Reviewer’s report

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

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Reviewer: ANDREA GALASSI

Reviewer’s report:

Dear Editor and Authors,

I read with interest the paper by Pateinakis P et al. This is a cross-sectional analysis, investigating the association of OPG and fetuin-A with PWV and IMT among 81 hemodialysis patients. The Authors conclude that both fetuin-A and OPG independently predict arterial stiffness but not the early atherosclerotic vascular damage represented by IMT. Although the topic is relevant, some major and minor considerations could be raised about the presentation of the data, their interpretation and the further conclusions.

Major Compulsory Revisions

- Abstract, Results and Conclusion: “prediction” is not appropriate for a cross-sectional study; the concept of “association” would be preferred
- Results: Authors may comment how the association between fetuin-OPG and IMT-PWV was influenced by diabetes (p=0.063 in Table 3, p=0.032 in Table 4). Scatter plots of univariate linear correlations between fetuin-OPG and IMT-PWV would be of interest in diabetic and non-diabetic patients
- Discussion, Page 9, first paragraph: “However, the strong...is in accordance with...and its negative association with mortality”. The message is too strong. The cross-sectional analysis in object cannot enforce any etiological relation between fetuin-A and vascular damage or survival
- Discussion, Page 9, second paragraph: “However a less consistent association...there is little evidence to support an effect of fetuin-A on endothelial function”. This conclusion is not entirely supported by the literature. Caglar K et al observed an independent association between fetuin-A and endothelial function in CKD patients (Transplantation 2007; 83(4):392-7; Nephron Clin Pract 2008;108(3):c233-40). Furthermore, Authors should highlight how any association between fetuin-A and CVD is potentially influenced by inflammation, insulin resistance, obesity and GFR. Authors may quickly consider the following points: 1) some investigations observed an independent association between fetuin-A and IMT in atherosclerotic (Fiore CE et al. Atherosclerosis 2007;195:110-5) and essential hypertensive patients (Guarnieri M et al. Hypertens Res 2013;36(2):129-33) while others did not (Ix JH et al. J Am Coll
Cardiol 2011;58(23):2372-9; 2) the presence or the absence of diabetes may influence the association between fetuin-A and CVD (Jensen MK et al. Fetuin-A, Type 2 Diabetes, and Risk of Cardiovascular Disease in Older Adults: The Cardiovascular Health Study. Diabetes Care 2012), 3) fetuin-A deficiency was associated with a higher risk of incident stroke (Chen HY et al. Eur J Clin Invest 2013;43(4):387-96) and poor AV access patency in dialysis patients (Chen HY et al. Am J Kidney Dis 2010;56(4):720-7)

- Discussion, Page 9, last paragraph. Authors may comment the recent data by Janda K et al about the independent association of OPG with IMT in peritoneal dialysis patients (Pol Arch Wewn 2013)

- Page 10: the conclusions are too strong. “we provide supportive evidence” could be converted into “the present data suggest...” or similar. The present data suggest fetuin-A and OPG as “independently associated” with PWV rather than “strong independent predictors” of PWV. The Author should remark that these data do not allow a clear distinction between arterial stiffness and atherosclerosis. The conclusions should be rearranged taking into account all the aforementioned revisions.

Minor Essential Revisions

- Abstract, Background: the term “osteoprotegerin” should be followed by “OPG”
- Abstract, Background: “probable associations” in unclear, the term “probable” is misleading and could be omitted.
- Abstract, Methods and Results: “osteoprotegerin” should be changed in “OPG”
- Abstract, Methods: the modalities adopted to assess ccIMT, fetuin-A and OPG could be excluded from the abstract
- Abstract, Results: it would be of interest to report the other main factors included in the multiple regression analysis with cfPWV as dependent variable, namely age, diabetes, history of CVD, hypertension and LDL
- Background, page 3: the first two sentences need to be quoted by proper references

Background, page 3, third paragraph last sentence: “...placing current understanding (VSMC)...” is unclear

- Methods, Page 4 first paragraph: “synthetic dialyzer” and “low molecular weight heparin” are bit generic expressions, the exact membranes and heparin may be reported
- Methods, Page 4, first paragraph, last sentence: have all the enrolled patients achieved a Kt/V > 1.2? If it was the case, it could be simply stated that “all the patients achieved a Kt/V > 1.2”
- Methods, Page 4, second paragraph: the description of patients characteristics pertains the results rather than the methods and is anyway redundant with table 1
- Methods, Page 6, Statistical Analysis: the Enter procedure adopted to select the best regression model should be explained otherwise than “(method=Enter)”
- Statistical analysis and Results: the statistical method used to test the linear correlation between IMT, PWV, Fetuin A, OPG and other risk factors should be reported; furthermore, the factors included in the correlation matrix could be listed in Methods, focusing the Results on the significant correlations only.

- Results, Page 6-7: “These correlations were independent of age...hypertension and CVD. In a multiple regression model...”; the independency should have been tested in the regression model described above. Thus it would not be cited in the context of univariate linear correlations. The presentation of beta values and the p-value of r² could be restricted to Table 3 and 4.

- Results: all the p=0.000 should be changed to p<0.001

- Results, Table 3 and 4: the tables seem to report the p-values of univariate linear correlation, t-test and multiple logistic regression models. This heterogeneity is misleading. The notes should clearly explain the methods adopted. Also the non significant beta values should be reported.

- Conclusion, Page 10: “pulse wave” “palse wave”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

Dr Andrea Galassi does not have any conflict of interest related to the present investigation.