Author's response to reviews

Title: Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus

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Version: 4 Date: 26 March 2014

Author's response to reviews: see over
Dear editors,

Dear Dr. Keenan,

Please find enclosed our revised manuscript:

**Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus**

Gudrun Leidig-Bruckner¹,², Sonja Grobholz², Thomas Bruckner³, Christa Scheidt-Nave⁴, Peter Nawroth², Jochen G Schneider²,⁵

that we would like to resubmit for publication in BMC Endocrine Disorders.

As recommended within your e-mail (10th March, 2014) we used the help of a professional language editing service (Edanz) to improve the style of written English. Beside of language editing no other changes were performed concerning the meaning or data of the manuscript.

We think that our data are of interest for the readership of BMC Endocrine Disorders and hope that the re-revised manuscript can now be considered for publication.

Yours sincerely,

Gudrun Leidig-Bruckner
Point to point answers - Review

Comments Reviewer 1 (Hillary Keenan)

1) Question of the study - the complexity of the questions are addressed within the purpose (Line 88-94) and within the Discussion describing the comparison between osteoporosis risk in type 1 and type 2 diabetes and possible risk factors / mechanisms and comparison between subgroups of patients with and without fractures.

2) Methods:

Definition of type 1 and type 2 diabetes was clarified (Line 121-141). A histogram on age of diagnosis was added as well as histogram of age at onset of the study subgrouped by diabetes type. It becomes evident that the majority of patients with type 1 had onset of disease in young age as expected.

   a) Description of pathological findings in respect to retinopathy was added (line 169-171). From the reports we had documented the following details: proliferative retinopathy, maculopathy, vitreous hemorrhage and nonproliferative retinopathy and whether patients had received lasertherapy. However at the time when the study was performed during routine care no standardized documentation of retinopathy was available (like ETDRS rating). Therefore and due to limits of sample size we restricted within the analysis to differentiate between those patients with and without pathological findings.

   b) The part about the statistical analysis was specified within the method section (Line 187-206)

3) Are the data sound?

   a. Data on systolic and diastolic blood pressure from the control population was not available – the EVOS – was a population based study focusing on prevalence and risk factors for osteoporosis and measurement of blood pressure was not part of the protocol.

   b. Histogram of age at diagnosis was added (Figure 1) for patients with type 1 and type 2 diabetes and shows clearly the expected younger age at diagnosis for type 1 diabetes. The 16 patients who were classified as type 1 and who were not on insulin therapy at time of the study were excluded from the analysis. Recalculation of the study without these 16 patients was performed and did not change the main findings – the respective corrections of within the tables and text as well as within the figures (2 and 3) were performed throughout the manuscript.

   c. Comorbidities and medications which were assessed by the questionnaire on possible risk factors for osteoporosis were added as Appendix and included within the result section (Line 228-236) and Discussion (Line 405-409)

   d. Models comparing T1 DM and T2 DM should adjust for duration and BMI: As suggested we included “duration of diabetes” and “BMI” into the ANCOVA beside of age and reported the “adjusted BMD-values” (LSMEANS ± SE) within table 2. In comparison to our first submission including only adjustment for age the values changed slightly (see Table 2), especially within patients with type 1 the consideration of BMI revealed
that adjusted BMD values were not significantly different between type 1 and type 2. Respective changes were made within the manuscript.

Within the multiple linear regression analysis (results now reported as table 3, in first submission as Appendix) we already had considered BMI and duration of disease as covariates.

4) **Discussion and conclusion**
   a. Duration of diabetes was longer in T1DM, indicating longer exposure to hyperglycemia, which is a major contributor to bone health and therefore could explain the higher risk of osteoporosis in type 1 although they were younger… This aspect has been considered within the **discussion** (LINE 431-433)

   b. Comorbidities of T1DM and medications – have been reported and discussed (LINE 405-409)

   c. **Postpubertal diagnosis** of T1 was associated with preservation of – about bone mass compared to those diagnosed before puberty: Discussion – within the discussion the possible influence of puberty in respect to bone mass in type 1 was considered (LINE 400-404).

   d. The discussion comparing femoral neck BMD between T1,T2 and control has to be considered with caution – BMI!

5) **Limitations:** were already addressed. The added clarification of definition of diabetes classified as type 1 and exclusion of those patients without insulin treatment from the analysis did not change the findings.

6) –

7) 

   a. Title was changed: we dropped the “chohort study”

   b. Abstract: Clarification in respect to BMD (lumbar, femoral neck) was performed

**Reviewer 2 (Andrea Montagnani)**

1) See: Material and Method section (statistics) and answers to Reviewer 1 - we reported T-scores, as the definition was used to assess fracture risk in respect to an assumed fracture threshold, as proposed by the WHO-definition – but we are aware of the limitation of this definition in respect to the younger study participants. However most of the patients of our subgroup with type 1 diabetes were older than 30 years and therefore have already passed peak bone mass.
Actually, the use of T-scores to compare type 1 and type 2 diabetes in respect to risk of osteoporosis does not overestimate the risk in our type 1 DM-group: T-scores were not different between type 1 and type 2 DM although due to the younger age of type 1 DM and the known age dependent loss of BMD one would expect T-scores to be higher in type 1 DM than in the older patients with type 2 DM (Table 2).

Furthermore "adjusted BMD values" were calculated considering age, BMI and duration of disease (see comments Reviewer 1, point 2) by ANCOVA. However we keep in mind that it is a limitation that we do not have an optimal age matched control group for our patients with type 1 diabetes. This limitation was addressed within the discussion (line 449).

We did not document Z-scores within our data base – therefore addition of Z-scores was not available now.

2) Figure 2: was dropped as suggested – we reported the information about the prevalence of osteoporosis and osteopenia (WHO-definition) for type 1 and type 2 within the table 2.

3) We agree with the reviewer about the limitations due to the low number of fractures found within our study – we therefore dropped the table 3 and only summarized this information within the text. However we feel that it is important to report the findings about fractures as this is the clinical important issue when considering bone health / osteoporosis and our data represent a cohort of consecutive unselected group of patients with type 1 and type 2 diabetes who were well characterized in respect to diabetes specific complications and also in respect to risk factors of osteoporosis.

Actually the finding of lower BMD in patients with fractures which was consistent for Type 1 and Type 2 and at both measurement sites underlines that bone health is impaired in these patients and needs more attention, especially also with respect to the fracture threshold of -2.5 SD which is probably lower in diabetic patients.

We added within the Discussion that BMD is only one of several determinants of fracture risk. (Line 461-464)

4) It adds new information: see above - fracture threshold in Type 1 and Type 2; assessment of diabetes related complications and bone health