Reviewer's report

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

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**Reviewer:** Samir S Patel

**Reviewer's report:**

In the manuscript entitled "Factors associated with chronic musculoskeletal pain in patients with chronic kidney disease", Dr. Hsu et al report on a cross-sectional survey of pain in patients with pre-dialysis chronic kidney disease. The pain survey focuses on chronic musculoskeletal pain and serves primarily for hypothesis generation as to factors in the causal pathway of this type of pain.

Strengths of the study are that it directly addresses pain, a common symptom that has been reported in patients with end-stage renal disease, and one that requires more attention to determine optimal assessment and management. Furthermore, there is a dearth of studies addressing pain specifically in the chronic kidney disease population pre-dialysis. Additional strengths are the fairly large study population and the focus on chronic musculoskeletal pain. More discussion on limitations of the study would be appropriate.

**Major Compulsory Revisions:**

#1 Details on how patients recruited would be helpful in determining the strength of the study. The very high patient recruitment rate (as detailed in Figure 1) and the fact that all of the patients were from a nephrology clinic could be a strength but also could open them to selection bias based on how patient were recruited (e.g. consecutively or some other selection process?). Another related issue is the rationale for excluding patients hospitalized for infection but not hospitalized patients for other reasons (line 80)?

#2 The CKD–EPI equation may be a better test (or another appropriate for the Taiwanese population) then MDRD. The MDRD equation may underestimate renal function in patients with a GFR greater than 60. The CKD-EPI may re-categorize some patients with stage 3 as actually stage 2.

#3 The designation of hyperuricemia as “gout” is problematic. Gout would be best defined thorough the American Rheumatology Association, Rome or New York criteria. It is not clear why the investigators did not evaluate this since they conducted a thorough interview of the patients at time of enrollment. Information regarding colchicine or allopurinol use may have been helpful. Perhaps the “gout” should be changed to hyperuricemia unless there was a very high correlation between tophi and hyperuricemia.

#4 There are a number of confounders that should be addressed before the assertions are made about gout as a major factor in chronic MS pain in patients
with CKD. I believe diuretic use is very significant potential confounder since it increases the risk of hyperuricemia and gout. Diuretics could be a cause of muscle cramping that may not be chronic but could be recurring frequently. Another potential confounder is Polycystic Kidney Disease as a cause of renal disease and also back pain that may have been classified as musculoskeletal pain. Other causes of chronic musculoskeletal pain should have been sought out: SLE was addressed, but Rheumatoid Arthritis, Spondylarthropathies, and even osteoarthritis of the spine (a location unlikely to be affected by gout). Finally, although not a confounder perhaps, but of interest, would be an inventory of prescription pain medication use such as opioids or agent used for neuropathic pain such as gabapentin or tricyclic agents.

#5 The discussion is over-reaching in terms of the association of gout and pain in this population. Line 220 to 222 should be adjusted accordingly.

Discretionary Revisions:

#1 A Quality of Life Survey (e.g. assessment of burden of illness, depression, anxiety, satisfaction) should be useful in any pain study, particularly one about chronic pain (Dworkin RH et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008 Feb;9(2):105-21.). If this information was included in the evaluation of the patients, then it would be helpful to analyze it along with the pain data.

#2 The finding of diabetes as protective factor from MS pain in patients with hyperuricemia/gout is interesting and perplexing based on my review of the association of gout and DM. Hyperuricemia is a risk factor for metabolic syndrome and perhaps diabetes. (Choi HK et al. Rheumatology 2008. Oct 47(10): 1567-70) but the relationship appears to be complicated and not well defined. More discussion of this finding in light of studies completed so far, may be warranted. The lack of association of NSAIDs use/Chinese Herbal medication use in the populations with pain should be discussed. Was there a difference in use of these agents between patients designated as having gout versus those without gout?

The title and abstract are appropriate. The Discussion should reflect of limitations of the study.

Minor Compulsory issues:

Line 63 Sentence starting with “There were 82% CKD patients…” needs to clarified and perhaps placed after the first sentence in the paragraph.

Line 69 “prevalence of use of “ is better written as prevalence of NSAID or Chinese Herb use for pain relief…”

Line 142 the parentheses symbol should be removed at start of this line

Line 158 remove the word “a “ before “chronic “ and remove the word “problem” after “MS pain…”

Line 203 remove the word “significantly” since it is redundant in this sentence
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests