Reviewer's report

Title: Anti-inflammatory effect of rosiglitazone is not reflected in expression of NFκB-related genes in peripheral blood mononuclear cells of patients with type 2 diabetes mellitus

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Reviewer: Paresh Dandona

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REVIEW OF THE PAPER ON THE ANTI-INFLAMMATORY EFFECT OF ROSIGLITAZONE AND THE ROLE OF MNC

This is an interesting paper showing that while rosiglitazone exerts a potent anti-inflammatory effect, the mononuclear cell (MNC) in which this effect was first demonstrated does not exhibit a suppression of a majority of the NFκB regulated genes that were looked for. The authors conclude that the suppression of the various mediators of inflammation in plasma by rosiglitazone is due to an effect in other organs and that MNC may not be an appropriate target to elucidate this anti-inflammatory effect.

The hypothesis, the methods and the statistical analysis with the conclusions in general are fine but the discussion needs to be elaborated.

1. MNC may not have shown the suppression of NFκB dependent genes but NFκB is suppressed by all TZDs. It is possible that the monocyte needs to be looked at specifically since it is central to the mechanisms of innate immunity and is also the cell that ‘takes’ inflammation to the atherosclerotic plaque and the adipose tissue and possibly to the skeletal muscle where it triggers and sustains inflammation.

2. From the point of view of the pathogenesis of insulin resistance, the deletion of IKK# in myeloid precursors which include monocytes protects animals from diet induced obesity related insulin resistance (Karin). Thus, the monocyte is clearly central to inflammation related insulin resistance. Since MNC fraction includes not only monocytes (20%) but also lymphocytes (80%), it is important to look for changes in pro-inflammatory cytokines and mediators in pure monocytes. In the meantime, we can accept that the MNC do not give us a complete and precise picture.

3. The authors should provide a complete list of the genes which were tested so that future investigators do not waste their time testing for those genes.

4. As far as their conclusions from the hyperinsulinemic euglycemic clamps are concerned, like others, they assume that when they infuse patients with insulin while co-infusing glucose to maintain euglycemia, that only insulin is exerting a biological effect. With the amounts of glucose usually infused during such a clamp glucose can exert both oxidative and inflammatory stress. 75g of orally administered glucose to normal subjects induces an increase of ROS generation
by MNC by 140% over the basal and an increase in NFkB binding by over 50% although the blood glucose concentration remains within the normal range. The anti-inflammatory effect of insulin was demonstrated with low dose infusions of insulin (2U/h) and 5-6g/h of glucose to maintain euglycemia (Dandona et al, JCEM, 2001; Chaudhuri et al, Circulation, 2004). It should also be noted that it takes longer than 10h of insulin infusion to demonstrate a fall in CRP concentrations (Chaudhuri et al, 2004; Wong et al, Diabetes Care,2004; Visser et al, Br J Anaesth, 2005; Kosenkari et al, Acta Anaesth Scand, 2006).

5. Please cite the work of Dhindsa et al (JCEM, 2003) in relation to the effect of rosiglitazone on both TG and FFA clearance.