Author's response to reviews

Title: Associations of fetuin-A and osteoprotegerin with arterial stiffness and early atherosclerosis in chronic hemodialysis patients

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Author's response to reviews: see over
Dear Editor

Thank you for kindly reviewing our manuscript MS: 5316324190654031 entitled “Associations of fetuin-A and osteoprotogerin with arterial stiffness and early atherosclerosis in chronic hemodialysis patients”. All the potential modifications have been made according to the reviewers comments. Please receive revised version of the manuscript together with a cover letter giving a point-by-point response to the reviewers comments.

Moreover, the full institutional name of the ethical committee that approved the study is now included (page 4) and we have thoroughly edited the manuscript to improve its linguistic style.

We hope that our manuscript meets now the prerequisites for publication in "BMC Nephrology".

Thank you for your consideration in this matter

Sincerely yours

Panagiotis Pateinakis, MD
Aikaterini Papagianni, MD, PhD
Stella Douma, MD
Georgios Efstratiadis, MD
Dimitrios Memmos, MD
RE: MS: 5316324190654031 "Associations of fetuin-A and osteoprotogerin with arterial stiffness and early atherosclerosis in chronic hemodialysis patients"

Reviewer Professor Giovanni Pertosa

Thank you very much for your constructive comments. We agree that our findings are not entirely novel, particularly given your important contribution to the subject, which is now included in our revised manuscript (ref. 31). However, we believe that our data provide additional information on the associations of fetuin-A and osteoprotegerin with vascular disease in chronic hemodialysis patients, contributing, in conjunction with results from previous similar studies, which have not given consistent results, to a better understanding of their role in uremic vasculopathy.

Furthermore the text has been thoroughly revised and edited to improve its linguistic style.

Reviewer Dr Andrea Galassi

Thank you very much for your valuable comments, according to which the following revisions have been made:

Major Revisions
- Abstract, Results and Conclusion: “prediction” was replaced by “association”.
- Results: The influence of diabetes on the associations between fetuin-OPG and IMT-PWV was analyzed, and scatter plots of univariate linear correlations between fetuin-OPG and IMT-PWV in diabetic and non-diabetic patients are now presented in Figures 2 and 3.
- Results, Page 7: The significant and independent association between LDL and cfPWV is now commented.
- Discussion, Page 8, first paragraph: The text has been revised according to the limitations of the study to infer causality, due to its cross-sectional design.
- Discussion, Page 8, second paragraph: The discussion has been modified to elaborate on the association of fetuin-A with endothelial dysfunction, and the influence of inflammation, diabetes, obesity and insulin resistance on the association of fetuin-A with CVD (page 10, 2nd paragraph). All the relevant and suggested references were included [19, 26-28, 32-38].
- Discussion, Page 11, third paragraph. Data regarding the independent association of OPG with IMT in peritoneal dialysis patients by Janda et al are now commented and the relevant reference is quoted [51].

- Conclusion, Page 12: The conclusions were rearranged and revised taking into account the limitations of our study to allow a clear distinction between arterial stiffness and atherosclerosis and to prove causality of associations.

Minor revisions
- Abstract, Background: the term “osteoprotegerin” was followed by the abbreviation “OPG”
- Abstract, Background: the term “probable” was omitted.
- Abstract, Methods and Results: “osteoprotegerin” was changed to “OPG”
- Abstract, Methods: the modalities adopted to assess ccIMT, fetuin-A and OPG were excluded.
- Abstract, Results: the main factors included in the multiple regression analysis with cfPWV as dependent variable (age, diabetes, history of CVD, hypertension, pulse pressure, and LDL) are reported.
- Background, page 3: References ([1], [2]) were quoted following the first two sentences.
- Background, page 3, third paragraph last sentence: “...placing current understanding (VSMC)...”. (VSMC) was a typing error and it was removed, thus restoring the meaning of the sentence.
- Background, Page 4, first paragraph: the term “probable” was omitted
- Methods, Page 4, first paragraph: “synthetic” was explained as “polysulphone or helixone”, and “low molecular weight heparin” was replaced by “tinzaparin”.
- Methods, Page 4, first paragraph, last sentence: the achieved Kt/V is reported.
- Methods, Page 4, second paragraph: the description of patients characteristics was omitted, with its contents now included in the revised Table 1.
- Methods, Page 6, Statistical Analysis: the method of inclusion of variables into the regression model was explained.
- Statistical analysis and Results: the statistical method (Pierson’s correlation) used to test the linear correlation between IMT, PWV, Fetuin A, OPG and other risk factors was reported.
- Statistical analysis and Results: The factors included in the correlation matrix are now listed in Methods/Statistical analysis section. Only the significant correlations are presented in the Results.
Results: The results of the partial correlation analysis evaluating bivariate associations after adjusting for single variables are explained and reported.

- Results: The presentation of beta values and the p-value of $r^2$ were removed from the Results and are now presented only in the revised Tables 3 and 4.

- Results, (including Tables and Figures): all $p=0.000$ were changed to $p<0.001$.

- Results, Table 3 and 4: The methods providing the listed p values are reported. The non significant beta values are now also reported.

- Conclusion, Page 12: “palse wave” was corrected to “pulse wave”

**Reviewer Professor Adrian Covic**

Thank you very much for your positive review and essential remarks, according to which the following revisions have been made:

1. It was clarified that the study subjects were all patients from the Dialysis Unit of the University Department of Nephrology at Hippokration General Hospital, who consented to the protocol and entered the study consecutively.

2. References describing the PWV and IMT measurement techniques were added (\[13,14\]).

3. In the Discussion section, physiological mechanisms by which fetuin-A and OPG can alter the vascular structure are now presented, along with relevant recent studies retrieved from an updated PubMed search. The relevant and suggested references were quoted \[9, 16-20, 30, 39-43, 49-51\]

4. Typing errors were corrected and a “Patients” subtitle was placed under “Methods”.