Author's response to reviews

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

**Authors:**

Marjolijn C.E. Bragt (m.bragt@hb.unimaas.nl)
Jogchum Plat (j.plat@hb.unimaas.nl)
Marco Mensink (marco.mensink@wur.nl)
Patrick Schrauwen (p.schrauwen@hb.unimaas.nl)
Ronald P. Mensink (r.mensink@hb.unimaas.nl)

**Version:** 4  **Date:** 12 February 2009

**Author's response to reviews:** see over
Dear Mr. Todd,

Please find enclosed our second revision of the manuscript entitled “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”, which we would like to re-submit for publication in BMC Endocrine Disorders.

We would like to thank the reviewers for the critical and useful comments regarding our manuscript. The reaction to the last remaining comment is given below.

Yours sincerely,

Marjolijn C.E. Bragt

Reaction of authors on reviewer’s comment:

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
Version: 3 Date: 21 January 2009
Reviewer: Paresh Dandona

Reviewer’s report:
The paper is much improved. However, the conclusion that the authors draw about the inadequacy of the mononuclear cell as a target for the study of inflammation is not appropriate. Inflammation is a systemic process and involves several organ systems, each with its own characteristic inflammatory products. It is not necessary that all will be reflected in each cell or organ. Thus, CRP and SAA are products of the liver and will not be expressed in MNC. The authors need to take this into their consideration. Furthermore, ROS generation, P47phox, NFκB binding, IkBα expression, AP-1 binding, Egr-1 binding and expression are all observed in the MNC. Furthermore, MNC is not only a cellular fraction containing inflammatory cells but it is also easily accessible. I have no vested interest in supporting the MNC but there is no question that this cell has contributed a lot to scientific investigation and discovery. It is appropriate to point to its limitations but not to reject it.

We completely agree with the reviewer that the mononuclear cell have contributed a lot to scientific investigation, knowledge and discovery. That is why we formulated our conclusion very specific and not general. Because we certainly do not want to give readers the impression that mononuclear cells would be inadequate to study inflammation in general, we have therefore again reformulated the conclusion:

Reformulated conclusion in abstract (page 2, lines 41-44):
• In type 2 diabetic patients, the anti-inflammatory effects of rosiglitazone are not reflected by changes in NFκB and PPARγ target genes in PBMCs in vivo. Furthermore, our results do not support that high insulin concentrations contribute to the pro-inflammatory profile in type 2 diabetic patients.

Reformulated conclusion in article (page 16, lines 352-358)
• In conclusion, 8 weeks of rosiglitazone treatment (2x4 mg/d) resulted in improved insulin sensitivity and lipid profile and reduced concentrations of plasma inflammatory markers (MCP1 and hsCRP) in type 2 diabetic patients. Furthermore, plasma inflammatory parameters did not change consistently during the clamp in both diabetic and control patients, which does
not suggest that high insulin levels contribute to the proinflammatory state in type 2 diabetic patients. Finally, the anti-inflammatory effects of rosiglitazone are not reflected by changes in NFκB and PPARγ target genes in PBMCs in vivo.