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Osteoarthritis and Cartilage

Letter to the Editor

Letter to the editor: Does long-term use of analgesics increase the risk of radiographic progression of knee osteoarthritis and future total knee replacement?

We read the paper of Hafezi-Nejad *et al.*[1], that addressed the question if long term use of analgesics increase the risk of osteoarthritis (OA) progression and knee replacement (TKR), with interest. To answer this question the authors used data of the well-known Osteoarthritis Initiative cohort. Outcomes were radiographic progression of knee OA within 3 years of follow-up assessed with the Kellgren–Lawrence score and the incidence of TKR within 8 years of follow-up. The authors concluded that long-term use of analgesics may be associated with radiographic progression of knee OA and increased risk of TKR.

Although this research question is certainly intriguing, as analgesics use may be associated with unintentionally overloading the joints, one might question whether the chosen design is appropriate to answer it. In fact, with the current design it might be established that there is an association between analgesics and OA progression but the direction of the association remains unknown. The following design issues have given us some reason for concern: First, the selection of the two groups that were compared: exposure to long term use of analgesics was defined as documented use of analgesics in all available follow-up visits during a period of 3 years. Defining exposure over a 3-year period may introduce selection bias, especially if we make the reasonable assumption that pain is related to OA progression. Patients that started and continued analgesics are more likely to have progression compared to starters that stopped using; the group of 3-year users is thus enriched with patients at high risk for progression. In a similar reasoning, people who do not take analgesics and continue not to take it will have lower progression risk than patients who start analgesics (and who will thus be excluded). Secondly, the authors tried to adjust for the differences in prognosis by using matching of propensity scores. Scores used for matching (WOMAC, SF-12, PASE) are (partly) based on pain and functioning. These pain and function levels are influenced by analgesic use because analgesic medication will lower pain levels and may improve function. As such, patients using analgesics have a worse stage of OA compared to matched patients without analgesics that achieve similar scores. The authors are aware of this as they state in the discussion: "[…] having similar WOMAC score while using analgesics may further contribute to the difference between the Analgesic+ and Analgesic−subjects." Hence, confounding by indication remained an issue here even after propensity matching. Lastly, some patients received arthroplasty within the first years of follow-up. Importantly, pain itself increases the risk of receiving TKR as pain still apparent after non-surgical treatment is an important indication for TKR (Fig. 1). Thus, patients receiving analgesics have a higher probability of receiving TKR, not because of the analgesics therapy, but because of pain that itself may be an indication for surgery or be a marker of underlying increased disease progression.

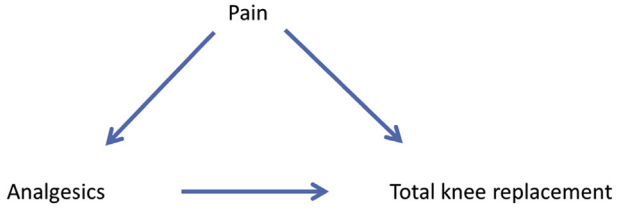

Fig. 1. Confounding by indication.

In conclusion, the clinically relevant question whether analgesics use leads to OA progression is difficult to answer, as analgesics use can both be a *cause* of disease progression (through physical activity that is not limited by pain and hence leads to excessive burden on the joints) as well as a *result* of disease progression (because pain is a marker for progression). Hence, to answer this question strict design methodology is necessary to minimise issues such as confounding by indication, selection bias and reverse causation, even more than generally in observational research[2]. While the authors have put a step in the right direction, their results are not yet sufficient to conclude on any causal relations.

Author contributions

MG: Drafting of the manuscript, final approval of the article.
SC: Critical revision of the article for important intellectual content, final approval of the article.
OD: Critical revision of the article for important intellectual content, final approval of the article.

Conflict of interest

There exists no conflict of interest in any of the authors.

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References

1. Hafezi-Nejad N, Guermazi A, Roemer FW, Eng J, Zikria B, Demehri S. Long term use of analgesics and risk of osteoarthritis progressions and knee replacement: propensity score matched cohort analysis of data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2016:597–604.
2. Hernán MA, Hernández-Diaz, Robbins M. A structural approach to selection bias. Epidemiology 2004:615–25.

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