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NSAID-associated Renal Injury: Mechanisms, Risks, and Safer Strategies

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used analgesics that have a high risk of renal injury, especially in susceptible populations such as the elderly, patients with chronic kidney disease (CKD), heart failure, or those on poly pharmacy. This commentary emphasizes the pathophysiological mechanisms of NSAID-induced kidney damage, including prostaglandin inhibition, renal vasoconstriction, and interstitial nephritis—and highlights recent evidence linking NSAIDs to acute kidney injury (AKI) and CKD progression. Despite relatively low incidence rates, the extensive use of NSAIDs increases the clinical burden of nephrotoxicity. Clinical challenges include delayed diagnosis due to modest symptomatology and under-recognition by both patients and healthcare providers. The article underscores the need for individualized NSAID prescribing patient education, informed consent, and enhanced regulatory oversight. It also explores safer pharmacological and non-pharmacological pain management alternatives, emerging nephron protective strategies, and the role of pharmacogenomics and early biomarkers in preventing NSAID-related renal damage. A multidisciplinary, patient-centered approach is advocated to optimize pain control while protecting kidney health.

Keywords: NSAIDs, AKI, Renal Ischemia, Renal protection

Introduction

Acute kidney injury (AKI) is defined as a sudden decrease in kidney function, marked by reduced urine output or raised serum creatinine ≥0.3 mg/dl. While non-steroidal anti-inflammatory drugs (NSAIDs) can cause AKI, it is rare. Advanced age, comorbidities, and medications (e.g., co-trimoxazole, aminoglycosides) that lower glomerular filtration rate (GFR) increase the incidence of nephrotoxicity [1]. NSAIDs constitute 5-10% of treatment plan in the U.S. Acetylsalicylic acid (ASA), discovered in 1893, was the first NSAID. NSAID-related AKI mainly affects patients with pre-existing kidney issues or conditions like chronic kidney disease (CKD), heart failure, liver failure, or volume depletion that activate the renin-angiotensin-aldosterone system (RAAS) [2].

A recent article by Ahsan *et al.*, discusses the risks of NSAID-induced kidney damage, including reduced blood flow, electrolyte imbalances, and nephrotic syndrome. These problems are more likely in patients with pre-existing kidney conditions, dehydration, or those on other nephrotoxic drugs. It calls for safer practices, including screening of high-risk individuals, using the minimal effective NSAID dose for the briefest duration, and regularly monitoring kidney function and electrolytes. The article stresses the importance for healthcare providers to be more careful with NSAID

prescriptions, ensuring better patient safety and minimizing the potential for renal injury through informed practices [3].

However, a detailed discussion is required to further explore the complexities of NSAID-related renal toxicity, particularly in specific populations like the elderly, patients with pre-existing kidney disease, and those on polypharmacy. A deeper look at alternative pain management strategies and their renal safety profiles would be significant, as well as discussing individualized dosing, renal function monitoring, and patient literacy. Additionally, the role of NSAIDs in the development of CKD and the prolonged outcomes for patients who experience acute renal injury due to NSAIDs needs more attention. By extending the conversation, we can address gaps in clinical practice, patient safety, and treatment protocols, ensuring more informed decision-making and declining the risk of kidney damage.

This commentary aims to highlight the risks of NSAID-associated renal injury, specifically in vulnerable populations like the elderly and those with pre-existing kidney conditions. It highlights knowledge gaps regarding the mechanisms of kidney damage and stresses the need for safer pain management strategies. Recent findings on NSAID-induced kidney injury and its role in CKD progression are discussed. The article structure includes an introduction to NSAIDs' risks, mechanisms of renal injury, vulnerable populations, current management strategies, and a conclusion urging safer prescribing and further research into alternative analgesics to mitigate renal damage.

Background and Recent Developments

AKI is a severe condition affecting over 13 million people yearly and causing 1.7 million deaths. It impacts 1 in 5 hospitalized patients and up to 50% of those are critically ill, with over half developing renal impairment shortly after intensive care unit (ICU) admission. Diabetes is the leading risk factor, present in 50% of AKI cases. Heart failure raises AKI risk to 26%, while sepsis-related AKI occurs in 11–70% of cases. Obstructive nephropathy contributes to 5–10% of cases [4].

Given the high incidence of AKI in hospitalized and critically ill patients, understanding the role of NSAID use in kidney injury is essential. The exact mechanism involved is that these drugs basically inhibit the cyclooxygenase (COX) enzyme, which converts phospholipids into prostaglandins (PGs), resulting in decreased production of prostaglandins (PGs) in the kidneys, which play an important role in vasodilation and maintaining kidney function. Prostaglandins, particularly PGI2 and PGE2, help regulate normal renal blood flow by dilating key blood vessels. Without these vasodilators, excessive vasoconstriction may occur, potentially causing severe kidney damage, including ischemia and acute tubular necrosis and finally AKI [2,5].

The systematic review and meta-analysis examined the link between long-term NSAID use and CKD. The study found that NSAID use raised the risk of forming CKD by 24% and the risk of CKD progression by 50%. For individuals without CKD at the start, the risk was 31% higher, while those with already CKD had a 67% higher risk. People without specific chronic conditions had a 60% higher risk, and those with diabetes or hypertension had a 35% higher risk. For individuals with rheumatic diseases, the risk was 36% higher. The findings highlight the increased risk of kidney problems from long-term NSAID use, especially in those with existing health conditions. Monitoring kidney function in patients using NSAIDs for extended periods is crucial [6]. Another study of 7,436 NSAID-associated renal injury cases, elderly patients were at increased risk and had greater chances of AKI. Ibuprofen had the leading reports (46.7%), succeeded by celecoxib (7.3%). Ibuprofen also revealed the majority renal injury signal (ROR 3.3), while celecoxib had the lowest (ROR 1.4). Aspirin had the highest mortality rate (18.7%), while ibuprofen had the lowest (3.8%). The median onset for renal injury was 6 days, with 79.3% of events occurring within 30 days [7]. The use of NSAIDs remains widespread among high-risk patients, including those with heart failure, hypertension, and CKD. A study on kidney transplant assignees found that 11% were prescribed NSAIDs, with about two-thirds of these prescriptions coming from primary care physicians [2].

Many people misunderstand the hazards of NSAIDs, assuming they all have similar safety profiles. However, different NSAIDs vary in their cardiovascular risks, and even short-term use can disturb kidney function, especially in vulnerable individuals. Gastrointestinal issues, like ulcers and bleeding, are common but often underestimated. The availability of NSAIDs over-the-counter leads to the false belief they are completely safe for regular use. Furthermore, the long-term effects on kidney, heart, and gastrointestinal health are often downplayed. Better education is needed to address these misconceptions.

Clinical Implications and Challenges

Although the occurrence of nephrotoxicity caused by NSAIDs is relatively low, ranging from 1% to 5%,their extensive use significantly increases the risk of renal damage in a large segment of population leading to both acute and chronic kidney complications posing a major health concern for physicians [8]. High acute doses of NSAIDs have been implicated as cause for AKI, particularly in the elderly as well as patients with CKD, cardiac and hepatic failure or hypervolemia as in patients using NSAIDS with diuretics and RAAS inhibitors [9]. Another mechanism is interstitial nephritis with nephrotic syndrome which occurs as a result of delayed hypersensitivity reaction and activation of T lymphocytes few days after initiation of NSAID therapy, however, resolves after discontinuation of the drugs. Moreover, NSAID-induced renal effects extend beyond AKI to include edema, sodium

retention, and electrolyte disturbances such as hypernatremia and hyperkalemia. Edema and sodium retention are often subclinical and occur due to inhibition of prostaglandin induced renal vasodilation inhibition. While hypernatremia and hyperkalemia are caused by ADH and RAAS antagonism respectively [8]. In addition, hypomagnesaemia and hypophosphatemia may ensue within one to two days after sudden excessive NSAID consumption [9].

Chronic use of NSAIDs in some patients, particularly in elderly with mildly decreased baseline kidney function, may result in progression of CKD [10]. Albeit there is a smaller number of studies showing long term effects of NSAIDS on CKD. However, studies show that NSAIDs, whether selective or non-selective, increase the risk of CKD in dose and duration dependent manner, particularly in individuals who continue to use these drugs after development of acute interstitial nephritis and interstitial fibrosis [9]. NSAID exposure of ≥7 defined daily doses (DDDs) per month was associated with an increased risk of AKI (aHR 1.2, 95% CI 1.1-1.4) and CKD (aHR 1.2,95% CI 1.0-1.3), with estimated annual excess cases of 17.6 per 100,000 for AKI and 30.0 for CKD [8]. A population based cohort study conducted in Taiwan reported the use of NSAIDs by 78% of the patients with end-stage renal disease receiving dialysis and this usage was found to be associated with increased risk of mortality in this group of patients. This finding strongly suggests the lack of awareness among patients and physicians regarding cautious administration of NSAIDs in patients with end-stage renal disease [11].

Detecting and monitoring NSAID-induced renal damage presents significant challenges, primarily due to the often-asymptomatic nature of early kidney injury. Traditional biomarkers, such as serum creatinine, may not reflect subtle changes in kidney function in a timely manner, which can delay diagnosis. Evidence shows that several instances of AKI resulting from the use of NSAIDs tend to be mild and non-oliguric and, hence, go unnoticed in the absence of repetitive serum creatinine checks. Appreciating these factors, constant surveillance for renal function changes in acute heart failure, particularly in high-risk subjects, is pivotal to promptly avert NSAID-induced renal injury [12].

Easy access to NSAIDs without prescription, coupled with inadequate patient counseling, often leads to abuse. Research indicates that a considerable number of patients remain uninformed, such as a study conducted in Saudi Arabia where only 25.5% reported being counseled on potential adverse effects [13]. The mere availability of these medications over the counter grants patients a false impression of their total safety, resulting in self-medication. Moreover, some general practitioners underestimate the risks of chronic NSAID use [14,15]. Balancing pain management with nephroprotection requires usage of comparably effective non-nephrotoxic drugs whenever possible [16]. With regards to this, acetaminophen remains the mainstay of treatment for moderate pain. However, adjuvant therapies such as gabapentin, topical analgesics and non-pharmacological approaches are also recommended for effective pain management while reducing adverse renal effects. Additionally, opioid analgesics are reserved for times when non-opioids and non-pharmacological therapies fail to sufficiently alleviate pain [17].

Legal norms mandate that physicians secure informed consent from individuals before conducting tests or initiating treatments, especially those involving ambiguity, to uphold patient autonomy [18]. Therefore, informed consent regarding NSAID use is crucial owing to its multiple adverse effects particularly in the high-risk population. According to the study conducted at the University of Alabama at Birmingham, physicians may benefit from integrating informed consent and shared decision making into patient communication as continuous engagement or repeated information exposure particularly during patient follow-ups significantly increase NSAID risk awareness [19].

Enhanced NSAID safety requires proactive educational initiatives directed towards patients and healthcare professionals. With regards to NSAID prescribing, effective pain control versus nephroprotection creates great ethical conflicts. At the heart of these issues lie informed consent and shared decision making, which are critical constituents to make sure that patients understand the risks and advantages of using NSAIDs. Besides that, collaboration from different disciplines including nephrologists, rheumatologists, and GPs is important in enhancing the outcomes of patients.

Safer Alternatives and Recommendations

Pharmacological interventions

Paracetamol is often considered as a safer option in comparison to NSAIDs, especially for those people who suffer from renal dysfunction. NSAIDs exacerbate the risk of nephrotoxicity because it does suppress the kidney's cyclooxygenase (COX) [20]. Nevertheless, acetaminophen has its own shortcomings like weak anti-inflammatory properties which render it to be less useful in conditions like arthritis. On the contrary, NSAIDs possess stronger anti-inflammatory properties but are more inclined to cause cardiovascular, renal and gastrointestinal problems [21]. Along with that, acetaminophen overdose may trigger hepatotoxicity especially when taken with alcohol [22].

Non-pharmacological interventions

In order to manage pain and alleviate dependency on NSAIDs, some non-pharmacological interventions are useful. Physiotherapy is one of the most important ways that lessen pain in conditions like osteoarthritis and chronic back pain by enhancing mobility [23]. In addition, acupuncture has had positive effects for minimizing pain, and some evidence implies that it could reduce the requirement for analgesics [24].

Furthermore, lifestyle improvements including maintaining weight, exercising frequently, and making dietary adjustments could contribute to reducing inflammation and the intensity of chronic pain, which will lessen the need for NSAIDs.

Newer drug therapies

There has been extensive research going on to discover the analgesics with less nephrotoxic effects. Celecoxib is one of those rare drugs that selectively inhibit COX-2 with less gastrointestinal effects and with good efficacy in producing analgesia [25]. Moreover, it also has safer cardio renal profile in comparison to NSAIDs [26]. Many new drugs that aren't disruptive with renal function are evaluated for the treatment of chronic pain. In the future, these more recent treatments might provide safer alternatives for chronic pain management.

Pharmacogenomics

Pharmacogenomics can assist in identifying people who are more susceptible to NSAIDs-induced problems. NSAID toxicity and metabolism are influenced by genetic variation in drug-metabolizing enzymes, including CYP2C9 [27]. Prolong use of NSAIDs can precipitate severe cardiovascular events and renal dysfunction. This is why it is necessary to tailor the prescription of every patient according to the needs of the patients and in this way, pharmacogenomics can be introduced to daily clinical practice.

Bio-markers of AKI

A study by Mishra *et al.* in 2012 demonstrated that biomarkers like kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) are essential in detection of AKI. In high-risk patients, routine monitoring of these biomarkers may help with early intervention and NSAID dosage modifications to preserve renal health [28]. Hence this study shows that early detection of these biomarkers can preserve further kidney damage in future.

Regulation of drug-use

Drug abuse and overdose is due to widespread availability of these drugs. NSAIDs are freely accessible as over the counter medicines. High rates of accidents and complication can be reduced by regulatory actions like limiting sales of big quantities and requiring more lucid warning labels regarding cardiovascular and renal hazards. In the UK, laws constraining the size of analgesic packs have been favorable. More deaths might be prevented if pack sizes are further reduced [29].

The potential risks of NSAIDs are often underestimated by medical professionals, especially when it comes to individuals who are already predisposed to cardio-renal issues. Programs for continuing education in medicine (CME) should place an enormous value on patient selection guidelines, alternative methods for alleviating pain, and NSAID safety. Adverse effects can be considerably diminished by teaching prescribers to use the NSAID at the lowest effective dose for the shortest amount of time required [30].

The risks correlated with NSAIDs are not commonly recognized by people who led to its overuse and abuse. Studies have demonstrated that pharmacist interventions like patient counseling and educational initiatives, can greatly increase patient awareness and lower the dangers linked with NSAIDs [31]. Thus, the patient should be made aware about the safe use of NSAIDs, possible adverse effects and other options as well.

More research is still needed to create NSAIDs with better safety profile. One of the interesting approaches for prevention of Kidney damage is by co-administration of nephroprotective drugs, such as sodium bicarbonate and N-acetyl cysteine [32].

Pharmacogenomic techniques and other future developments in personalized medicine may further optimize NSAID therapy by customizing medication to each patient's unique genetic profile, increasing effectiveness and reducing side effects.

Conclusion

NSAID-associated AKI remains a significant yet underestimated clinical concern, especially in susceptible populations such as the elderly, patients with CKD, and those on polypharmacy. Although, NSAIDs are essential in pain management, their nephrotoxic potential demands careful use, individualized risk assessment, and vigilant monitoring. Education of both patients and healthcare providers is critical to eliminate misconceptions about NSAID safety, especially given their widespread over-the-counter availability. The integration of informed consent, interdisciplinary collaboration, and the development of safer analgesic alternatives can help mitigate the burden of NSAID-induced renal injury. Continued research, especially in pharmacogenomics and early biomarkers, is required for enhancing personalized approaches to NSAID prescribing, ensuring a better balance between pain control and renal protection.

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