Osteoarthritis and Cartilage 25 (2017) e3–e4

Osteoarthritis and Cartilage

Letter to the Editor

Reply to the letter: Long term use of analgesics and risk of osteoarthritis progressions and knee replacement

Dear Editor,

We would like to thank the authors for the careful evaluation of our published manuscript[1]. We agree with a significant portion of the comments. The results of our observations should be interpreted only after considering the limitations in the selected study design and data availability. As we clearly mentioned in the manuscript (*please see the last paragraph of the methods section*) establishing a cause and effect pathway is beyond the limits of our observation. Given that the understanding of any disease pathophysiology and risk factors is formed by small contributions from various investigations (with considerable limitations of their own), the purpose of our study was to make a contribution using a different analytic approach.

Selection bias is a major concern when an observed association between the two variables (i.e., exposure and outcome with a common effect) is conditional, when the association is measured within the certain level of common effect, and therefore is different between the selected population (cases and controls) and the entire cohort population for which the study interpretations are implied[2]. In this regard, as discussed in the main text, it's critical to acknowledge that the Analgesic+ and Analgesic− groups are not representative of the majority of community-dwelling subjects with knee osteoarthritis (OA) such as osteoarthritis initiative (OAI). In fact, the selected groups are two opposite ends of a spectrum and thus, were hypothesized in our methodology, to be able only to demonstrate the association using the available samples.

With respect to knee replacement, we agree with the accurate concern that was re-emphasized by the authors. While Analgesic+ and Analgesic− groups had similar levels of symptoms, the Analgesic+ subjects had achieved it with the aid of analgesic medications, and therefore, were more likely to exhaust non-surgical treatment options and consecutively, more likely to receive knee replacement. While the association between knee pain and knee replacement is well documented and clinically intuitive, the association between worsening of knee pain and radiographic progression of knee OA is not as clear[3–5]. Patients' symptoms may be related to OA-related specific structural damage, rather than OA severity and state[6]. It's been suggested that pain and function worsening may be related to structural damage in knee OA[7]. However, this may not hold true when the direction is reversed; pain and functional disability may or may not result in radiographic knee OA and its progression[3,5]. The issue can be more perplexing when considering the difference in the amount of joint loading[8]. In other words, Analgesic+ group may have had worse structural damage in the setting of suppressed symptoms in overtime, which could have been directly associated with greater knee OA progression. Additionally, in these subjects, more joint loading due to suppressed pain by analgesics might have caused more OA progression. In either case, while other approaches like using directed acyclic graphs may serve this purpose, the extent of the available data and our study design prevented us from providing speculations about the causation diagram and the temporal precedence of events. Nevertheless, we managed to demonstrate the observed association by acknowledging the room for potential moderators, recognition of which fall outside the scope of our study.

Author contributions

NHN and SD prepared the draft of this letter. All authors approved the final version.

Conflicts of interest

Nima Hafezi-Nejad has no conflicts of interest. Ali Guermazi is president and shareholder of Boston Imaging Core Lab, LLC. He is a consultant to Genzyme, MerckSerono, TissueGene and OrthoTrophix. Frank W Roemer is CMO and shareholder of Boston Imaging Core Lab, LLC. John Eng and Bashir Zikria declare no conflicts of interest. Shadpour Demehri has grants from GERRAF 2014–2016; Carestream Health Inc. 2013–2015 for Cone-beam CT clinical trial. He is a consultant to Toshiba Medical Systems.

Acknowledgements

None.

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DOI of original article: http://dx.doi.org/10.1016/j.joca.2016.07.022.

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26 August 2016