High Dose of NSAIDs May Increase Kidney Disease Risk

Exposure to high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) shows a modest but significant association with kidney disease in a military population, reports a study in the open-access journal *JAMA Network Open*.

The retrospective analysis included data on more than 764,000 US Army soldiers on active duty from 2011 through 2014. Eighty-six percent of participants were men; median age was 27 years. Dispensing and dose of prescription NSAIDs were evaluated for association with incident diagnoses of acute kidney injury (AKI) and chronic kidney disease (CKD).

The participants received a total of 1.6 million distinct NSAID prescriptions during the observation period: mean 2.1 prescriptions per person. Nearly two-thirds of personnel had no NSAID prescriptions in the previous 6 months. About 18% were dispensed 1 to 7 mean total daily defined doses (DDDs) per month, while 16% received more than 7 DDDs. There were a total of 2356 AKI outcomes, affecting 0.3% of participants; and 1634 CKD outcomes, affecting 0.2% of participants.

Participants with 7 or more DDDs per month had significant increases in both kidney disease outcomes: adjusted hazard ratio 1.2 for both AKI and CKD. At this level of exposure, there were 17.6 additional cases of AKI and 30.0 additional cases of CKD per 100,000 exposed individuals. Obese individuals were at significantly increased risk of both outcomes: adjusted hazard ratio 1.5 for AKI and 1.6 for CKD. The hazards were more than doubled for individuals with a history of hypertension and rhabdomyolysis. For diabetes, the hazard ratio was 1.8 for both outcomes.

Most studies of NSAID associations with kidney disease have focused on older adults or patients with chronic diseases. There has been little concern about the renal effects of these widely used medications in young, healthy adults. Some studies have suggested a possible increase in kidney disease risk among NSAID users engaging in endurance exercise.

This large study of Army personnel finds "modest but statistically significant" associations between high doses of NSAIDs and the risk of acute and chronic kidney disease outcomes. "Dosage reduction represents an approach that may decrease associated kidney disease outcome rates," the researchers write. They also note the contribution of modifiable factors such as body mass index and hypertension [Nelson DA, et al. Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults. *JAMA Netw Open* 2019; 2 (2):e187896. doi:10.1001/jamanetworkopen.2018.7896].

Markers of Tubule Cell Dysfunction Predict AKI

Among patients with chronic kidney disease (CKD), baseline biomarkers of tubule cell function are independent predictors of the later development of acute kidney injury (AKI), reports a study in *Kidney International*.

The researchers analyzed data on 2351 participants from the randomized Systolic Blood Pressure Intervention Trial (SPRINT). All had CKD (mean estimated glomerular filtration rate [eGFR] 49 mL/min/1.73 m^2) and hypertension at baseline, but not diabetes. Participants were assigned intensive or standard systolic blood pressure targets: less than 120 versus less than 140 mm Hg. Study outcomes showed lower rates of cardiovascular disease and death with intensive blood pressure-lowering therapy, but a higher risk of AKI.

The current study analyzed baseline data on urinary markers of renal tubule dysfunction (alpha-1-microglobulin [α1m], beta-2 microglobulin [β2m], and uromodulin [UMOD]) and markers of renal tubule injury (kidney injury molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1]) and chitinase-3-like protein [YKL-40]). The two types of markers were analyzed for association with the risk of AKI, with adjustment for other factors.

Over a mean follow-up of 3.8 years, AKI developed in 184 participants—a rate of 7.8%. Acute kidney injury was more frequent in men and in black patients, as well as those assigned to the intensive blood pressure–lowering therapy.

Two markers of kidney tubular dysfunction—UMOD and α1m—were associated with AKI, independent of eGFR and albuminuria. Hazard ratios were 0.68 per twofold increase in UMOD and 1.20 per twofold increase in α1m. At the highest versus lowest quartiles, baseline UMOD and α1m were more strongly associated with AKI risk (HR 2.04 and 1.57, respectively) compared to the 3-month change in serum creatinine (HR 1.27). In contrast, increases of tubule cell injury markers occurred mainly after the AKI event.

Identifying CKD patients at particularly high risk of AKI may help to inform monitoring and prevention strategies. This study identifies markers of tubule cell dysfunction—lower UMOD and higher α1M—as predictors of future AKI risk. The researchers conclude: "[T]ubular cell function markers may reflect a vulnerable kidney with diminished capacity to counter acute insults and thus identify CKD individuals at heightened risk of future AKI" [Bullen AL, et al. The SPRINT trial suggests that markers of tubule cell function in the urine associate with risk of subsequent acute kidney injury while injury markers elevate after the injury. *Kidney Int* 2019; DOI: https://doi.org/10.1016].

Dual Therapies for Black African Patients: Randomized Trial

Combination therapies including amlodipine improve blood pressure (BP) control in sub-Saharan African patients with hypertension, concludes a trial in *The New England Journal of Medicine*.

The randomized controlled "Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans" (CREOLE) trial included 728 black patients with uncontrolled hypertension in six sub-Saharan African countries. Enrolled patients had BP of 140/90 mm Hg or higher on no antihypertensive therapy or a single-drug regimen. The patients' average age was 51 years; 63% were women.

Patients were assigned to one of three antihypertensive drug combinations: the calcium-channel blocker amlodipine (5 mg) plus the thiazide diuretic (HCTZ) (12.5 mg); amlodipine plus the angiotensin-converting enzyme inhibitor perindopril (4 mg); or perindopril plus HCTZ. After 2 months, the dose of each drug was doubled for another 4 months (amlodipine 10 mg, hydrochlorothiazide 25 mg, perindopril 8 mg). Change in 24-hour ambulatory systolic BP from baseline to 6 months was compared between groups.

On analysis of primary outcome data in 621 patients, reductions in BP were greater with the two amlodipine-containing regimens. Compared to perindopril plus HCTZ, between-group differences in systolic BP were 3.14 mm Hg with amlodipine plus HCTZ and 3.00 mm Hg with amlodipine plus perindopril. There was no significant difference between the two amlodipine regimens.

Other outcomes showed a similar pattern, including ambulatory diastolic BP, office BP, and BP response rate. Six-month BP control rates were 76% with amlodipine-HCTZ and 74% with amlodipine-perindopril versus 60% with perindopril-HCTZ. Patients receiving amlodipine-HCTZ had significant reductions in plasma potassium and higher rates of hypokalemia.

Black African patients have a high prevalence of hypertension and typically need at least two antihypertensive drugs to achieve BP control. There is uncertainty regarding the most effective two-drug regimen for black patients with hypertension, reflected by differences in current recommendations.

The CREOLE results suggest a better response with amlodipine, combined with either HCTZ or perindopril, compared to HCTZ plus perindopril in black African patients with uncontrolled hypertension. The researchers note some limitations of their study, including whether the findings can be generalized to black patients with diabetes or those outside of sub-Saharan Africa [Ojji DB, et al. Comparison of dual therapies for lowering blood pressure in black Africans. *N Engl J Med* 2019; DOI: 10.1056/NEJMoa1901113].