Author's response to reviews

Title: Influencing factors on serum 25-hydroxyvitamin D3 levels in Japanese chronic hepatitis C patients

Authors:

Masanori Atsukawa (momogachi@yahoo.co.jp)
Akihito Tsubota (atsubo@iikei.ac.jp)
Noritomo Shimada (noritomos@hotmail.com)
Kai Yoshizawa (kaiyoshiza@yahoo.co.jp)
Hiroshi Abe (hiroshiabe222@aol.com)
Toru Asano (tasanobkttokyo@yahoo.co.jp)
Yusuke Ohkubo (yusuke-ohkubo@mtg.biglobe.ne.jp)
Masahiro Araki (ma-araki@chubyoin.pref.ibaraki.jp)
Tadashi Ikekami (ikekamit@tokyo-med.ac.jp)
Chisa Kondo (s8042@hotmail.co.jp)
Norio Itokawa (mid@mtc.biglobe.ne.jp)
Ai Nakagawa (a0520i@nms.ac.jp)
Taeang Arai (taeang@yahoo.co.jp)
Yoko Matsushita (yokoyymym18s@yahoo.co.jp)
Katsuhisa Nakatsuka (kaynet@nms.ac.jp)
Tomomi Furihata (momogachi@yahoo.co.jp)
Yoshimichi Chuganji (chuganji@gmail.com)
Yasushi Matsuzaki (ymatsuzaki-gi@umin.ac.jp)
Yoshio Aizawa (aichanyoshi@yahoo.co.jp)
Katsuhiko Iwakiri (k-iwa@nms.ac.jp)

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Professor Philippa Harris

Executive Editor, BMC Infectious Disease

Revision 1

Manuscript title: Influencing factors on serum 25-hydroxyvitamin D3 levels in Japanese chronic hepatitis C patients

Dear Prof. Philippa Harris

We were pleased to read the fair assessment of the reviewers and the encouraging comments by members of the Editorial board. We believe that adequate modifications were successfully made in our revision, taking into
consideration the comments raised by the expert reviewers. We also carefully proofread the revision including the text.

We take this opportunity to express our gratitude to the reviewers for their useful and critical remarks. Their comments allowed us to identify areas in our manuscript that needed modification and clarification.

We hope that the revision is now acceptable for publication in BMC Infectious Disease.

Sincerely Yours,

Masanori Atsukawa, M.D. PhD.
Division of Gastroenterology,
Department of Internal Medicine,
Nippon Medical School Chiba Hokusoh Hospital
1715, Kamakari, Inzai, Chiba, 270-1694, Japan.
Phone: +81-476-99-1111
Fax: +81-476-99-1908
E-mail: momogachi@yahoo.co.jp

Point by point

We are grateful to the Referees for the helpful comments. We have revised the manuscript accordingly, and hope that it is now suitable for publication.

Editor’ comment

# The revised manuscript has been proofread by a native English speaking specialist.

Reviewer 1

none

Reviewer 2

We thank the reviewer for the comments. We carefully polished and thoroughly re-wrote the manuscript including title, abstract, and text.

Would you please see the re-revised version on our manuscript?

- It is well established in the literature that total 25OHD deficiency is common among individuals with chronic hepatitis C. This has been shown in Asian cohorts as well. The investigators need to provide a stronger justification for their largely
descriptive study. This should not be the stated objective of the study.

#As suggested by the reviewer, we rewrote manuscripts including title, abstract and background, and added some phrases.

Title; Relationship between chronic hepatitis C and serum 25-hydroxyvitamin D3 levels in Japan

#Influencing factors on serum 25-hydroxyvitamin D3 levels in Japanese chronic hepatitis C patients

Abstract, line 95-96; The purpose of this study is to clarify the factors which affect serum 25-hydroxyvitamin D3 levels using data obtained Japanese chronic hepatitis C patients.

Background, line 169-170; The purpose of this study was to investigate serum 25-hydroxyvitamin D3 levels and to analyze factors influencing these levels using data obtained from Japanese chronic hepatitis C patients.

- The lack of association between total 25OHD levels and FIB-4 is interesting. Many studies have reported high rates of 25OHD deficiency among patients with cirrhosis and suggested a linkage between 25OHD levels and fibrosis progression/cirrhosis. This large study is an opportunity to suggest otherwise – that possibly low 25OHD levels are due to the fact that decompensated cirrhotics simply do not go outside as much. I think that this point should be highlighted more, and perhaps even an explicit aim of the study.

- What are potential explanations for the associations between low hemoglobin levels and vitamin D deficiency? One might speculate that low hemoglobin is a surrogate marker for chronic illness, and patients who are chronically ill go outside in the sun less frequently. This makes collecting information regarding sun exposure all the more important – otherwise this association between low hemoglobin and 25OHD deficiency seems a bit spurious. The investigators should consider whether including it in the model at all is clinically relevant. If the investigators do wish to include it in their model, then it needs to be discussed.

#In accordance with above referee’s advice, a discussion on serum vitamin D levels according to liver fibrosis (fib-4 index) and hemoglobin levels has been added to the Discussion section.

“Decreased activity or not going out frequently may contribute to lower serum
vitamin D levels. Specifically, in elderly female subjects who have anemia and/or advanced liver fibrosis, reduced sunshine exposure may result in poor vitamin D synthesis. In deed, it was shown that seasonal variation in the amount of sunlight exposure influences the serum vitamin D level: a season with low-level sunshine was an independent factor associated with a decreased serum vitamin D level, whereas, a season with more sunshine was the second most important factor associated with a sufficient serum vitamin D after sex differences. It was reported that in patients with advanced liver fibrosis, there was a decreased level of serum vitamin D. In such patients, active exposure to sunshine may increase the serum vitamin D level. Thus, our study suggests that the progression of liver fibrosis may not influence the serum vitamin D level, depending on a patient’s environmental factors.”

- Information regarding sun exposure and vitamin D supplementation should be included. If this information was not collected, then it needs to be discussed as a limitation.

#As suggested by the reviewer, limitation was added to Discussion as follows: “In addition, although we gathered seasonal data on serum vitamin D measurement, data on the number of hours of sunshine per day were not available.”

Exclusion criterion was added in line 187-188; “taking drugs and/or supplements containing vitamin D”

- Please explain the clinical relevance of evaluating factors predictive of 25OHD sufficiency after evaluating factors predictive of deficiency. If not relevant, then the authors should consider taking it out.

#In accordance with referee’s advice, a mention about a factor predictive of 25OHD sufficiency was added to Discussion as follows: “We showed another important reason which an environmental factor gives to serum vitamin D level. In this study multivariate analysis of a factor contributing to serum 25-hydroxyvitamin D3 sufficiency identified the factors of warm season as an independent factor.”