Title: Can Chitosan Chewing Gum Reduce the Serum Phosphate of Hemodialysis Patients? A Multi-Center Randomized Double-Blind Placebo-Controlled Trial

Authors:
Tadao Akizawa (akizawa@med.showa-u.ac.jp)
Yoshinari Tsuruta (ytsuruta@meiyokai.or.jp)
Yoichi Okada (okada@maruyamakai.or.jp)
Yoshihiro Miyauchi (yomiya@hospital.asahi.chiba.jp)
Akio Suda (sudaclinic@sudaclinic.jp)
Hiroshi Kasahara (hirosi-kasahara@suwa.jrc.or.jp)
Nobuhiro Sasaki (sasanobu@jichi.ac.jp)
Yoshitaka Maeda (yoshimaeda43@yahoo.co.jp)
Takako Suzuki (takako10@aol.com)
Noriaki Matsui (matsui_syun@ethnic.co.jp)
Jun Niwayama (j.niwayama@sumiyoshi-clinic.or.jp)
Toshiaki Suzuki (se8t-sz@asahi-net.or.jp)
Hideaki Hara (hidehara@gifu-pu.ac.jp)
Yasushi Asano (asanoy@koga.jrc.or.jp)
Sadao Komemushi (volvo.s80.classic386@gmail.com)
Masafumi Fukagawa (fukagawa@tokai-u.jp)

Version: 4
Date: 1 May 2014

Author's response to reviews:

Title: Effect of chitosan chewing gum on reducing serum phosphorus in hemodialysis patients: a multi-center, randomized, double-blind, placebo-controlled trial

Authors:
Tadao Akizawa (akizawa@med.showa-u.ac.jp)
Yoshinari Tsuruta (ytsuruta@meiyokai.or.jp)
Yoichi Okada (okada@maruyamakai.or.jp)
Yoshihiro Miyauchi (yomiya@hospital.asahi.chiba.jp)
Akio Suda (sudaclinic@sudaclinic.jp)
Hiroshi Kasahara (hirosi-kasahara@suwa.jrc.or.jp)
Nobuhiro Sasaki (sasanobu@jichi.ac.jp)
Yoshitaka Maeda (yoshimaeda43@yahoo.co.jp)
Takako Suzuki (takako10@aol.com)
Dear Dr. Gutierrez,

Object: MS: 5311023681198829- Effect of chitosan chewing gum on reducing serum phosphorus in hemodialysis patients: a multi-center, randomized, double-blind, placebo-controlled trial by Prof. Tadao Akizawa et al.

Thank you consideration of our manuscript for publication in your journal.

We have reviewed the above manuscript according to your and reviewer’s comments.

=====================================
EDITORIAL COMMENTS
=====================================

1. You use phosphate, phosphorus and phosphorous in the manuscript. Please just use phosphorus throughout the manuscript to be consistent. Also please note that the spelling of this word is "phosphorus" not "phosphorous"

We have revised the text to use only "phosphorus" according to your suggestion.

2. Please indicate which assays were used to measure intact PTH and whole PTH.

We revised our Method section regarding PTH assay as depicted on page 8, lines 171-173: " Serum levels of whole PTH and iPTH were analyzed by immunoradiometric assay and electrochemiluminescence immunoassay, respectively, at SRL Inc., Tokyo, Japan."

3. Page 10, lines 221-226: "Sixty-three patients chewed at least one tablet... Sixty-one patients completed the 3-week treatment phase. Two patients were not included because of withdrawal of consent and one was not included for failure to comply with the study protocol because of a change in dialyzer during the
treatment phase." According to my read of Figure 1, it seems that in this last sentence one patient (not two) was not included because of withdrawal of consent and one was not included for failure to comply with the study protocol. Please clarify and/or correct the text.

We have confirmed our mistake in the number of patient withdraw from the study as pointed out by you, and corrected as depicted on page 10, lines 225-226: "One patients was not included because of withdrawal of consent"

4. Page 11, lines 230-232. "Changes in mean phosphorus levels... with no significant difference between the two groups (p = 0.65)" Nowhere in the text is it indicated that you are referring to Table 2 here. Please revise the text as necessary to point the Readers to the relevant Table here.

Table 2 has been indicated in the text "Changes in mean serum phosphorus levels... with no significant difference between the two groups (p = 0.65) (Table 2)." (page 10, line 233).

5. Page 5, Lines 84-86. "Therefore, patients should take a lot of pills of a phosphate binder three time daily with meal, and this is associated with a risk of gastrointestinal symptoms and decrease adherence." While the English and grammar have greatly improved, this sentence still needs work. Please consider the following re-write: "Therefore, patients often have to take many phosphorus binder pills three times daily with meals, and this is associated with a risk of gastrointestinal symptoms and decreased adherence.

We have revised the sentence according to your suggestion as depicted on page 5, lines 84-86: "Therefore, patients often have to take many phosphorus binder pills three times daily with meal, and this is associated with a risk of gastrointestinal symptoms and decrease adherence."

Reviewer #2 (Dr. Shishido)

MINOR ESSENTIAL REVISION

1. In this paper, the authors use two similar terms, “phosphorus” and “phosphate”. Please confirm to use the two words suitably and properly in the context.

We have revised the text to use only "phosphorus" according to your suggestion.

We hope that you will now consider this study acceptable for publication in BMC Nephrology.

We look forward to hearing from you soon.

Yours sincerely,

Prof. Tadao Akizawa
Division of Nephrology
Department of Medicine,
Showa University School of Medicine
1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
Phone: +81-3-3784-8686
Fax: +81-3-3784-3751
E-mail: akizawa@med.showa-u.ac.jp