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Editorial

Are nonsteroidal anti-inflammatory drugs safe for the kidney in ankylosing spondylitis?

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for controlling pain and inflammation in rheumatic and musculoskeletal diseases. NSAIDs reduce the production of prostaglandin (PG) by inhibiting cyclooxygenase, thereby reducing inflammation. However, PGs are involved in renal hemodynamics to preserve renal blood flow. PGE2 and PGI2 exert vasodilatory action at the afferent arteriole, which maintains glomerular filtration and blood supply to the kidney [1]. Therefore, inhibition of PGs by NSAIDs can cause vasoconstriction of afferent arterioles and leads to renal injury. In addition, PGs also play roles in the regulation of systemic blood volume and blood pressure. By inhibiting natriuresis and diuresis, NSAIDs can cause sodium and water retention and blood pressure elevation [1].

Previous cohort studies have shown that NSAID use can have negative impacts on renal function. Dose-response relationships between NSAID cumulative dose and changes in renal function have been observed in community-based elderly populations [2]. In a retrospective longitudinal cohort study of US Army soldiers, the highest exposure level of NSAIDs was associated with modest but significant increases of acute kidney injury and chronic kidney disease [3]. These findings highlight concerns regarding renal toxicity associated with long-term use of NSAIDs in patients with ankylosing spondylitis (AS).

A recent study by Koo et al. [4] published in the *Journal of Rheumatic Diseases* investigated the relationship between long-term use of NSAIDs and renal function using the electronic medical records of 1,280 patients with AS. NSAID exposure was determined by the Assessment of Spondyloarthritis International Society (ASAS) NSAID Intake Score for time intervals of 6 months, 1 year, 2 years, 3 years, 5 years, and 10 years. The authors concluded that there was no clinically significant correlation between NSAID Intake Score and change in estimated glomerular filtration rate (eGFR) in AS patients.

To interpret the results of this study, some points need to be considered. First, the finding that there was no clinically significant deterioration of renal function in patients treated with higher doses of NSAIDs might be due to channeling bias, where patients with better renal function and less comorbidities may have been prescribed more NSAIDs than those with poorer renal function and more comorbidities. In a Swedish national population-based cohort study of spondyloarthritis patients examining the cardiovascular and renal safety of nonselective NSAIDs and selective COX-2 inhibitors, the relative risk of renal insufficiency was higher in the NSAID-nonexposed group compared with the nonselective NSAID-exposed group, reflecting selection of patients being prescribed NSAIDs [5]. Second, considering the young age of the study population, relatively few patients experienced decline in renal function. In the ASAS-comorbidities in spondyloarthritis (COMOSPA) cohort, the prevalence of renal impairment defined as an eGFR <60 mL/min/1.73 m^2 was 5.2% [6], which was higher than that in a study by Koo et al. [4]. The mean age was 45.3 years in the ASAS-COMOSPA cohort, while much younger patients (mean age, 30.2 years) were included in the present study [4]. Age is a strong risk factor for renal impairment in the general population, as

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well as in patients with AS. Older age was an independent risk factor for renal impairment in spondyloarthritis [6]. Current NSAID intake was associated with renal impairment in univariate analysis, but the association disappeared after adjustment for confounding factors including age [6]. In Supplementary Table 1 of Koo et al. [4], the NSAID Intake Score increased and eGFR decreased as age increases from 18~40 years to 60~80 years, suggesting that age is a more important factor in the decline of eGFR. Third, the risk of decline in renal function may differ in subgroups of baseline eGFR and comorbidities. In a large rheumatoid arthritis patient cohort, NSAID use was an independent predictor for renal function decline only in patients with baseline eGFR <30 mL/min/1.73 m^2 [7]. In a study assessing the effects of TNF inhibitors on renal function in patients with AS, there was a significant decline in renal function only in patients with preexisting risk factors for renal insufficiency such as eGFR <60 mL/min/1.73 m^2, older age, and high blood pressure [8]. These findings indicate that the effects of NSAID on renal function could differ depending on baseline renal function and presence of risk factors. Fourth, the ASAS NSAID Intake Score might not be adequate to evaluate the long-term use of NSAIDs. The ASAS NSAID Intake Score facilitates comparisons between different studies by using uniform recording, analysis, and reporting to evaluate NSAID intake in AS patients. However, this score evaluates the "intensity" of NSAID intake, rather than cumulative dose of NSAIDs, a measure that lacks validity regarding its relationship with long-term use of NSAIDs [9]. Fifth, our readers are likely wondering the implications of COX-2 selectivity in the effects of NSAIDs on renal function. A recent publication which investigated the cardiorenal risk of celecoxib compared with naproxen or ibuprofen in the secondary analysis of PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen) trial showed that celecoxib had a fewer renal events and more favorable cardiorenal safety outcomes than ibuprofen or naproxen at the doses studied [10].

In summary, the occurrence of renal function decline is very low in patients with AS, particular in younger patients. NSAIDs can have negative impacts on renal function in patients with preexisting risk factors such as older age, decreased renal function, and comorbidities, suggesting more careful use in such patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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