Reviewer’s report

Title: Plasminogen activator inhibitor-1 concentrations and bone mineral density in postmenopausal women with type 2 diabetes mellitus

Version: 0 Date: 22 Oct 2015

Reviewer: Claire Higham

Reviewer's report:

The premise of this study is that there is low bone quality observed in type 2 diabetes and this may relate to low grade inflammation.

PAI-1 is a pro-inflammatory cytokine increased in type 2 diabetes and metabolic syndrome. There is also evidence (mainly animal studies) that PAI-1 is involved in bone metabolism.

The hypothesis would be that low grade inflammation increases PAI-1 levels and that this influences bone turnover.

General comments:

Line

58 beneficial

76 others

78 there "is" growing evidence of the importance of PAI in bone metabolism

108 in centimetres single layer

126 immunoanalysis

154 according "to" L-BMD

193 increased

201 osteoporosis
The authors have divided 117 post menopausal women with type 2 diabetes according to lumbar spine BMD into 3 groups, osteoporosis, osteopenia and normal BMD.

A number of other measurements pertaining to diabetes, metabolic status, bone turnover and inflammatory status have been taken and compared between these three groups.

Of note the group with normal BMD had a significantly shorter time from menopause cf to the osteoporosis group and a significantly greater BMI compared to both osteopenic and osteoporotic group.

Patients with normal BMD also had reduced bone turnover markers and higher PAI-I than the osteoporosis group (P 0.042).

The strongest (BMI and age corrected) explanatory variables for PAI-1 were insulin, TG's and duration of Diabetes none of which were significantly different between the 3 groups.

Overall the strongest determinants of PAI-I activity were TG and insulin levels. Pyrilinks was second.

General comments:

The study appears carefully conducted and the article is generally well written and clear

I have some comments/questions

Are the authors able to comment on the accuracy of their DXA scanner at higher levels of BMI?

The authors state that there is a significantly different PAI-1 level in the osteopenic group compared to the normal BMD group but the P value was 0.052. Can the authors comment on this level of significance?

As I understand it, once BMI was corrected for, the strongest predictors for PAI-1 levels were insulin and triglyceride levels neither of which differed between the 3 groups. Could the authors comment on this? Does this not imply that the differing PAI-1 levels between the 3 groups could relate to BMI rather than the BMD? What implications does this have for the conclusions?

Line 203: do the authors mean suppression of bone formation rather than increased resorption? If so is the only evidence for increased inflammation in this group the fact that PAI-1 levels are increased in this group (CRP and fibrinogen were not different)?

Line 216 I would argue that the authors have demonstrated an association of higher PAI-1 levels in patients with diabetes with normal BMD compared to osteoporosis but this does not allow the conclusion that it is the PAI-1 which is protecting the BMD.
There are a number of explanations for these data which should be discussed and explored.

Line 217 - 220 I am unclear about this sentence and conclusion. It needs clarification. The insulin levels were not significantly different between the 3 groups despite the difference in BMI and so how does this explain the difference in PAI-1 in relation to BMD?

Line 230. The authors comment that the influence of bone markers on PAI-1 levels was weaker compared to metabolic parameters. This is confusing as throughout the authors are suggesting that the PAI-1 actually suppresses the bone turnover. I don't think it is possible to distinguish which way round it is from correlative data and so this would better remain as variables that are correlated.

Summary

As I understand the data, what the authors have demonstrated is that post-menopausal women with normal BMD are more likely to have a high BMI, have shorter time from menopause, reduced bone turnover and higher PAI-1 compared to those with osteoporosis. The levels of PAI-1 correlated mainly with insulin and TG levels. There are a number of explanations for these findings and the data presented are not able to distinguish between them. This needs to be clearer throughout. I think the strong suggestion that PAI-1 has a protective effect on bone loss by suppression of bone turnover is not justified from the results presented.

Are the methods appropriate and well described?

If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?

If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?

If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?

If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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