Author’s response to reviews

Title: Association of osteoprotegerin with impaired glucose regulation and microalbuminuria: the REACTION study.

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Author’s response to reviews:

Dear Editor:

Our manuscript has been extensively revised in accordance with the enclosed reviewers’ comments. All changes in manuscripts emphasized by red characters.

Reviewer reports:
Reviewer #1:

This is an interesting cross-sectional study which examined the association between serum osteoprotegerin (OPG) levels with impaired glucose regulation and microalbuminuria. The authors found that serum OPG levels increased slightly but significantly in patients with impaired fasting glucose/impaired glucose tolerance/type 2 diabetes in comparison with those with normal glucose tolerance and in those with type 2 diabetes mellitus and microalbuminuria in comparison with those without microalbuminuria.

Strength of the study is the large number of the participants. A limitation is its cross-sectional design which does not allow drawing robust conclusions for a cause and effect relationship between serum OPG and impaired glucose regulation or microalbuminuria.

Comments:

1. In page 12, lines 9-16, the authors describe factors related with serum OPG levels. Did they check if there was an association between serum OPG and estimated GFR (eGFR)? This issue needs clarification because renal function may be a certain confounder on the association between serum OPG and impaired glucose regulation or microalbuminuria. If there a significant association between these variables in univariate analysis, the authors should adjust in addition to the other variables and for eGFR in multivariate analysis.

Answers:

We are sincerely appreciative of reviewer’s insightful and thought-provoking comments. According to reviewer’s instruction, we have re-analyzed the association between serum OPG and estimated GFR. There was no significant association between serum OPG and eGFR in univariate analysis (r=0.031, p=0.467). So we didn’t adjust in addition to the other variables and for eGFR in multivariate analysis.

2. Regarding the association between serum OPG concentrations and microalbuminuria, the authors should provide more data on the potential use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers, because these medications reduce albumin/creatinine ratio.
Answers:

It’s a very constructive and thought-provoking suggestion! Given the ACEI and ARB could reduce albumin/creatinine ratio, the use of these medications might affect the association between serum OPG concentrations and microalbuminuria. In this study, approximately 3.29% individual took ACEI/ARB as antihypertensive medications. According to reviewer’s instruction, we have added this data in the manuscript, and further take ACEI/ARB use as a adjustment variable in logistic regression analysis.

Reviewer #2:

The authors report the results of a cross-sectional study, concerning the association of circulating OPG with newly diagnosed impaired glucose regulation, namely IFG, IGT and type 2 DM). The manuscript is generally well written and of appropriate length. However there are some issues that must be addressed before the manuscript is considered suitable for publication to the "BMC Endocrine Disorders".

1. Given that OPG levels differ significantly according to menopausal status, were the groups equally balanced? The authors do not report menopausal status nor they adjust for it.

Answers:

We are sincerely appreciative of reviewer’s profound and thought-provoking comments. As reviewer’s description, the serum OPG levels differ significantly according to menopausal status. In this study, approximately 76.6% female subjects were postmenopausal women. According to reviewer’s suggestion, we have added this data in the manuscript (Table 1), and further take menopausal status as a adjustment variable in statistical analysis.

2. The observed association between OPG and glycemic status is relative small and of marginal statistical significance, given that large sample. The authors should critically comment on this finding.

Answers:

We appreciate the constructive comments made by reviewer. As reviewer’s description, given that large sample in this study, the observed association between OPG and glycemic status is relative small and of marginal statistical significance. Due to the cross-sectional nature of the
present study, admittedly we could not determine whether OPG plays a causal role in the pathogenesis of impaired glucose regulation. Certainly prospective studies with solid clinical end points are urgently needed to clarify whether a high OPG level plays a causal role in the development of impaired glucose regulation. According to reviewer’s suggestion, we have added the critically comment on this finding in the manuscript.

3. The authors must also comment on the different forms of OPG (monomer, dimer, etc/plasma vs. serum) measured with the several commercial kits for OPG and also more extensively comment on the multiple sources of circulating OPG and whether there are data linking circulating OPG with local production (eg the data linking circulating OPG with bone OPG are rather disappointing.

Answers:

We are sincerely appreciative of reviewer’s insightful comment. This study was just to evaluate the levels of serum monomer OPG. As reviewer’s comments, given osteoprotegerin, a soluble glycoprotein that belongs to the tumor necrosis factor (TNF) receptor superfamily, is produced by a variety of tissues including heart, arteries, veins, lung, kidney, immune system and bone, the circulating OPG may come from multiple sources. This study was just to investigate the association of serum osteoprotegerin levels with impaired glucose regulation and microalbuminuria. In view of the study design limitation, we couldn’t assess the relation between circulating OPG and local tissue OPG production. According to reviewer’s advice, we have revised in the manuscript.

4. Finally there are some other markers possibly better associated with glycemic status such as undercarboxylated osteocalcin.

Answers:

We thanks for reviewer’s constructive comments. As reviewer’s comments, there are some other markers possibly better associated with glycemic status such as undercarboxylated osteocalcin. The mechanism of impaired glucose regulation is so complex, this study was just to preliminary examine the association of osteoprotegerin with impaired glucose regulation.

Minor issues
Introduction

Line 13-23: please rephrase

Answers:

We thanks for editor’s reminder. According to reviewer’s instruction, we have revised this part in the manuscript.

Results

Along the results section it would be better to use the term higher instead of increased when commenting on OPG levels given the cross-sectional nature of the study.

Answers:

We thanks for editor’s reminder. According to reviewer’s instruction, we have revised this part in the manuscript.