

July 8, 2013

Dear Editor,

I am resubmitting to World J Diabetes the manuscript #3890 entitled "*High adiponectin levels fail to protect against risk of hypertension and, in women, against coronary disease: involvement in autoimmunity*". The response to the comments of the five Reviewers is presented below.

All changes in the manuscript are highlighted in blue.

With kind regards,

Altan Onat, MD, FESC

**Reviewers 1-4:**

Plasma IL-6, TNF- $\alpha$ , leptin and resistin levels have not been measured in the TARF study, and we think their availability is not indispensable to the interpretation of our main findings. However, hs-CRP has been determined nephelometrically in this study sample, as stated on page 6. CRP was included in the Cox models used for the three outcomes in Table 3 and in the Results section.

On top page 9 had been described that: "...in Model 2, CRP emerged a further inverse covariate in men, beyond the persisting female sex, circulating SHBG and insulin as significant and, in women, creatinine as borderline significant covariates.

We have added on page 9 that "CHD risk was predicted **in a multivariable Cox model adjusted also for CRP** by non-HDL-cholesterol only...".

In the Discussion, page 10, line 16, had been described that "...lack in protective function of the intermediate and high adiponectin tertiles in either sex, was independent of waist girth and CRP concentrations."

It had been commented also (bottom page 11) that "The involvement of adiponectin in immune activation in women may result both in endothelial dysfunction-mediated renal dysfunction (CRP elevation) and failure to protect against CHD risk."

**Reviewer 631914:**

Regarding your suggestion that the title of the manuscript does not accurately describe the content, we have not modified the title due to not finding a better explicit brief title, but have changed the conclusion in the abstract to read as follows.

High adiponectin levels failed to protect against the development of hypertension and, in women, against CHD, **presumably paralleling** impairment in renal function **as well**. Involvement **of adiponectin** in autoimmune complex with loss of antioxidative-antiatherogenic properties may be underlying.

The concluding sentence of the text reads now as follows. “We propose that involvement of adiponectin in autoimmune activation may underlie both the lack of stated protection and a concomitant presumable contribution to renal functional impairment.”

Ref. 24 on creatinine has been added and cited on page 11.

Sex-specific differences in impact of serum adiponectin have been emphasized in this manuscript, as well as previously in Refs. 8 and 9, and these are derived from the underlying autoimmune processes which operate more strongly in peri- and postmenopausal women than men.

Dividing the manuscript into two papers does not appeal to us, not in the least because such differences recur in this cohort with respect to numerous variables (Lp(a), Lp-PLA<sub>2</sub>, creatinine, TSH, ASP, ADMA apoE, SHBG); hence, it is beneficial that the reader is exposed to them simultaneously.

HR was defined as hazard ratio (abstract and top, page 8).

The use of ANOVA p-trend analysis has been additionally specified in the Data Analysis and in Table 1.