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

Authors:

Gudrun Leidig-Bruckner (thomas.bruckner@t-online.de)
Sonja Grobholz (sgrobholz@gmx.de)
Thomas Bruckner (bruckner@imbi.uni-heidelberg.de)
Christa Scheidt-Nave (scheidt-navec@rki.de)
Peter Nawroth (pater.nawroth@med.uni-heidelberg.de)
Jochen G Schneider (jochen.schneider@mailbox-js.de)

Version: 3 Date: 28 February 2014

Author’s response to reviews:

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.

We would like to express again our thanks for the very helpful editor’s and reviewer’s comments. We have addressed the comments and suggestions in the revised version of the manuscript and in the point-to-point response.
We think that our revised version of the manuscript is 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 2 (Hillary Keenan)

1) Question of the study-
Q: The reviewer did find our study question on the presence and comparison of osteoporosis in diabetes patients well defined. She did however, pointed out that the underlying question is more complex and touches the risk factors and mechanisms of bone health deterioration in type 1 vs. type 2 diabetes. The reviewer acknowledged that we are comparing diabetic subjects, with and without fractures with non-diabetic controls as novelty of the study.

A: We are pleased that the reviewer did find our study question interesting. The complexity of the question is addressed in more detail now within the purpose (Line 89-94) 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:
Q: The reviewer asked for more clarification with regards to the diabetes diagnosis.

A: Definition of type 1 and type 2 diabetes was clarified (Line 118-136). We have utilized the diagnosis criteria from the appropriate associations that were available at the time the subjects were recruited (ADA 2006, WHO/IDF 2006). We have put special emphasis on the correct discrimination between T1DM and T2DM. 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) A: The reviewer requested a more detailed description on the retinopathy assessment

A: Description of pathological findings with regards to retinopathy was added (line 159-164). From the reports we were able to document the following details: proliferative retinopathy, maculopathy, vitreous hemorrhage and nonproliferative retinopathy and whether or not patients had received laser coagulation therapy. However, at the time 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 opted to discriminate only
between those patients with and without pathological findings.

b) Q: The reviewer pointed to missing covariates in the legends
A: The reviewer is correct and we have modified the part about the statistical analysis specified within the method section (Line 181-199).

3) Are the data sound?
   a. Q: The reviewer asked for adding blood pressure data of the control group.
   A: We thank the reviewer for pointing out this option to improve the study. However, 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 original protocol.

   b. Q: The reviewer asked for age clarification of the T1DM subjects and for omitting the T1DM subjects without insulin therapy.
   A: The requested 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 mellitus. There were 16 patients who were classified as type 1 diabetics and who were not on insulin therapy at time of the study. We have these subjects excluded from the analysis as suggested by the reviewer. 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. Q: The reviewer wanted to have Co-morbidities and medication mentioned in the manuscript.
   A: We appreciate this helpful comment. Comorbidities and medications which were assessed by the questionnaire on possible risk factors for osteoporosis (Line 143-150) are now added as Appendix and included within the result section (Line 221-228) and Discussion (Line 381-385).

   d. Q: Models of comparisons between T1DM and T2DM should be adjusted for disease duration and BMI and appropriately assessed.
   A: As suggested we included “duration of diabetes” and “BMI” into the ANCOVA in addition to age and reported the “adjusted BMD-values” (LSMEANS ± SE) within table 2. Compared to the original submission, including only adjustment for age changed the values slightly (see Table 2). Especially in patients with T1DM 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. Q: The reviewer pointed out that despite younger age the hyperglycemia effect on diabetes was greater in T1DM than in T2DM has requested this fact to be discussed.
A: We appreciate the reviewer’s advise and considered this fact within the discussion (Line 406-410)

b. Q: Question with regards to comorbidities and medications
A: Comorbidities of T1 DM and medications – have been reported and discussed (Line 221-228 and 381-385)

c. Q: Postpubertal diagnosis of T1DM should be considered as factor indicating the preservation state of bone mass
A: The reviewer raised an important point. We have considered this point now in the revised version of the manuscript Discussion – within the discussion the possible influence of puberty in respect to bone mass in type 1 was considered (Line 374-380).

d. Q: The reviewer pointed to a careful interpretation of differences in femoral neck BMD between groups because it is often associated with BMI.
A: The discussion comparing femoral neck and lumbar BMD between T1, T2 and control has been adjusted. The influence of BMI was considered by adjusted BMD-values (BMI, age, duration of disease, HbA1c),

5) Limitations:
Q: The reviewer referred to the missing co-morbidities and concomitant medications.
A: These issues were already addressed as pointed out above. 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. Q: The reviewer critized the nomenclature of the study as cohort
A: We thank the reviewer for pointing out this mistake. The title was changed and we dropped the term “cohort study”

b. Q: The abstract was requested to be more precise with regards to each BMD group (FN, LS)
A: Abstract: Clarification in respect to BMD (lumbar, femoral neck) was performed

Reviewer 1 (Andrea Montagnani)
The reviewer pointed to several issues that have now been addressed in the revised version:
Q: The reviewer asked for an explanation on how the BMD was adjusted for age and suggested Z scores as better variable to compare the different populations.

A: We appreciate the reviewer’s critics as to a potential improvement of BMD comparisons between the different groups. 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. 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. Thus, we opted to use T scores which is one appropriate measure to assess fracture risk. We also could, at this point, not use the Z-scores because they were not available from our database.

- Actually, the use of T-scores to compare type 1 and type 2 diabetes in respect to osteoporosis does not overestimate the risk in our type 1 DM-group: The T-scores were not different between type 1 and type 2 DM although 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 lacking an optimal age matched control group for our patients with type 1 diabetes is a limitation. This limitation was addressed within the discussion (line 432-436).

1) Q: The reviewer requested Figure 2 to be deleted.

A: 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.

2) Q: The reviewer raised the important point that fractures were not frequent in our study group, which limits the possibility to make conclusions about fracture risk. The reviewer emphasised the fact that besides BMD there are other important risk factors for fractures in the general population.

A: 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. Our data represent a population of consecutively recruited, unselected patients with type 1 and type 2 diabetes who were well characterized in respect to diabetes, 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 T1DM and T2DM and at both measurement sites which underscores the fact that bone health is impaired in these patients. We conclude that this topic needs more attention, especially also with regards to to the suggested lower fracture threshold in diabetic patients.

We added within the Discussion hat BMD is only one of several determinants of fracture risk. (Line 431-450)
3) Q: The reviewer is of the opinion that the manuscript does not add new data to the body of literature

A: We appreciate the critical appraisal to our manuscript. Yet, we do politely disagree on that point. In accordance to the other reviewer we believe that the present manuscript adds new information to the body of knowledge. We are first to study a very unique consecutively recruited study population of subjects with T1DM and T2DM from a clinical setting. The phenotypic information is carefully collected and the statistical evaluation has been performed under consideration of all possible confounding factors. The conclusion are sound and not overstated. Still, there are several sound conclusion. These refer to the support of a different fracture threshold in T1DM nd T2DM in comparison to nondiabetic as well as to assessment of diabetes related complications and bone health.

Comments Editor:
Q: This is an interesting manuscript with potential value with revision. Yet, as detailed by the reviewers further details need to be provided. Most importantly, the method used to adjust BMD for age and gender. Clarification of T1D and T2D diagnoses need to be included in the methods section and is a mandatory revision

A: We thank the editor for the encouragement to submit a substantially revised version of the manuscript.

We have now described the methods to adjust the BMD assessment for age and gender in more detail (Line 178-196).

In the method section, we have explained the diagnosis criteria and classification of diabetes assessment in the study (Line 115-133)