Author’s response to reviews

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

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REVIEWER No1

1. Additional statistical analysis was performed and results have been shown in new Table 4. Three new models were calculated, in the first dependent variable was L-BMD, in the second dependent variable was pyrilinks and in the third dependent variable was osteocalcin. Former Tables 3 and 4 are now in the supplement material. All new results were explained in the section Results and highlighted in red (lines 197 to 214)

2. The statement “These results support the hypothesis that an inflammatory process in overweight and obese women achieves its effect through suppression of bone formation rather than resorption which is consistent with previous studies [21].” in the discussion are removed.

3. References in the introduction and discussion to type 1 are removed.

4. Our diabetic patients were admitted in the hospital because of poor metabolic control. HbA1c is high in the all three groups but there is no difference between groups.

5. We added Supplement Table 1 with numbers and percentage of patients receiving diabetic drugs and combinations, statins, BB and ACEi/AT. In the section Results, line 158-9, the sentence is added: “No one received pioglitazone nor SGLT-2 inhibitors."

6. In the section Biochemical assays, lines 117-9, we added sentence „All blood samples, including samples for determining bone turnover markers, were obtained after overnight fast. “
7. Comment on weight /body composition changes are removed from discussion.

REVIEWER No2

1. All DXA measurements were performed using Hologic, while majority published data regarding accuracy of measurement in adipose subjects were preformed on Lunar. Also our patients were not morbidly obese (115 kg was the upper limit). We didn't calculate percentage of coefficient of variation for each group.

2. This is corrected in the results (significant to “not statistically significant”)

3. That is why we performed adjustment analysis for BMI and age, and after the adjustment the association between insulin and triglycerides and PAI-1 was still present independently of both BMI and age. (Table 3) We also added analysis of lumbar BMD with all parameters and as it turns out there was significant correlation between L-BMD and insulin which remained significant after adjusting for age and BMI (Table 4.A.). L-BMD correlated positively with PAI-1, but after adjusting for age and BMI the association between L-BMD and PAI-1 did not remain significant. The strongest determinants of L-BMD were osteocalcin and insulin levels Also, the association between pyrilinks and PAI-1 remained significant after adjusting for age and BMI (Table 4B). (This is inserted in the results section). In the discussion section line 257 we did say that concentration of PAI-1 is primarily influenced by metabolic parameters such as hyperinsulinemia, hypertriglyceridemia, obesity and adipose distribution while BMD and bone turnover have a smaller effect on circulating PAI-1.

4. The only evidence for increased inflammation is elevated PAI, with no difference in CRP and fibrinogen. Whereas previous work suggests that osteoporosis is linked to inflammation, it is not yet clear whether higher CRP levels are associated with bone loss. In recently published study CRP was associated inversely with composite strength index but not associated with femoral neck or lumbar spine BMD which is consistent with our observation. This is inserted in discussion section.

5. Our assumption that PAI levels are associated with suppression of bone resorption are based on the fact that pyrilinks was independently and significantly associated with PAI-1. Again as in comment 3 this association was weaker opposed to association with metabolic
parameters and we corrected all sentences where we implied that PAI influenced BMD by inhibiting bone resorption.

6. Answer is the same as in comment 3.

7. The conclusion is corrected according to your comments.