Author’s response to reviews

Title: Factors associated with chronic musculoskeletal pain in patients with Chronic kidney disease

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Author's response to reviews: see over
Dear Editor in Chief:

Please find enclosed the revised version of our manuscript (MS: 1920040968021932) entitled "Factors associated with chronic musculoskeletal pain in patients with Chronic kidney disease" by Heng-Jung Hsu, Chiung-Hui Yen, Kuang-Hung Hsu, I-Wen Wu, Chin-Chan Lee, Ming-Jui Hung, Chiao-Yin Sun, Chia-Chi Chou, Yung-Chih Chen, Ming-Fang Hsieh, Chun-Yu Chen, Chiao-Ying Hsu, Chi-Jen Tsai, and Mai-Szu Wu.

As requested by the reviewers, we had provided detail information about recruiting patients to enhance strength of this study. Besides, we also excluded the patients which hospitalized for other reasons in the 3 months before the start of the study to remove the possible unspecific pain complaint related to acute illness. We also re-calculated the eGFR of CKD patients by the CKD-EPI equation to provide more precise estimation of eGFR in those patients with eGFR greater than 60. Moreover, we changed the term “gout” to “hyperuricemia” by suggestion. Possible confounders such as use of diuretics or allopurinol, co-morbidities of polycystic kidney disease, rheumatoid arthritis, spondylarthropathies, and spine osteoarthritis were also been considered and analyses in the revised manuscript. Additionally, language correction was done in the whole manuscript.

Accordingly, the manuscript has been rewritten in part. The responses to the comments of the two reviewers are provided in separate letters of the revised manuscript is also enclosed. We hope that the revised manuscript will now be suitable for publication in your journal.

Yours sincerely,

Mai-Szu Wu M.D
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As requested, a copy of revised manuscript with changes highlighted is included.

Index of Changes made in the revised manuscript:

Page 4, line 5-10: Patients satisfying the following criteria were included in this study consecutively: age >18 to <80 years and with no spontaneous improvement or progression of renal disease in the 3 months before the start of the study. Patients with acute illness requiring hospital admission in the past 3 months, cancer without remission, or were unwilling to participate in the trial were excluded from the study. The statement about method of enrollment study patients is suggested by the reviewer 1.

Page 4, line 10-13: CKD was defined as presence of persistent proteinuria or a decreased estimated glomerular filtration rate (eGFR) of <90 mL/min per 1.73 m² [determined by the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation] in 2 separate measurements within an interval of 3 months. The statement about CKD staging by CKD-EPI equation was suggested by the reviewer 1.

Page 5, line 11-19: Basic demographic data were collected, including information on age, gender, nutrition status (body mass index [BMI] and waist circumference), history of smoking, alcohol, and betel nut consumption, current use of NSAIDs or Chinese herbal medicines, and the presence of diabetes, hypertension, coronary artery disease (CAD), peripheral arterial occlusive disease (PAOD), congestive heart failure (CHF), stroke, hyperuricemia, systemic lupus erythematosus (SLE), urolithiasis, polycystic kidney disease (PKD), rheumatoid arthritis (RA), spondylarthropathies, spine osteoarthritis (OA), and back pain. Current use of diuretics or allopurinol was also collected. The statement about confounders was suggested by the reviewer 1.

Page 6, line 13–19: The presence of PKD was defined by kidney echo report. The presence of RA was defined by the 2010 ACR / EULAR Rheumatoid Arthritis Classification Criteria. The presence of spondylarthropathies was defined by the European Spondylarthropathy Study Group criteria for spondylarthropathy. Spine OA was defined by clinical history, findings on physical examination, and radiographic findings suggested by
rheumatologists. The statement about confounders and definition was suggested by reviewer 1.

Page 9, line 14–16: Chronic MS pain was not associated with age, smoking, alcohol/betel nut consumption, or co-morbidities such as hypertension, CAD, PAD, CHF, stroke, SLE, urolithiasis, PKD, RA, Spondylarthropathies, spine OA, and diuretics use. The statement about consideration of confounders was suggested by the reviewer 1.

Page 11, line 12–14: These findings suggested that co-morbidity of hyperuricemia may be one of the major co-morbidities that contribute to chronic MS pain in CKD patients after adjustment other confounders. The statement about the possible association between hyperuricemia and chronic MS pain was suggested by reviewer 1.

Page 12, line 24–Page 13, line 3: Moreover, several studies had found high prevalence of gout in patients with Type 2 diabetes. Choi et al. found that hyperuricemia is a risk factor for diabetes mellitus. Moreover, Lai et al. found that gout and type 2 diabetes mellitus shared the most common genetic factors which explain why there existed a mutual inter-dependent effect on higher incidences. The discussions about finding of diabetes as protective factor form MS pain in CKD patients were suggested by the reviewer 1.

Page 13, line 11–page 14, line 1: The study found the chronic MS pain patients had similar prevalence of NSAIDs use or Chinese Herbal medication use with those patients without chronic MS pain. In our study patients, there was no difference in use of NSAIDs or Chinese Herbal medication between patients with hyperuricemia and without hyperuricemia. The possible explanation about lacking association between NSAIDs use in CKD patients with pain may be owing to our CKD center good education to reducing the rate of NSAIDs use in chronic MS pain patients. Our CKD education provided CKD patients lots of information about protecting renal function, including better blood pressure control and avoidance of NSAIDs and Chinese Herbal medication use. There were significant lower rate of NSAIDs use (7.8%) in our CKD study patients with chronic MS pain as comparing with the report of Pham et al. (23.2%). It is possible why our study patients had lower prevalence of NSAIDs use and Chinese Herbal medication. Another explanation is that CKD patients in nephrology clinics were usually be reminded not using NSAIDs agents to
protect their kidney function. This information may let those chronic MS pain patients not be honest to answer the questionnaire about NSAIDs use items, which was the limitation of the questionnaire. The discussions about lack association of NSAIDs/Chinese herb medication use in CKD patients with pain were suggested by the reviewer 1.

Page 14, line 25 – Page 15, line 2: This study had some limitations. The information regarding pain relief agent in study patients was lacking. Furthermore, the colchicine use for gout relief in study patients was also not collected. In addition, the quality of life survey was not evaluated in this study. The statement about limitations of the study was suggested by reviewer 1.
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Answers to Reviewer 1

1. The reviewer suggested the detail information about recruiting patients may be helpful. We agreed the reviewer’s suggestion that more detail information about the recruiting patients can provide the strength of this study. In our study, we recruited study patients from our nephrology clinics in which the rheumatologist was nearby our clinics. We recruited the chronic kidney disease (CKD) patients with age between 18 and 80 years old, consecutively. The possible high patient recruitment rate may be related to convenience for evaluation by rheumatologist who is nearby and also good doctor-patient relationship. The statements about the patients’ recruitment were added in the “materials and methods” part of revised manuscript (page 4, line 5-6).

2. The reviewer indicated the exclusion criteria about patients hospitalized for infection but not hospitalized for other reasons was not proper. We agreed the reviewer’s point and had corrected our exclusion criteria and also excluded the patients which hospitalized for other reasons in the 3 months before the start of the study. There were 56 patients excluded from our study due to other reasons hospitalization and the results were re-analyses in final recruit patients (n = 456). The statements about the exclusion criteria of patients’ recruitment were corrected in the “materials and methods” part of revised manuscript (page 4, line 8-10). Besides, the results of our study had corrected after re-analyses due to study numbers change and the final results of our study were corrected in the “result “part of revised manuscript.

3. The reviewer indicated that CKD-EPI equation may be a better method than MDRD to prove precise estimation in CKD patients with GFR greater than 60. We had re-categorized the study patients into CKD stage 1, 2, 3, 4, and stage 5 by CKD-EPI equation. The statements about CKD staging by CKD-
EPI equation was corrected in the “material and method’ part of revised manuscript (page 4, line 10-13).

4. The reviewer indicated that hyperuricemia is better than gout due to those study patients did not fulfill the criteria of gout by American Rheumatology Association, Rome or New York criteria. We had changed the term “gout” to “hyperuricemia” in the revised manuscript.

5. The reviewer suggested that information regarding colchicines or allopurinol use may have been helpful. We agreed the suggestion by the reviewer and had added the information of allopurinol use into the “table” and “result” part of revised manuscript. However, the information regarding colchicines use was lacking and we had stated this weakness in the limitation portion of “discussion” part of revised manuscript (page 14, line 26 –page 15, line 1).

6. The reviewer indicates that a number of confounders that should be addressed before the assertion mad about hyperuricemia as a major factor in chronic MS pain in CKD patients. We agreed that these confounders were important and should be addressed, including co-morbidities of polycystic kidney disease, back pain, rheumatoid arthritis, spine osteoarthritis, spondylarthropathies, and diuretics use. We had corrected our study and added these confounders and the result after re-analysis showed that hyperuricemia was a major factor in chronic MS pain in CKD patients after considering these confounders. The statements about collecting the confounders were added in the “material and method” part of revised manuscript (page 5, line 11-19; page 6, line 13-19). The result of above statement was added in the “result” part of revised manuscript (page 9, line 14-16).

7. The reviewer suggested that information regarding medication prescription for pain relief may be interesting. We agreed that this information about different kinds of medication prescription for pain relief is interesting. However, the information about medication prescription for pain relief was not collected in this study. We had stated this weakness in the limitation portion of “discussion” part of revised manuscript (page 14, line 25-26).

8. The reviewer indicated that the discussion about the association of gout and pain in this population is over-reaching. We agreed that association between
gout and pain in CKD patients were not clear even after this study. Co-morbidity of gout may be one of the major co-morbidities that contribute to chronic MS pain in CKD patients after adjustment of other confounders. We had modified our statements in the “discussion” part of revised manuscript (page 11, line 12-14).

9. The reviewer suggested that a Quality of Life Survey would be useful in chronic pain study. We agreed that Quality of Life Survey is useful and interesting in chronic pain study in CKD patients. However, we didn’t collect this information about quality of life parameters in this study. We had added this weakness in the limitation portion of “discussion” part of revised manuscript (page 15, line 1-2).

10. The reviewer suggested that more discussion about diabetes as a protective factor from MS pain in CKD patients with hyperuricemia. We agreed that the complexity of the association between hyperuricemia and diabetes and the discussion about our finding of diabetes as a protective factor from MS pain in patients with hyperuricemia is needed. We had added the discussion about the association between hyperuricemia, diabetes, and chronic MS pain in the “discussion” part of revised manuscript. (page 12, line 24 – page 13, line 3)

11. The reviewer indicated that the discussion about lack association of NSAIDs use/Chinese herbal medication use in the populations with pain is needed. We agreed that the discussion about lack association of NSAIDs use/Chinese herbal medication use in the populations with pain is warranted. The study found the chronic MS pain patients had similar prevalence of NSAIDs use or Chinese Herbal medication use with those patients without chronic MS pain. In our study patients, there was no difference in use of NSAIDs or Chinese Herbal medication between patients with hyperuricemia and without hyperuricemia. The possible explanation about lacking association between NSAIDs use in CKD patients with pain may be owing to our CKD center good education to reducing the rate of NSAIDs use in chronic MS pain patients. Our CKD education provided CKD patients lots of information about protecting renal function, including better blood pressure control and avoidance of NSAIDs and Chinese Herbal medication use. There were significant lower rate of NSAIDs use (7.8%) in our CKD study patients with chronic MS pain as comparing with the report of Pham
et al. (23.2%). It is possible why our study patients had lower prevalence of NSAIDs use and Chinese Herbal medication. Another explanation is that CKD patients in nephrology clinics were usually be reminded not using NSAIDs agents in order to protect their kidney function. This information may let those chronic MS pain patients not be honest to answer the questionnaire about NSAIDs use items, which was the limitation of the questionnaire. The above statements were added in the “discussion” part of revised manuscript. (page 13, line 11- page 14, line 1)
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Answers to Reviewer 2

1. The reviewer indicates some language errors in the manuscript need corrections. We agreed that there were some language errors in the manuscript and we had corrected the language errors through whole manuscript by suggestion.