Medications associated with fracture risk in patients with rheumatoid arthritis

Statins have been widely used to control dyslipidaemia, and there is strong evidence for beneficial effects for patients at risk for cardiovascular diseases.[1 2] In particular, statins may influence bone metabolism by increasing bone formation.[3 4] Recently, Ozen *et al*[5] reported that medication with opioids, selective serotonin reuptake inhibitors, and glucocorticoids were associated with an increased risk of osteoporosis-related site fractures (vertebra, hip, forearm and humerus) in patients with rheumatoid arthritis, whereas statins and tumour necrosis factor-α inhibitors were associated with a decreased risk of vertebral fractures. These findings were published in the August 2019 issue of the *Annals of the Rheumatic Diseases*. Certainly, the findings of Ozen *et al*[5] will be significant for clinicians; however, four points remain unaddressed that we would like to communicate with the authors.

First, the prevalence of osteoporotic fracture has been reported to be significantly higher in patients with chronic diseases compared with healthy subjects, particularly in women.[6–8] The association between chronic diseases and osteoporosis-related fracture (OF) has been reported in many studies. For example, a cross-sectional study by Watanabe *et al*[8] reported that the prevalence of osteoporotic vertebral fracture was as high as 79.4% in Japanese men with chronic obstructive pulmonary diseases (COPD). Similarly, Reyes *et al*[9] reported an independent association between COPD and an increased risk of hip OF in Catalonians. The results of the Ozen *et al*[5] study are in direct contrast with these other studies and demonstrated that the comorbidity of rheumatoid arthritis in statin-treated patients with dyslipidaemia affected the risk of OF. The differences between Ozen *et al*[5] findings and those of previous studies[6–9] may be attributed to the differences in baseline patient characteristics and the effects of the statin.

Second, statins are effective agents that control dyslipidaemia and are widely used in the prevention of cardiovascular diseases.[10] In addition, statins may influence bone metabolism by increasing bone formation.[11] However, the risk reduction among statin users might be that a high dose–response effect on OF risk was observed in Ozen *et al*'[5] s study. In the past, we have demonstrated that high exposure to statins has the dose–response effect of lowering new-onset dementia risk.[12]

Furthermore, in another study, we reported a beneficial effect of statin use with regard to OF risk, but not all statins.[13] The patients who took atorvastatin or rosuvastatin were at a lower risk of OF, whereas the use of lovastatin was associated with a significantly increased risk of developing new-onset OF (NOF) during the 10-year follow-up. It was also highlighted that a lower risk of NOF was associated with the more commonly prescribed high-potency statins.[13]

Third, it should be noted that OF may result from accidental occurrences, such as falls.[14] Patients with chronic disease experience muscle weakness, mobility impairment and exercise intolerance, and are prone to falls. An observational cohort study reported that COPD was associated with the increased risk of falls (OR, 1.6) compared with patients without COPD.[15] However, in this study have examined only the association between osteoporosis-related site fractures (vertebra, hip, forearm and humerus) and the medications taken by patients with rheumatoid arthritis.[5] Thus, the observed OF and associations may be underestimated in this study.

Fourth, many medications were associated with OF and included statins, antidepressants, proton-pump inhibitors, opioids, non-steroidal anti-inflammatory drugs, anticonvulsants, antipsychotics, benzodiazepines and antihypertensives.[16–18] Previous observational studies have shown that antihypertensives use has a positive or negative effect on emerging OF.[18 19] In a case–control study from Denmark[19] that evaluated 124 655 cases and 373 962 controls with hypertension, the investigators found that the risk of OF was lower among users of calcium channel blockers (OR, 0.94; 95% CI, 0.91 to 0.96) than among non-users. On the other hand, patients who took ACE inhibitors (OR, 1.64; 95% CI, 1.01 to 2.66) were at a higher risk of developing OF than non-users in our previous study.[20] Since the data for antihypertensives, such as diuretics, beta-blockers, calcium channel blockers, alpha-blockers, ACE inhibitors, and angiotensin receptor blockers were not available from this study,[5] there might be residual confounding bias because of the unmeasured factors.

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