Author’s response to reviews

Title: Investigating the Risk of Bone Fractures in Elderly Patients with Type 2 Diabetes Mellitus: a retrospective study

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Author’s response to reviews:

Dear Dr. Saisho

Thank you for the thoughtful and constructive comments regarding our manuscript, “Investigating the Risk of Bone Fractures in Elderly Patients with Type 2 Diabetes Mellitus: a retrospective study.” Taking into consideration your comments and suggestions, we have considerably revised our manuscript. We are certain that this revised manuscript will clarify all the main issues that have been indicated in your response.

With these changes to our final manuscript, we hereby resubmit our manuscript for a secondary evaluation. Thank you once again for considering our paper.

Sincerely,

Takeshi Horii

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Reviewer #1

The manuscript describes the results of a retrospective analysis of factors associated with fractures (requiring hospital treatment) among over 2000 elderly (>65 years of age) patients with type 2 diabetes mellitus. The main finding is that treatment with thiazolidine drugs is associated with increased odds for fractures among both men and women.

The study is clinically relevant. In general, the manuscript is well written.

However, I miss some important information regarding the collection of data, and I believe that some findings of the study should be discussed more in depth.

Response

We thank the reviewer for the time and effort spent in reviewing our manuscript. We greatly appreciate your comments and suggestions, based on which we have revised our manuscript.

1. Please specify more clearly, how the data about hypoglycemic treatment were collected. Did you record only the data on drugs administered during the hospital stay / at admission? If so, what about the patients hospitalized twice or more times during the study period? Moreover, this should be discussed as a limitation of the study, as in such case, there are no data on long-term treatment before admission.

Response

We appreciate the reviewer’s insightful comment. We revised the Methods and Discussion sections accordingly.

Page 4, Lines 95–96

“…or (4) hospitalized ≥ 2 times within the study period. Data regarding patient characteristics and medicines used were recorded on the first day of hospitalization.”

Page 10, Lines 227–230
“Fourth, as this was a cross-sectional study, it was not possible to examine the effect of the length of administration period of the hypoglycemic agent on fracture risk.”

2. A high proportion of patients (one third) did not use any hypoglycemic drugs - why? Please discuss the issue.

Response

We appreciate the reviewer’s comment. According to a previous study that investigated the treatment situation of patients with Type 2 diabetes in the outpatient clinic, 50% of patients were reportedly followed-up with diet and exercise only. In this study, approximately 30% of the patients who did not receive medication with diet and exercise alone had fewer reports than previously reported. As the present study targeted hospitalized patients, we believe that patients with poor glyemic control may have been selected.

Thus, we have not made any revisions in the text because we did not consider the frequency of the use of the hypoglycemic agent for each drug group.

3. Is that possible to include the details about the fractures (percentage of hip fractures, other locations)?

Response

We appreciate the reviewer’s comment. The details of the fracture site have been added on Page 6, Lines 126–129.

4. The finding of lower GFR values associated with less fractures should be investigated with more care. I suggest performing the analysis including GFR as a continuous variable, or more categories of GFR as the predictor variable. Probably similar analysis should be also done with HbA1c. It would be interesting to know the ranges of GFR and HbA1c values among patients with and without fractures.

Response

We appreciate the reviewer’s comment. As correctly pointed out, I believe that finely-divided risk assessments, such as that based on CKD grade (G1–5), are very important. However, stratification based on patient context and concomitant medications is more complex and the interpretation of the calculated risks is challenging. In addition, the present study did not use any data collected for research purposes, and therefore, it lacks data regarding renal function, such as
albuminuria, and information regarding Vitamin D3 and calcium preparations used for advanced renal dysfunction. Fracture risk, especially in advanced renal dysfunction, may not be accurately calculated. The present study examines the fracture risk in a wide range; therefore, a separate study must be conducted to elucidate the relationship between renal function and fractures. As the fracture risk in chronic kidney disease is reported to increase at less than 60 mL / min / 1.73 m2, the discussion regarding renal function remains as it is.

In addition, HbA1c (%) was stratified into <7.0, 7.0–8.0, >8.0 and OR was calculated; however, no significant difference was observed.

We have modified Table 3 and have added the following sentence in the Limitations section on Page 10, Lines 230–233:

“Finally, because this study did not use data collected for research purposes, it lacks data regarding renal function, such as albuminuria, and information regarding Vitamin D3 and calcium preparations used for advanced renal dysfunction. Therefore, a detailed study stratifying kidney function could not be conducted.”

5. Page 6, lines 143, 144: The statement "HbA1c (≥7.0 %), age (≥75 years), eGFR (<60 mL/min/1.73 m2), and BMI (≥25 kg/m2) increased the odds ratios of bone fractures [11,20]." is somewhat misleading in the results, as it does not describe the findings of the study presented in Table 3.

If I understand the authors correctly, this statement justifies the categorization of HbA1c, age, GFR and BMI values. Please clarify the paragraph containing the statement.

Response

We appreciate the reviewer’s comment. As the cutoff was described in the Methods section, the corresponding part has been deleted on Page 4, Lines 118–120.

Reviewer: 2

Comments to the Author

Horii et al used repurposed EHR data to investigate factors associated with fracture risk in elderly patients with diabetes. They found that being female and the use of thiazolidine were associated with increased risk while chronic kidney disease was associated with decreased risk. While the manuscript is of interest, I have some comments and concerns presented below.
Response

We thank the reviewer for the time and effort spent in reviewing our manuscript. We greatly appreciate your comments and suggestions, based on which we have revised our manuscript.

1. In the abstract, the authors state that there is a lack of clinical data on fracture risk. Is this true? Please see for example, Conway et al "Glycemic Control and Fracture Risk in Elderly Patients with Diabetes”. Diabetes Research and Clinical Practice 2016; 115: 47-53.

Response

We appreciate the reviewer’s comment. We have revised the Abstract accordingly on Page 2, Lines 28–31.

“Fractures requiring hospitalization greatly affect quality of life, and although elderly patients with T2DM have several risk factors associated with fractures, only a few studies have evaluated these in detail in the Asian population.”

2. Please provide some description of the EHR the study uses. A hospital in Japan? A clinic? A conglomerate of clinics? A university medical center?

Response

We appreciate the reviewer’s comment. We have revised the Abstract as follows on Page 2, Lines 33–38: “We conducted a retrospective study using electronic medical records (EMR) of patients aged ≥65 years with T2DM mellitus who were admitted to a public general medical institute in central Tokyo, Japan.”

3. In the conclusion something needs to be said about the protective relationship of an eGFR less than 60 since it is very strong, effectively cutting risk in half, and not what one would have expected. (in the limitations section, this also needs to be discussed in issues related to repurposing operational data for research since the data were not collected for research purposes-is data for calculating eGFR routinely collected in the patients, particularly as consistently as mediation use and glycemic control or is it disproportionate collected in select patients for reasons indicating a need to measure kidney function?)

Response
We appreciate the reviewer’s comment. We have accordingly revised the Abstract and the Conclusion section on Page 2, Lines 48–51 and Page 10, Lines 240–243, respectively, as follows:

“Information bias, selection bias, and the effect of concomitant drugs may be the underlying reasons for why eGFR <60 mL / min / 1.73 m2 reduced the fracture risk. However, details are unknown, and additional investigations are needed.”

4. The one paragraph introduction is much too long. Please split it into multiple paragraphs. For example, the sentence beginning with "In Japan, the frequency..." can be the start of a new paragraph. Likewise, the sentence starting with "Elderly patients with T2DM can be the start of a third paragraph.

The sentence, "Moreover, patients with type 1 and T2DM..." can be removed since it is immaterial to the manuscript.

Response

We appreciate for the reviewer’s comment. We have divided the section as indicated into separate paragraphs. In addition, we have deleted the specified sentence.

4. Page 4, line 85. Greater clarity on what is meant by cutoff should be provided so that it is clear immediately. Cut off in which way? Good vs. poor (or not good) glucose control?

Response

We appreciate the reviewer’s comment. We have revised the Methods section on Page 5, Lines 98–100 as follows:

“On the basis of the blood glucose target levels recommended by the Japanese Diabetes guidelines for patients with diabetes, the cutoff value for HbA1c was <7.0 and that for BMI was <25 kg/m2.”

5. Perhaps the authors should simply state that risk associated with TZDs did not differ by sex and then provide the ORs and 95% CIs.

Response

We appreciate the reviewer’s comment. We have accordingly revised the Results section on Page 7, Lines 166–169 as follows:
Factors affecting the incidence of fractures in both sexes

Multivariate analysis with fracture as the objective variable (Table 3) revealed a statistically significant difference associated with TZD use (males: OR, 4.70; 95% CI, 1.14–19.3; p = 0.03, females: OR, 4.71; 95% CI, 1.43–15.5; p = 0.01).

6. Perhaps the authors should simply state that risk associated with TZDs did not differ by sex and then provide the ORs and 95% CIs.

Response

We appreciate the reviewer’s comment. As correctly pointed out, this information was already stated. Therefore, I have deleted it from the text.

7. Lines 164-169 provide explanations for very specific findings and is not usually provided in the opening paragraph of the discussion

Response

We appreciate the reviewer’s comment. Accordingly, we have changed the relevant part to a new paragraph on Page 8, Lines 178–183.

8. Page 8, lines 186-191. Perhaps further stratification by HbA1c level in your study would reveal a difference. Is it possible that an HbA1c of 6.5 to <7 is optimal in terms of fracture risk and that an HbA1c below or above this range increases risk?

Response

We appreciate the reviewer’s comment. We considered HbA1c stratification and addition. As a result, no significant difference was found. In addition, we have revised Table 3.

8. Page 8, line 190. What is meant by only previous HbA1c levels were used? Was there only one HbA1c level that was used?

Response

We appreciate the reviewer’s comment. We have revised the Discussion section on Page 9, Lines 204–205 as follows:
“…only the HbA1c value targeted for investigation were used and no subsequent observations were made.”

8. Page 9, 200 to 202. I disagree with the authors statement here since all patients were 65 years and older unless TZD users were substantially more likely to be older than nonusers.

We appreciate the reviewer’s comment. Reportedly, thiazolidine use increases the risk of fractures in male patients with type 2 diabetes aged >50 years, which includes elderly patients. The present study reported on elderly patients aged >65 years and showed that using thiazolidine in male patients increases the risk of bone fractures; thus, we believe that the results of the present study are similar to those of previous studies. Based on this, the suggested text has not been revised.

9. Lines 208 on. Please provide other limitations to using EHR data for research. For example, the problems with missing data since the data were not originally collected for research; the problems with validation of fracture cases since it was based on ICD codes; the problem with renal data in the EHR.

We appreciate the reviewer’s comment. There may be information and selection biases when EHR is used. Thus, I have revised the first limitation on Page 10, Lines 221–223 as follows:

“First, it was a retrospective study conducted at a single institution and using EHR; therefore, information and selection biases that may have affected results could not be eliminated.”

10. Table 1, lines 36-40. This row should be removed from the table.

Table 1, line 46. What is meant by agent? Perhaps removed this word since it is distracting

We appreciate the reviewer’s comment. We have deleted the corresponding part.

11. Table 3 has serious problems. In the second column, under "All patients" the label "Univariate Analysis" is missing. There seems to be a serious formatting problem, with data in many columns often missing. For example, for the final multivariate column in women is very often missing.
We appreciate the reviewer’s comment. The label “Univariate Analysis” is listed under “All patients” in the second column.

Explanatory variables with a significance of \(p < 0.2\) were extracted using univariate analysis, and ORs were calculated using multivariate analysis. For items excluded in univariate analysis, “-” is entered in the multivariate analysis column.