

## Association between bisphosphonate use and risk of undergoing knee replacement in patients with osteoarthritis

Osteoarthritis (OA) is the most common joint disorder and the major cause of chronic musculoskeletal pain and mobility disability in elderly populations worldwide.<sup>1</sup> Currently there is no effective pharmacological treatment for OA, necessitating joint replacement to reduce joint pain and improve physical functions at advanced stages of the disease.<sup>2</sup> It has been reported that abnormal subchondral bone resorption and bone loss play an important role in both OA initiation and progression.<sup>3-5</sup> Therefore, antiresorptive drugs are suggested to be potential OA therapies.<sup>6</sup> We read with deep interest a recent article published in this journal by Neogi *et al*, who found that in elderly women with newly diagnosed knee OA, those who use bisphosphonates had lower risk of knee replacement than non-users, and suggested that treatment with bisphosphonates has a potential beneficial effect on knee OA.<sup>7</sup> We really appreciate the great work performed by the authors; nevertheless, some worthwhile issues need to be further explored.

First, the definition of knee OA at baseline is not clearly described in the study. Nowadays there is no consensus on the classification criteria of knee OA despite extensive epidemiological and clinical studies. The two criteria most frequently used are the American College of Rheumatology (ACR) classification criteria<sup>8</sup> and the Kellgren and Lawrence (K-L) system.<sup>9</sup> The ACR classification criteria depend on clinical (such as pain, aching or stiffness in joint), radiographic and laboratory aspects of OA. On the other hand, the K-L system identifies and grades OA based on radiographs. With this system, most subchondral bone changes in OA, such as osteophyte, bone sclerosis, bone cyst and joint space narrowing, can be observed on radiographs.<sup>10</sup> Furthermore, due to the heterogeneity of OA, there are subgroups of patients who have only radiographic but not symptomatic OA and vice versa.<sup>11</sup> For example, it was reported that the prevalence of radiographic knee OA was 35.3% in women and 31.2% in men, while self-reported knee pain was found in 62% of women and 35% of men in a sample of 170 men and 488 women.<sup>12</sup> It is likely that the effects of bisphosphonates on radiographic OA are different from that on symptomatic OA. Thus, differences in knee OA definition at baseline may lead to increased heterogeneity of the severity of the disease and result in bias of the results. It would be better to clarify the definition of knee OA in the study.

Second, the only outcome of this study is the incidence of knee replacement. The purpose of the study was to explore the potential beneficial effect of bisphosphonates on knee OA process.<sup>7</sup> To achieve this, the authors evaluated 'the relation of bisphosphonate use to knee replacement surgery'. We agree with the authors that knee replacement can serve as an indication for knee OA severity. But more precisely, utility of knee replacement does not indicate the 'end-stage' of OA. On the one hand, as knee replacement surgery develops and more and more patients demand for higher quality of life, the number of knee replacement has increased greatly.<sup>13</sup> For example, it was reported that low-grade OA (K-L grade <3) comprised 12% of the total sample of 176 patients with knee OA who underwent total knee arthroplasty in Denmark.<sup>13</sup> This condition may increase the heterogeneity of knee OA severity at baseline. On the other hand, studies have demonstrated that in K-L grade 4

OA knees, MRI-detected cartilage loss and fluctuation of bone marrow lesions, effusion and synovitis occurred frequently over a 30-month period,<sup>14</sup> suggesting that even K-L grade 4 knee OA does not represent the true 'end-stage' of the disease. Thus we have no idea if the use of knee replacement as the only outcome is enough. Furthermore, the information on the important characteristics of knee OA and direct indications for knee replacement, the level of knee pain (eg, Western Ontario McMasters Osteoarthritis Index pain score) and dysfunction (eg, knee society score)<sup>1</sup> were not demonstrated in the paper. If use of bisphosphonates did have beneficial effects on subchondral bone structure in OA, there should be significant relationships between bisphosphonate use and knee pain relief and improvement in function. Thus, knee pain and knee function as outcomes are worthy of expectation.

Third, the criteria for patient selection should be described with more details. Studies have shown that previous knee injuries such as fracture, anterior cruciate ligament injuries, meniscal tear and/or knee operation appeared to be important risk factors for the development of knee OA.<sup>15</sup> Hence, it is interesting to know whether patients with previous knee injuries or knee operation had been excluded. Additionally, some other confounders needed to be addressed, such as physical activity level, occupation, races and so on. Is it possible that non-users of bisphosphonates had lower social status and consequently higher physical work load and higher severity of OA than the users? It would be interesting to know more details of these confounders, which may influence the results.

Last but not the least, the information regarding the treatment of knee pain of these patients was not shown in detail in the paper. These treatments, especially the use of pain medication, such as non-steroidal anti-inflammatory drugs and glucosamine sulfate, may have affected the knee pain and knee function, and in turn the need for knee replacement. Furthermore, it has been reported that bisphosphonate users had higher rates of comedication compared with non-users.<sup>16</sup> It is likely that users of bisphosphonates in this study took more pain medication, got more pain relief, and thus had lower rate of knee replacement. The significant associations of bisphosphonate use and knee replacement, as shown in the paper, may probably be no longer significant after the adjustment by use of pain medication. In addition, it was reported that high adherence to bisphosphonate treatment during 24 months of follow-up was associated with a significantly decreased risk of knee replacement (propensity score-adjusted HR, 0.66 (95% CI 0.43 to 0.99); P=0.048).<sup>16</sup> As there was only one follow-up period (ie, '3.13 years' for bisphosphonate users and '2.91 years' for non-users) in the study, it is very important to analyse the bisphosphonate treatment adherence of the patients during this long period. And we are confused about the results of the mean follow-up time of the study, which has no SD or 95% CI. This needs to be clarified.

We respect the great contributions of the authors and we would also be very interested in the authors' response regarding the above issues.

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