Author's response to reviews

Title: Age-related increases in parathyroid hormone may be antecedent to both osteoporosis and dementia

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Author's response to reviews: see over
To Whom It May Concern:

We have carefully reviewed the comments of the reviewer’s report and have incorporated all necessary changes. Please see the point-by-point response below:

**Noboru Horiuchi:**

Minor Essential Revisions: Spelling mistakes have been corrected. New, clearer figures have been created and are included in the paper.

Comments:

1. *What are the molecular mechanisms of delaying neural processing speed by PTH? The authors should discuss how PTH affects to blunt cognitive function in central nervous system (CNS)? Are there PTH receptors in the CNS? Can PTH go through blood-brain barrier?*

This comment has been addressed in the discussion, see page 13. “PTH has been shown to cross the blood-brain barrier [29]. PTH has been considered a candidate risk factor for senile dementia because sustained high levels of PTH in the brain may cause degeneration of specific brain regions due to Ca(2+) overloading via activation of dihydropyridine-sensitive Ca(2+) channels [30].”

2. *Page 5, paragraph 2, line 1; What is Path? This should be defined.*

See page 4. PATH Medical is an integrative care center and research foundation, and the source of subjects for this study.

3. *Page 7, Test of Normality; Figure 3 and 4 are the same. Figure 3 looks like data on Distribution of PTH.*

New figures have been created and labeled properly. See page 6 and attached figures.
4. Page 9, Number 4 of Table 2; PHT may be PTH.

Yes. This has been corrected in the text. See page 8.

5. Page 12, Title of Table 6; Bone D should be BMD.

Yes. This has been corrected in the text.

6. Page 14, paragraph 2, line 2; OP may be osteoporosis. This abbreviation should be defined.

See page 13. OP is defined as osteoporosis.

7. Page 15, line 3-6; Doteriparitide injections delay onset of dementia? Please explain this issue. Relationship between teriparatide injections and GH treatment is argued in detail.

See page 14. While we found no study as of yet on teriparatide injections and dementia, parathyroidectomy has improved cognitive decline. We have shown that teriparatide lowers endogenous PTH (similar effects to surgical removal of the parathyroid glands). The connection between teriparatide and cognitive decline/dementia warrants further study.

8. Page 19, last reference; Number (28) is missing.

This reference has been added.

Jun Iwamoto:

Comments:

1. When assessing serum PTH levels and BMD, please include factors that could affect them in the analysis; age, vitamin D and calcium supplementation, smoking, alcohol consumption, steroid use, family history of osteoporosis, physical activity, drugs to control bone and calcium metabolism, rheumatoid arthritis, other diseases that cause secondary osteoporosis, and sex hormones, etc. Because
Menopause in females results in marked bone loss, the data analysis would be separated in males and females and in premenopausal and postmenopausal women.

In the discussion we included a remark related to this important caveat. We also included the fact that we are currently separating males and females and pre and post menopausal women. Please see page 13, paragraph 2.

2. Please detail the PTH and BMD measurements. Which method was used to measure serum PTH levels? Which skeletal site was assessed? What kind of DXA was used?

We detailed the PTH measurement by referring to the reference laboratory that carries out standard tests. We described the DXA method and device and sites. Please see last paragraph on page 4.

3. The reference #28 may be missing.

Reference 28 was included. See page 19.

Additional Changes:

We reworked the figures for better clarity.

In the discussion section on page 14, we added a reference on a recent study in JCEM about parathyroidectomy improving cognitive decline [31]. This further supports our findings on the connection between P300 latency, a measure of cognitive decline, and elevated PTH/osteoporosis.

It is our belief that the paper is better and meets all requirements for publication.

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