Rosiglitazone reduces ischaemia-reperfusion injury in patients with the metabolic syndrome

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In animals, thiazolidinediones reduce ischaemia-reperfusion injury. A clinical meta-analysis raised suspicion that rosiglitazone increases the incidence of myocardial infarction (Nissen et al., N Engl J Med 2007;356:2457–2471). However, human data on a possible benefit on infarct size (i.e. ischaemia-reperfusion injury) are not available. Therefore, we investigated the effect of rosiglitazone on ischaemia-reperfusion injury in 10 insulin resistant participants without hyperglycaemia. We used a thoroughly validated human in vivo model to quantify ischaemia-reperfusion injury in skeletal muscle by annexin-A5-scintigraphy (Rongen et al., Circulation 2005;111:173–178). At the end of each treatment period (rosiglitazone 4 mg b.d. vs. placebo), the participants were subjected to 10 min of forearm ischaemia, combined with standardized intermittent handgripping. At reperfusion, 500 MBq 99mTc-annexin-A5 was administered intravenously. Annexin-uptake (counts per pixel) was measured in thenar muscle 1 h post-reperfusion using a gamma camera. Ischaemia-reperfusion injury was quantified as the percentage difference in uptake between experimental and control side (annexin-targeting). Rosiglitazone reduced annexin-targeting from 8.4% (median; range 0.6–49%) to 4.7% (0.7–20%) (P = 0.037). We present the first human in vivo data on the beneficial effects of rosiglitazone on ischaemia-reperfusion injury. This observation puts the disputed elevation in myocardial ischaemic events during rosiglitazone treatment in perspective.

Panel A. Study design.

Panel A. Randomized, double blind, placebo-controlled cross-over study.

Panel B. Individual plots of the effects of rosiglitazone on 99mTc-annexin-targeting in insulin resistant subjects.

Panel C. Typical 99mTc-annexin-uptake one hour after reperfusion at the end of the placebo period. Left: control hand; right: post-ischaemic hand. Counts increase from blue to yellow.

Panel D. Same patient, but at the end of the rosiglitazone treatment period.