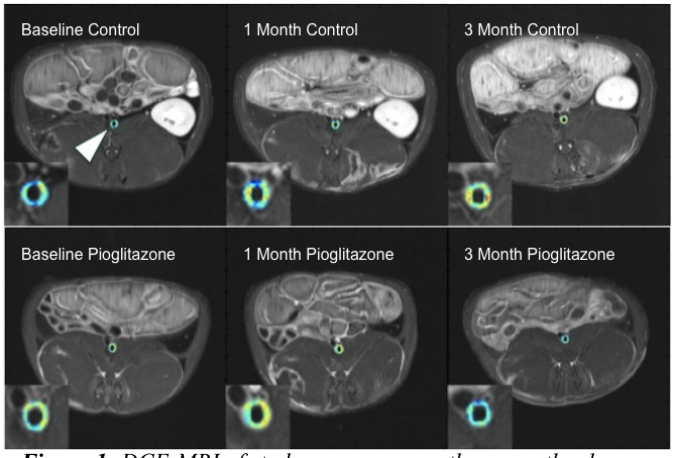

***Figure 1**: DCE-MRI of study groups across three months shows signal decrease in pioglitazone group and not control group (low AUC high AUC)*

Results: Three months after pioglitazone treatment, DCE-MRI showed a significant reduction in AUC values compared to baseline (p =0.045, Figure 3a) while controls exhibited no difference (p=0.83, *Figure 3a*). FDG PET/CT showed similar SUVs between control and treated animals at baseline (p=0.97, *Figure 3b*) and lower SUVs between groups at one month (p=0.010, *Figure 3b*) and three months (p=0.0025, Figure 3b). Immuno-histochemistry showed decreased LDL plaque density in the treated group as compared to controls (p=0.062) and a significant decrease in macrophage density (p=0.046). No significant change in vessel wall area was detected with multicontrast MRI from baseline to three months in the control group (p=0.48) or treatment group (p=0.77).

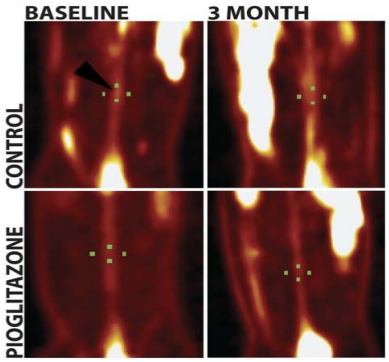

***Figure 2:** FDG PET/CT of study groups, arrow shows region of high SUV*

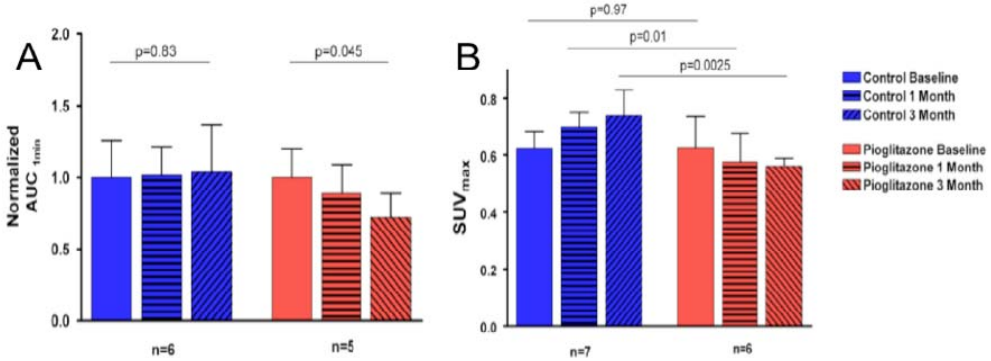

***Figure 3:** A- MRI AUC values after 1 min of contrast enhancement across 3 months. B- FDG uptake values in rabbit abdominal aorta across 3 months*

Conclusion: In this study we showed the ability of DCE-MRI to detect a decrease in vessel wall inflammation after three months of pioglitazone treatment. Positive changes were also observed with FDG PET/CT. These results were validated with macrophage-targeted immuno-histochemistry, indicating therapeutic efficacy of pioglitazone after three months of treatment in a balloon-injured atherosclerotic rabbit model. This multimodality imaging approach could represent a non-invasive technique for future (pre)clinical cardiovascular drug efficacy evaluation.

References: [1] Rocha VZ, Libby P. Nat Rev Cardiol. 2009. [2] Nakaya *et al*. Am J Pathol. 2009. [3] Calcagno *et al*. Art Thromb Vasc Biol. 2008.