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Original Research Article

NSAIDs and Kidney Health: A Review of the Silent Threat to Renal Function

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Abstract: Nonsteroidal anti-inflammatory medications (NSAIDs) are frequently recommended to treat rheumatologically and inflammatory diseases as well as to relieve pain. Acute kidney injury (AKI), chronic kidney disease (CKD), acute interstitial nephritis, and renal papillary necrosis are among the serious renal hazards that NSAIDs are linked to, despite their effectiveness, particularly in people who already have kidney disease or those using NSAIDs long-term or at high doses. This umbrella review consolidates evidence from multiple meta-analyses and systematic reviews to clarify the nephrotoxic potential of NSAIDs. The review reveals that NSAID use, including both traditional and selective COX-2 inhibitors, is linked to a 50% to 70% increased risk of AKI and CKD. Adverse effects are primarily related to intrarenal vasculature disruption, glomerular damage, and sodium imbalance. Although some NSAIDs offer specific renal protections, overall, the harm often outweighs the benefits. Further research is needed to better understand these risks, especially the molecular mechanisms underlying NSAID-induced kidney damage and to identify at-risk populations. This understanding will aid in balancing the therapeutic benefits of NSAIDs against their potential renal risks, ensuring safer clinical use.

Keywords: Non-Steroidal Anti-Inflammatory Drugs, Acute Kidney Injury, Chronic Kidney Disease, Nephrotic Syndromes.

1. INTRODUCTION

One of the most commonly prescribed pharmaceuticals in the world, nonsteroidal anti-inflammatory drugs (NSAIDs) are mainly used to treat inflammatory and rheumatologically disorders and relieve pain [1]. Acute kidney injury, acute interstitial nephritis, renal papillary necrosis, and worsening of chronic kidney disease are among the serious dangers associated with their usage, despite the fact that they are useful in these capacities. Those who use NSAIDs frequently or in large dosages, or who have pre-existing kidney diseases, are more at risk [2].

The widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) in modern medicine is largely due to their effectiveness in managing pain and treating various inflammatory and rheumatological conditions [3]. However, alongside their therapeutic benefits, there is increasing evidence that links NSAID use to significant kidney-related complications, particularly when these drugs are taken long-term, in high doses, or by patients with pre-existing kidney issues [4].

The nephrotoxic risks associated with NSAIDs are not consistent across all drugs within this class; certain NSAIDs may pose greater risks than others. Moreover, the mechanisms by which NSAIDs cause kidney damage—such as the inhibition of prostaglandin synthesis, which leads to reduced renal blood flow—can vary depending on the specific

drug and the patient population [5]. Despite the extensive research conducted on this subject, the literature remains fragmented, with some studies presenting conflicting results or duplicative findings.

This study aims to address these issues by conducting an umbrella review, which consolidates evidence from multiple meta-analyses and systematic reviews. The goal is to provide a clearer understanding of the nephrotoxic potential of NSAIDs, both as a class and as individual drugs. We will specifically evaluate the comparative risks of different NSAIDs, examine how these risks vary across different patient groups, and identify patterns of redundant or cumulative data in the current literature.

1.2 Comprehending NSAIDs

A class of pharmaceuticals known as nonsteroidal anti-inflammatory drugs (NSAIDs) is frequently prescribed to treat fevers, reduce inflammation, and ease pain. They function by blocking the cyclooxygenases (COX) enzymes, which are essential for the synthesis of prostaglandins, which are chemicals that cause heat, pain, and inflammation. By blocking these enzymes, NSAIDs help to reduce the symptoms associated with various conditions such as arthritis, headaches, muscle pain, and menstrual cramps [6].

Despite their effectiveness, NSAIDs can have side effects, particularly when used over a long period or in high doses. The most common side effects include gastrointestinal issues like ulcers, bleeding, and stomach pain. This occurs because prostaglandins also help protect the stomach lining, and their reduction can make the stomach more susceptible to damage. NSAIDs can also impact kidney function and increase the risk of cardiovascular problems, especially in individuals with pre-existing heart conditions [7, 8]. There are different types of NSAIDs available, both over-the-counter and by prescription. Common examples include ibuprofen, aspirin, and naproxen. Each NSAID may vary in its strength, duration of action, and side effects, making it important for individuals to consult with healthcare providers to determine the most appropriate medication for their needs [9].

1.3 Classification of (NSAIDs)

Acetylated salicylates (e.g., aspirin), non-acetylated salicylates (e.g., diflunisal, salsalate), propionic acids (e.g., naproxen, ibuprofen), acetic acids (e.g., diclofenac, indomethacin), enolic acids (e.g., meloxicam, piroxicam), anthranilic acids (e.g., meclofenamate, mefenamic acid), naphthylalanine (e.g., nabumetone), and selective COX-2 inhibitors (e.g., celecoxib, etoricoxib) are among the NSAIDs that are typically grouped according to their chemical structure and selectivity [10]. Acute tenosynovitis, ankle sprains, and soft tissue injuries are among the ailments that are frequently treated with topical NSAID formulations, such as diclofenac gel [11].

1.4 Mechanism of Action NSAIDs

The mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) primarily revolves around the inhibition of cyclooxygenase (COX) enzymes, which are critical in the biosynthesis of prostaglandins. Prostaglandins are lipid compounds that play a significant role in inflammation, pain, and fever. There are two main types of COX enzymes: COX-1 and COX-2 [12]. Prostaglandins that shield the stomach lining, promote platelet function, and preserve kidney blood flow are produced by the enzyme COX-1, which is constitutively expressed in the majority of tissues. The inducible enzyme COX-2, on the other hand, is mostly expressed at inflammatory areas and is in charge of generating prostaglandins, which mediate inflammation and pain [13].

NSAIDs exert their effects by non-selectively inhibiting both COX-1 and COX-2 enzymes, thereby reducing the synthesis of prostaglandins. This reduction leads to decreased inflammation, pain, and fever. However, because COX-1 is also inhibited, NSAIDs can cause side effects such as gastrointestinal irritation, ulcers, and increased bleeding risk due to reduced protective prostaglandins in the stomach and impaired platelet function [14]. Some newer NSAIDs, known as COX-2 inhibitors (e.g., celecoxib), are designed to selectively inhibit only the COX-2 enzyme. This selectivity aims to reduce inflammation and pain while minimizing gastrointestinal side effects associated with COX-1 inhibition. However, even COX-2 inhibitors can have side effects, including an increased risk of cardiovascular events, which highlights the importance of careful consideration and monitoring when using these medications [15].

2. Kidney Health: An Overview

The kidneys play a crucial role in regulating the concentration of substances in the body, maintaining electrolyte balance, and eliminating metabolic waste through urine production. Renal failure, which is a reduction in kidney function, can occur as either an acute or chronic condition and can ultimately be life-threatening [16]. Compounds that disrupt normal kidney function are considered "risk factors for acute kidney injury (AKI) or chronic kidney disease (CKD). Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to potentially impair kidney function. Although NSAIDs are widely used for their anti-inflammatory and analgesic effects, their renal risks are significant" [17].

NSAIDs exert their effects by inhibiting cyclooxygenases (COX), which leads to a reduction in prostaglandin synthesis. This disruption can cause renal vasoconstriction, reducing blood flow to the kidneys and potentially leading to acute renal failure. Long-term use of NSAIDs may also result in ischemic damage to the kidneys. In addition to acute renal failure, NSAIDs are associated with other renal issues such as acute interstitial nephritis and a condition known as NSAID-induced renal disease, which includes both AKI and CKD [18]. NSAIDs can also cause damage to distal tubular cells, contributing to nephrotic syndrome and electrolyte imbalances. Naproxen and diclofenac, in particular, have been shown to have a higher risk of inducing renal disease, with naproxen being approximately seven times more likely and diclofenac about eight times more likely to cause renal complications. Furthermore, the concurrent use of NSAIDs with angiotensin II receptor blockers can exacerbate renal risks. Despite these findings, there is ongoing debate and controversy regarding the overall impact of NSAIDs on kidney health, with varying evidence on their long-term renal outcomes [19].

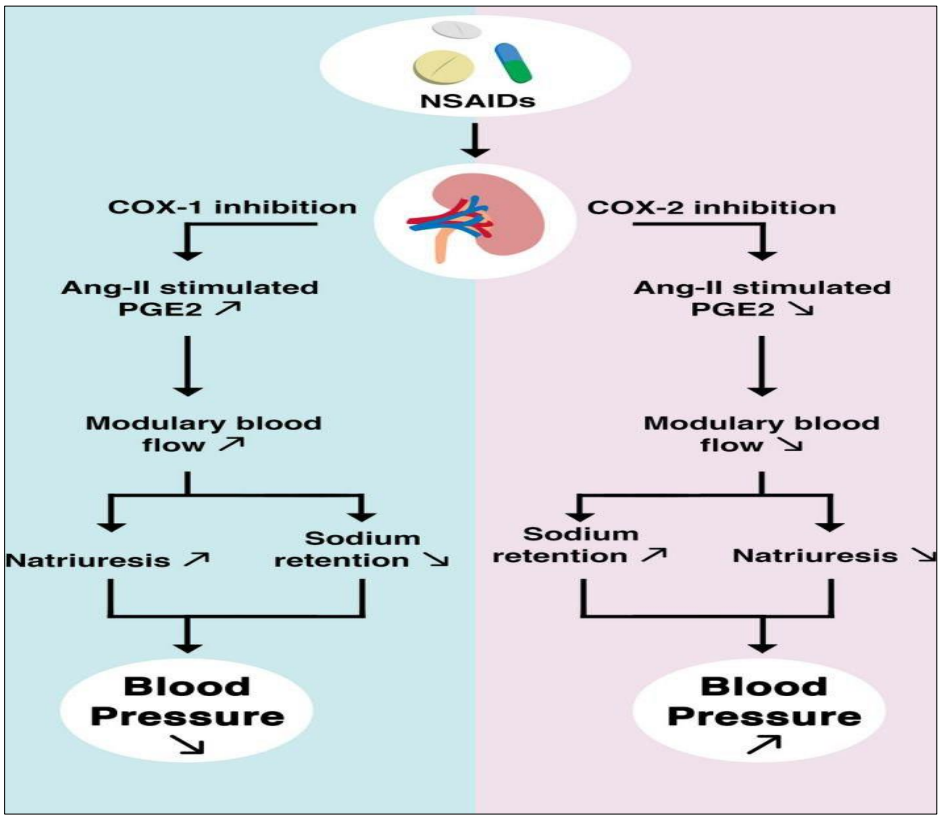

Figure 1: "Renal effects of COX-1 and COX-2 inhibition. Ang-II, angiotensin II; NSAID, nonsteroidal anti-inflammatory drugs; PGE2, prostaglandin "E2 [20]

2.1. Anatomy and Function of the Kidneys

The kidneys are two bean-shaped organs, each roughly the size of a fist, positioned on either side of the spine. Under normal conditions, they filter approximately 200 liters of blood per day, resulting in the production of 1-2 liters of urine. Besides this, the kidneys play a key role in regulating electrolytes, maintaining acid-base balance, and controlling blood pressure. In the general population, the likelihood of developing acute kidney disease—commonly due to drug-induced nephrotoxicity, septic shock, reduced blood flow to the kidneys, tubulointerstitial nephritis, acute allergic interstitial nephritis, or acute tubular necrosis—occurs in about 1% of patients. Chronic kidney disease, characterized by impaired kidney function or kidney damage persisting for at least three months, affects 7%-10% of individuals [21].

As previously mentioned, the kidneys are vital for drug excretion, making them susceptible to numerous adverse drug reactions. Currently, over 100 different medications, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), targeted therapies, and antibiotics, pose potential risks to kidney health. However, the effects of some of these drugs on kidney function have either been underestimated or only identified long after they were introduced to the market. Additionally, a decline in kidney function can create a cycle of drug-kidney interactions, leading to worsening kidney damage and excessive drug buildup. These interactions have significant implications for both public health and economic costs [22].

2.2. Factors Affecting Kidney Health

Kidney health is influenced by a variety of factors, each playing a role in the development and progression of kidney disease. One major factor is medication use. Long-term and high-dose use of certain drugs, particularly non-

steroidal anti-inflammatory drugs (NSAIDs), poses significant risks to kidney function. These medications, commonly used to treat conditions ranging from mild pain to chronic inflammatory diseases, can cause nephrotoxicity and acute kidney injury [23].

Comorbidities also play a crucial role in kidney health. Conditions such as heart disease and diabetes can exacerbate kidney problems, making individuals with these health issues more susceptible to kidney damage. Managing kidney disease becomes more complex in the presence of these comorbidities. Age is another important factor, with advanced age being a well-established risk factor for declining kidney function [24]. As people age, their kidneys naturally lose some of their ability to function effectively, increasing their vulnerability to kidney-related problems. Gender and race can further influence kidney health. Certain racial groups may have a higher predisposition to specific types of kidney disease, and gender differences can also impact the likelihood of developing kidney issues [25]. Genetic factors contribute significantly to kidney health. Individuals with a family history of kidney disease are at a higher risk of developing similar conditions, highlighting the role of genetics in kidney health. In addition to these factors, the use of other nephrotoxic drugs, such as some antibiotics and chemotherapy agents, can also harm the kidneys. Lifestyle choices and diet, including high salt intake, inadequate hydration, and lack of exercise, further affect kidney function [26].

3. NSAIDs and Kidney Health: The Link

Nonsteroidal anti-inflammatory drugs (NSAIDs) alleviate pain, inflammation, and fever by blocking cyclo-oxygenase (COX) enzymes. They are commonly prescribed for managing musculoskeletal and rheumatic conditions and are frequently available over the counter due to their effectiveness and affordability. Despite their benefits, NSAIDs are linked to significant renal adverse effects, particularly in high-risk groups [1]. The potential renal complications of NSAID use include tubular-interstitial nephritis, which can present as nephrotic or nephritic syndrome, as well as worsening chronic kidney disease, hypertension, and disturbances in blood pressure regulation. These issues are particularly pronounced with COX-2-selective inhibitors, which are often used to minimize gastrointestinal side effects. Additionally, NSAIDs can exacerbate renal problems in conditions of salt depletion or dehydration, but similar risks are observed with traditional NSAIDs in the general population [27]. Prolonged or high-dose use of NSAIDs can lead to acute kidney injury, characterized by a reversible decrease in glomerular filtration rate. Regular monitoring of kidney function is essential for individuals using NSAIDs, especially those with pre-existing renal conditions or comorbidities. Alternative pain management strategies or NSAIDs with a more favorable renal safety profile should be considered to mitigate these risks [28].

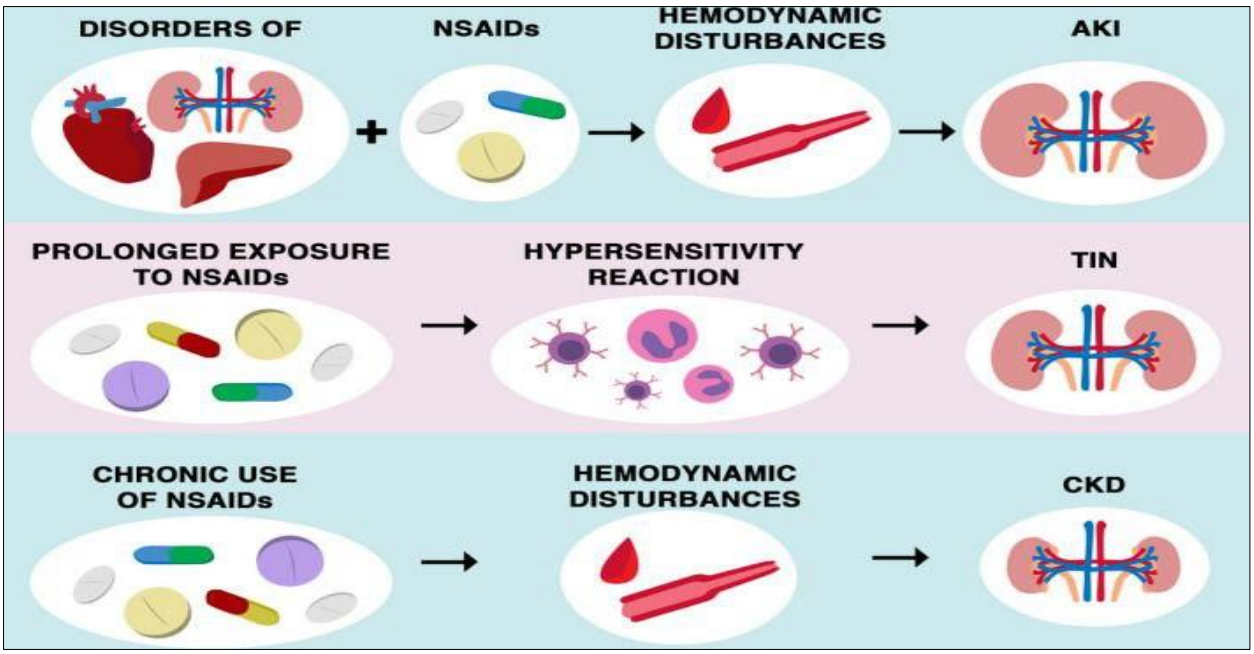

Figure 2: "An overview of the primary renal pathomechanisms linked to the use of NSAIDs. NSAID use may impair kidney function in a number of ways. Chronic NSAID use may cause haemodynamic abnormalities that result in chronic kidney disease (CKD). One possible outcome of long-term NSAID exposure is the TIN. A delayed hypersensitive reaction with interstitial infiltration of T lymphocytes and eosinophils is suggested as a potential cause. AKI may also result from NSAID use, particularly in patients who have polypragmasia and comorbidities. NSAIDs, or nonsteroidal anti-inflammatory medicines; TIN, or tubulointerstitial nephritis; AKI, or acute kidney injury; CKD, or chronic kidney disease "[20]

3.1. Historical Context

The modern era of nonsteroidal anti-inflammatory drugs (NSAIDs) began in 1950, when a group of easily synthesized, simple carboxylic acids was found to be effective in traditional pharmacological tests designed to identify anti-inflammatory agents. This research, focused on agents that inhibit carrageenin-induced edema in rats, marked the start of a series of innovative experiments that contributed to the groundbreaking work of John R. Vane, a Nobel laureate who made significant contributions to understanding the mechanisms of these drugs. Despite ongoing research worldwide, progress in grasping the fundamental chemistry and pharmacological actions of these drugs was slow and often hindered by erroneous theories aimed at explaining the observed effects [29].

Several key developments occurred in this quest for knowledge. By 1960, Goodfellow and colleagues identified that various compounds could inhibit prostaglandin synthetase, the enzyme crucial for producing these powerful bioactive molecules. They accurately predicted that inhibiting cyclooxygenase (COX) would affect hormone release from the kidneys, which eventually led to the development of ACE inhibitors and converting enzyme inhibitors (ACEIs) over the next three decades. These inhibitors have become widely used as protective treatments for drug-induced acute kidney injury (AKI) [30].

3.2. Epidemiology of NSAID-Induced Kidney Injury

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely available in various formulations, many of which can be purchased over the counter. This accessibility contributes to their extensive use globally. NSAIDs are used by billions of people for managing conditions ranging from mild pain to chronic inflammatory diseases. Despite their benefits, NSAIDs are associated with significant risks to kidney health, leading to increased healthcare costs, especially during periods of widespread use. Many cases of NSAID-induced kidney injury could potentially be prevented with appropriate precautions [31].

The prevalence of NSAID-induced kidney injury is notably high, with NSAIDs being a common cause of acute kidney injury (AKI), accounting for 1-1.5% of hospitalizations for this condition. The risk of developing kidney damage from NSAIDs increases with higher baseline serum creatinine levels, the use of high doses, and the concurrent use of other nephrotoxic drugs [32].

Several individual factors exacerbate the risk of NSAID-induced kidney injury. These include advanced age, estrogen therapy, reduced blood volume, and pre-existing conditions such as decreased glomerular filtration rate and hypertension. The complexity of managing kidney health is heightened by these factors. Research indicates that NSAIDs can cause kidney damage through mechanisms such as renal vasoconstriction, altered responses to vasoactive factors, reduced salt and water excretion, and inflammatory changes [33]. NSAIDs can also impact kidney function indirectly by affecting other organs. An increase in vasoconstrictor substances and a decrease in vasodilator components raise the tone of the kidney's afferent arterioles, which in turn reduces the glomerular filtration rate (GFR). This reduction in GFR is primarily due to the suppression of prostaglandin synthesis, which plays a crucial role in maintaining renal blood flow and function. Understanding these epidemiological aspects of NSAID-induced kidney injury is essential for improving patient management and mitigating risks associated with NSAID use [4].

3.3. Search Strategy and Selection Criteria

In this umbrella review, a systematic search was conducted in MEDLINE (PubMed), Embase (OVID), the Cochrane Database of Systematic Reviews, and Epistemonikos to identify meta-analyses and systematic reviews of randomized controlled trials (RCTs) or observational studies. The focus was on assessing the effects of traditional NSAIDs or selective COX-2 inhibitors on kidney outcomes, including acute kidney injury (AKI), chronic kidney disease (CKD), albuminuria, and hematuria.

4. RESULT AND DISCUSSION

The findings of the current study highlight the need for increased caution when prescribing nonsteroidal anti-inflammatory drugs (NSAIDs), particularly for individuals at heightened risk of chronic kidney disease (CKD) or those with pre-existing renal conditions. Meta-analyses with the strongest evidence showed that NSAID use is associated with a 50% to 70% increased risk "of acute kidney injury (AKI)" and the development of CKD. Notably, both traditional and selective COX-2 inhibitors, commonly used for preventing colorectal adenomas in high-risk patients, were linked to an increased risk of renal complications [34].

In terms of clinical practice, our comprehensive review revealed a connection between NSAID use and adverse kidney outcomes. The data suggest that kidney-related side effects from NSAIDs, rather than their anti-inflammatory benefits, have consistently been shown to be harmful in several meta-analyses. This harm is likely related to the negative effects on intrarenal vasculature, the glomerulus, and sodium balance, with significant renal protection demonstrated only in a few meta-analyses focused on very specific renal conditions [31].

Further research is urgently needed to better understand these adverse effects, as NSAIDs remain a commonly used therapeutic option. Exploring the molecular mechanisms behind NSAID-induced kidney damage, along with identifying the most at-risk populations, could help minimize harm while preserving the therapeutic benefits of these drugs [35].

5. CONCLUSION

NSAIDs, while effective for reducing inflammation and pain, can have significant side effects, particularly on the gastrointestinal system and kidneys. They work by inhibiting COX enzymes, which are involved in prostaglandin production. Prostaglandins contribute to inflammation, pain, and fever but also protect the stomach lining and support kidney function. Long-term or high-dose use of NSAIDs can lead to ulcers, bleeding, and kidney impairment. Additionally, NSAIDs can increase the risk of cardiovascular problems, especially in individuals with pre-existing heart conditions. It is crucial for users to consult healthcare providers to determine the most appropriate NSAID and to monitor for potential side effects.

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