Author's response to reviews

Title: Low concentrations of serum testosterone predict acute myocardial infarction in men with type 2 diabetes mellitus

Authors:

Bledar Daka (bledar.daka@allmed.gu.se)
Robert D Langer (rlanger@medicine.nevada.edu)
Charlotte A Larsson (charlotte_a.larsson@med.lu.se)
Thord Rosen (thord.rosen@medic.gu.se)
Per Anders Jansson (per-anders.jansson@medic.gu.se)
Lennart Råstam (lennart.rastam@me.com)
Ulf Lindblad (ulf.lindblad@gu.se)

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Author's response to reviews: see over
Dear Editor,

Thank you for the review of our manuscript “Low concentrations of serum testosterone predict acute myocardial infarction in men with type 2 diabetes mellitus”, and the opportunity to resubmit a revised version. We indeed appreciate the constructive criticism raised by the reviewers and we tried to address them as careful as possible.

Below, You will find the answer to the reviewer.

We hope you will find that our revised manuscript meets all issues from you and the reviewers.

Gothenburg, 2015-06-11

Bledar Daka
Reviewer Giulia Rastrelli

Thank you for the excellent comments.

We agree completely with you comments. We changed our manuscript as follows


We agreed in this comments as these meta-analyses have shown the strong support of the association between low T and CVD-mortality in men and we have changed the Introduction and the Discussion.

Now it is
"Observational prospective studies and meta-analysis studies have also shown that low concentrations of testosterone predict both all cause and cardiovascular mortality in elderly populations [7-12]."

"Moreover a previous meta-analyses study have shown that TRT trend to improve the glycaemic control and fat mass in individuals with type 2 diabetes[17]"

" Previous studies in elderly men have shown an association between low levels of testosterone and higher risk for CVD [7, 9, 12]. While the evidence in elderly men is very large [10-12] prospective studies in younger men are lacking".

2. Methods: the use of estradiol in men, when it is measured by immunologic methods, is not reliable. Conversely the use of estradiol in women, without information on their phase of cycle or menopause is useless. For these reasons, analyses including estradiol among covariates must be deleted.

Answer: We agree with the comment and results including models with estradiol have been erased

“In men with type 2 diabetes, a model also including concentrations of estradiol and SHBG was computed and the association with testosterone remained significant (HR=0.704 95% CI 0.53-0.93 p=0.014).” Moreover,
results in tables including estradiol measurements were also erased.

3. Page 5, line 146 must be better specified. Referring to “standard methods” does not give any information on descriptive statistics. Furthermore, the normality or non-normality of distribution of data, information that leads all the statistical analyses, must be verified by the Kolmogorov-Smirnov test. In particular, looking at the data reported in table 1, HOMA-IR and insulin seem not to be normally distributed. Please verify for all the variables used.

Answer: We have changed the statistic paragraph in methods and now it is “Analyses were performed using SPSS Statistics for Mac, version 20. Normal distribution of testosterone was observed while Homa-ir and s-insulin had a very skewed distribution and logarithmic variables were used when we adjusted for them. Schoenfeld proportional hazards were used to determine the feasibility of Cox regression analysis. Cox Proportional Hazards Regression was employed to investigate the associations between levels of sex hormones at baseline and outcomes. Multivariate models were used to assess interactions and to estimate the roles of possible confounders. Stratified analyses for Type 2 Diabetes Mellitus were computed to investigate possible effect modification by diabetes. All analyses were two-sided, and p<0.05 was used as level of statistical significance.”

4. In table 3 also note that several units of measurement are lacking, the unit of T is incorrect and, when T is expressed as nmol/L, free T should be expressed as nmol/L or pmol/L, too.

Answer: Thanks for the comment. We have changed it as it is suggested
Reviewer: Giovanni Corona

Thank you for the excellent comments.

We agree completely with you comments. We changed our manuscript as follows

1. The mean age of the patients enrolled as well as the immunometric nature of steroid method must be reported. A statement for the age and the immunoassay used is added in the Abstract as suggested.

   Answer: The mean age and the use of immunoassay is now stated in the abstract. "The study comprised 1109 subjects ≥40 years of age (mean age 62 ±12 years) participating in a baseline survey in Sweden in 1993-94……. Serum concentrations of testosterone and sex hormone-binding globulin (SHBG) were obtained using radioimmunoassay.” A statement for the use of the immunoassay is now in the methods ” Immunoassays were used to analyse concentrations of sex hormones.”

2. Introduction. This section must be improved. In particular it should be recognize the bidirectional relationship between low T and MetS as well as T2DM since both associated with reduced T but low T itself can predict the development of MetS and T2DM (Corona et al., J Sex Med 2010; Brand et al., PloS ONE 2014).

   Answer: The bidirectional relationship between testosterone and Diabetes is included in the introduction and it is now “This bidirectional relationship between low testosterone and metabolic syndrome as well as type 2 diabetes has been described in previous studies[5].”

3. A correctly stated by the authors the contribution of T in the stratification of CV risk is conflicting. 3 independent meta-analyses have documented an association between low T and CV mortality but not CV morbidity (Araujo et al., JCEM 2011; Corona et al., Eur J Endocrinol 2011; Ruige et al., 2011). All these paper must be quoted and discussed. Previous meta-analysis documented a positive outcome of TRT in subjects with type 2 diabetes (Corona et al., Best Pract Res Clin Endocrinol Metab. 2013). However, a more recent meta-analysis (Grossman et al., Clin Endocrinol 2015) reported no effect of TRT in patients with MetS or T2DM. These points must be recognized and discussed.

   Answer

   We agreed in this comments as these meta-analyses have shown the strong support of the association between low T and CVD-mortality in men and we have changed the Introduction and the Discussion.

   Now it is

   “Observational prospective studies and meta-analysis studies have also shown that low concentrations of testosterone predict both all cause and
cardiovascular mortality in elderly populations [7-12]."

"Moreover a previous meta-analyses study have shown that TRT trend to improve the glycaemic control and fat mass in individuals with type 2 diabetes[17]"

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