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Review Article

Acute kidney injury associated with non-steroidal anti-inflammatory drugs

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are ones of the commonly prescribed drugs worldwide. They primarily inhibit cyclooxygenase (COX) enzyme which is responsible for conversion of phospholipids to various prostaglandins (PGs). Disruption in PGs production affects the kidneys in several ways, including vasoconstriction that may result in ischemic acute kidney injury (AKI) in at-risk patients. They also impair salt and water excretion, leading to edema and hypertension. Other complications include hyperkalemia, hyponatremia, nephrotic syndrome, acute interstitial nephritis and chronic kidney disease progression. AKI from NSAIDs is usually reversible with favorable prognosis after discontinuation of NSAIDs. Avoidance of NSAIDs exposure is extremely important, especially among high-risk patients.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed drugs that are accounted for 5–10% of all prescriptions in the United States. [1] Acetyl salicylic acid (ASA) is the first agent that was discovered in 1893. [2] Since then, many agents have been developed and widely used for various conditions. NSAIDs exert their anti-inflammatory effect via cyclooxygenase (COX) inhibition. Their common adverse effects include gastrointestinal ulcers, cardiac toxicity, bleeding diathesis, allergic reaction and renal complications, [3,4] with acute kidney injury (AKI) being the most common form of NSAIDs-induced renal injury. Other renal manifestations include hypertension, edema, hyponatremia, hyperkalemia, nephrotic syndrome, papillary necrosis and interstitial nephritis. [5] In addition, several studies have demonstrated a relationship between exposure to high dose NSAIDs and progression to advanced stage chronic kidney disease (CKD) [6]. Unfortunately, despite the well-established adverse effects, the frequency of NSAIDs utilization among high risk patients, such as those with heart failure, hypertension and CKD, remains high. [7] A study of kidney transplant recipients demonstrated that 11% of them were prescribed NSAIDs, in which about two-third of the prescriptions were from primary care physicians and less than 50% had appropriate laboratory monitoring. [8]

The purpose of our review is to summarize the current evidence on mechanism of action of NSAIDs and their effects on the kidneys. We also provide detailed information on each renal complication with a focus on clinical presentation, treatment and outcome.

1.1. Mechanism of action of NSAIDs

NSAIDs inhibit cyclooxygenase (COX) which is also known as prostaglandin H synthase. [9] There are two distinct isoforms of COX: COX-1 and COX-2. COX-1 is ubiquitous and constitutively expresses in normal cells. On the other hand, COX-2 is largely upregulated in inflammatory state. [10] However, several studies have demonstrated an expression of COX-2 during normal state in several organs such as brain, reproductive organs and kidneys. [11] The two isoforms of COX are 60% identical and located at luminal compartment of endoplasmic reticulum and nuclear membrane. [9] NSAIDs bind with COX-1 via reversible hydrogen bond whereas the binding of COX-2 is an irreversible active process. [12] COX enzyme primarily involves in eicosanoid biosynthesis which converts arachidonic acid to prostaglandin (PG) G_2. PGG_2 is then converted to PGH_2 via peroxidase enzyme. [13] Ultimately, PGH_2 is metabolized to various types of PG including PGE_2, $PGF_{2\alpha}$, PGI_2 and thromboxane (TX) A_2 via isomerase enzymes (Fig. 1). [2] NSAIDs exert their anti-inflammatory property mainly via COX-2 inhibition whereas COX-1

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inhibition often results in adverse effects. NSAIDs can be classified based on their COX-2 selectivity: non-selective COX inhibitors and selective COX-2 inhibitors. [11] NSAIDs can also be classified based on their chemical structure and property such as carboxylic acids, acetic acids and propionic acids.

1.2. Pathophysiology of NSAIDs-induced acute kidney injury

NSAIDs primarily incite AKI via hemodynamic alteration from prostaglandins imbalance. [14] As previously mentioned, COX-1 is generally expressed in the kidneys during non-inflammatory state. Additionally, low level of COX-2 expression can be found in macula densa. [15] PGs are expressed in several parts of nephron, including glomeruli, juxtaglomerular apparatus (JGA), loop of Henle, interstitial and tubular cells. Their function and site-specific expression help maintaining and modulating renal function (Fig. 1).

PGI_2 (Prostacyclin) is up-regulated by vasoconstrictive hormones such as angiotensin II, vasopressin, endothelin and norepinephrine. Various injuries, including renal ischemia and autoimmune process in renal parenchyma, can stimulate PGI_2 production. [16] Its receptors are located at glomerular mesangial cells, endothelial cells and podocytes. [17] It enhances arteriolar vasodilation, decrease vasopressin and increase sodium excretion, thus promote diuresis. It can also attenuate podocytes contraction and inhibit leukocyte adhesion and aggregation. [18]

PGE_2 is expressed in all type of renal cells but mostly in glomeruli and collecting ducts. There are three types of PGE_2 synthase, including microsomal PGE synthase (mPGES)-1, mPGEs-2 and cytosolic PGE synthase. PGE_2 binds to EP receptor which has 4 subtypes (EP_1-EP_4). [19] EP1/EP3 act as vasoconstrictor whereas EP2/EP4 act as vasodilator of afferent arterioles. EP2/EP4 also serve as vasodilator for vasa recta. It is a mediator of renin-angiotensin aldosterone synthesis (RAAS) that can stimulates renin release via EP3 from the macula densa. [19] Overall, PGE_2 promotes vasodilation, natriuresis and aquaresis. [5]

TXA_2 is widely expressed and can be found in macrophages, lung, peritoneum and kidneys. Expression of TXA_2 particularly abundant in platelet which promotes platelet activation and aggregation. [20] In the kidneys, TXA_2 is primarily expressed in glomeruli. It promotes vasoconstriction and podocytes contraction, thus decrease renal blood flow and glomerular filtration (GFR) [6].

$PGF_{2\alpha}$ is converted from PGD_2 via 11-ketoreductase. It is highly expressed along genitourinary tract, including ovaries and kidneys. [21] Distal convoluted tubule and cortical collecting duct are the main sites of renal expression. It promotes sodium and water excretion via transcellular transport of sodium independently of blood pressure and GFR. [6,22] It also stimulates thiazide-sensitive Na-Cl- cotransporter in distal convoluted tubule. [23]

NSAIDs deplete locally produced PGs in the kidneys and, thus, blunt vasodilatory and other compensatory effects. These effects are especially crucial for high-risk patients who already have up-regulated RAAS and vasoconstrictive mediators (endothelin-1 (ET-1) and norepinephrine) as they are dependent on vasodilation properties of PGs to maintain normal renal hemodynamics. PGI_2 and PGE_2 are the main vasodilators. PGI_2 enhances afferent, efferent and capillary tuft dilatation. PGE_2 also dilates afferent arterioles. [24] Removal of vasodilators can impose unopposed severe renal vasoconstriction. Ultimately, this may lead to irreversible renal ischemia and acute tubular necrosis. [25] Several animal studies have shown that prostacyclin reduction increases risk of

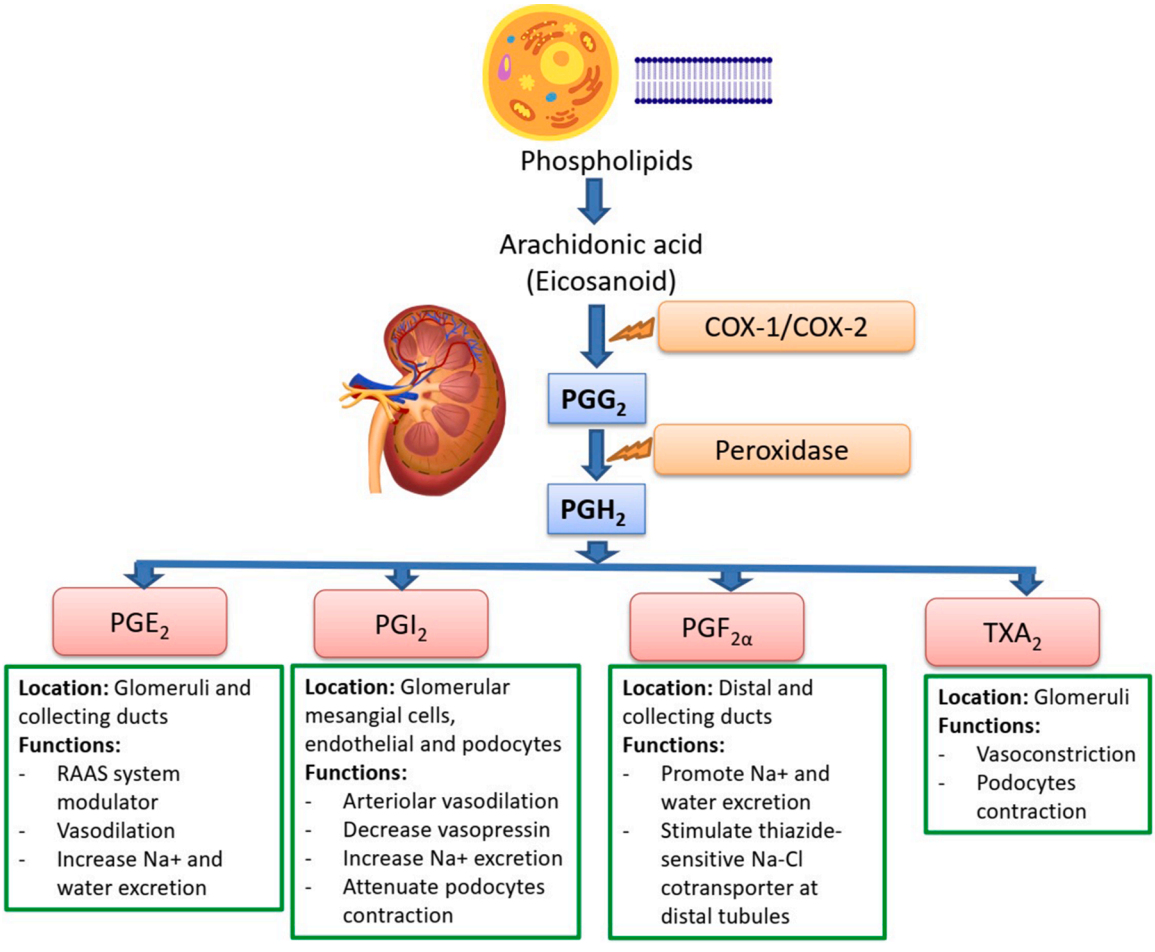

Fig. 1. Prostaglandins production cascade, locations and their functions. Abbreviations: PG, prostaglandin; TXA2, thromboxane A2.

ischemic kidney injury [26] and endothelial PGs could protect kidneys from ischemic insult. [18] These studies confirm the inhibitory role of NSAIDs in PGs production leading to ischemic injury (Fig. 2).

1.3. Risk factors for AKI in NSIADs user

NSAIDs associated AKI typically occurs in patients with pre-existing compromised kidney hemodynamics [27]. Studies have shown that NSAIDs do not alter kidney functions in otherwise healthy people. There are several risk factors as summarized in Fig. 2. Patients are characteristically dependent on vasodilatory effect of renal prostaglandins to maintain renal blood flow and GFR. This typically occurs in patients with RAAS activation, such as those with heart failure, liver cirrhosis, nephrotic syndrome and volume depletion [5,28]. In a case series of pediatric patients without significant underlying medical conditions, all patients with NSAIDs associated AKI had a history of volume loss [29]. A salient study of patients with severe congestive heart failure has demonstrated RAAS activation along with systemic upregulation of PGI_2 and PGE_2, suggesting the importance of vasodilatory effect of PGs in these patients [30].

Other risk factors include older age, male gender, hypertension, diabetes, CKD and concomitant use of nephrotoxic agents [24,31]. The risk of AKI is doubled in older population [32]. Nonetheless, NSAIDs can increase risk of AKI in pediatric population who are at risk for volume depletion [33,34]. Kidney transplant recipients are also at higher risk of NSAIDs associated AKI with the risk of almost three times higher than in native kidneys [35].

Selective COX-2 inhibitors were previously thought to have less renal effect due to the specificity toward COX-2. However, subsequent studies demonstrated that both traditional NSAIDs and selective COX-2 inhibitors can enhance the risk of AKI although the association of selective COX-2 inhibitors and AKI may not be as strong as traditional NSAIDs [36,37]. A retrospective cohort study demonstrated that selective COX-2 inhibitors use was associated with rapid eGFR decline in both short term (<1 year) and intermediate term (1-2 year) among CKD patients and eGFR continued to decline after NSAIDs discontinuation [38]. However, a recent meta-analysis did not display a significant association between AKI and selective COX-2 inhibitors [37]. Among traditional NSAIDs, indomethacin may confer the highest risk of AKI compared to other NSAIDs [37].

NSIADs users who are on concomitant diuretic and RAAS inhibitor (RAASi) have 30-60% increased risk of AKI which is higher than the risk of AKI from NSIADs alone or NSIADs with either diuretics or RAASi. [39,40] The risk is at the highest within one month of initiation [40]. Notably, the risk of AKI in concomitant users advances as the age increases [39]. Due to its high AKI risk, patients who use of NSAIDs, diuretics and RAASi concomitantly is typically known as the "triple whammy". In this circumstance, there is an overwhelming disruption of renal autoregulation, resulting in a drastic reduction in GFR and ischemic insult [41]. Other medications that appears to heighten the risk of AKI when used in conjunction with NSAIDs include acyclovir, valacyclovir, tenofovir and proton-pump inhibitor [42,43].

2. Clinical presentation

Renal manifestation of NSAIDs is protean, including fluid retention leading to edema, hypertension, hyperkalemia, AKI, nephrotic syndrome, papillary necrosis and interstitial nephritis [28]. Clinicians should be aware of these manifestations and promptly ask for history NSAIDs exposure. These manifestations are demonstrated in Fig. 3.

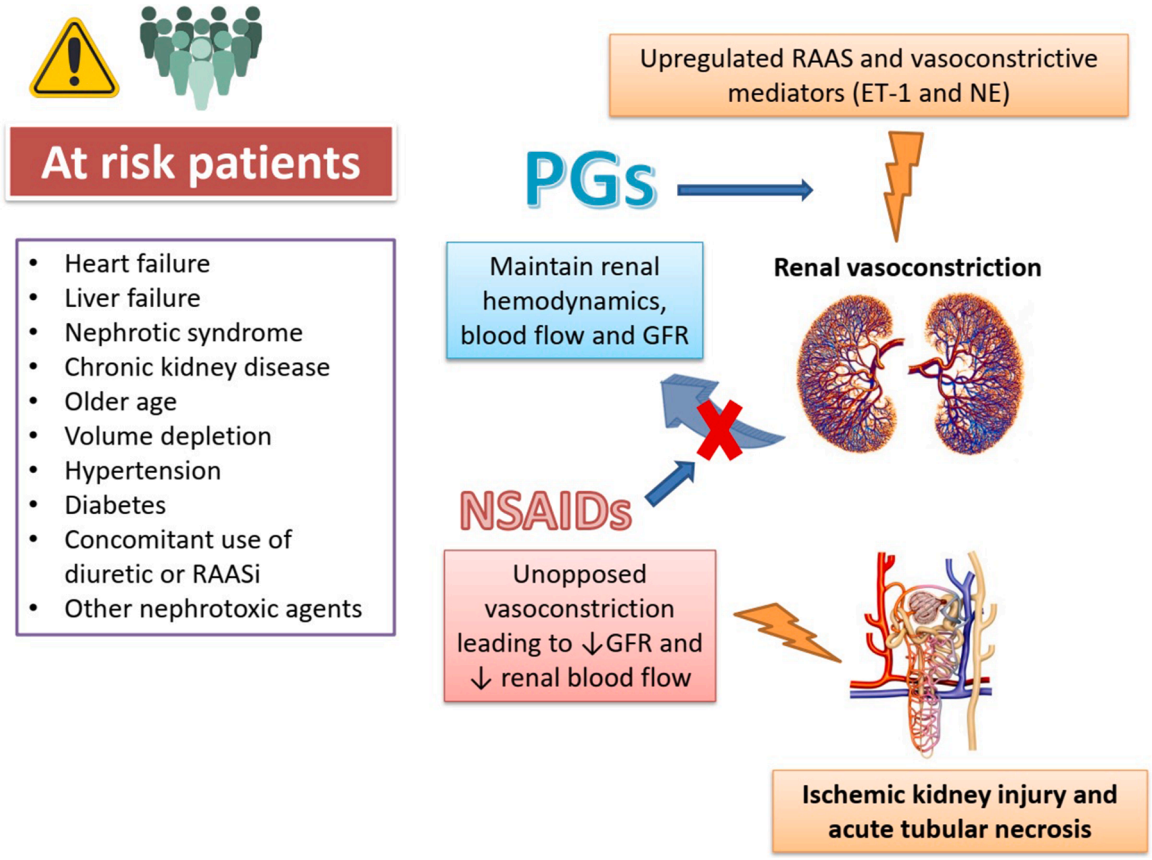

Fig. 2. Risk factors of NSAIDs induced nephrotoxicity and mechanism of acute kidney injury. Abbreviations: RAASi, renin angiotensin aldosterone system inhibitor; PGs, prostaglandins; NSAIDs, nonsteroidal anti-inflammatory drugs; ET-1, endothelian-1; NE, norepinephrine.

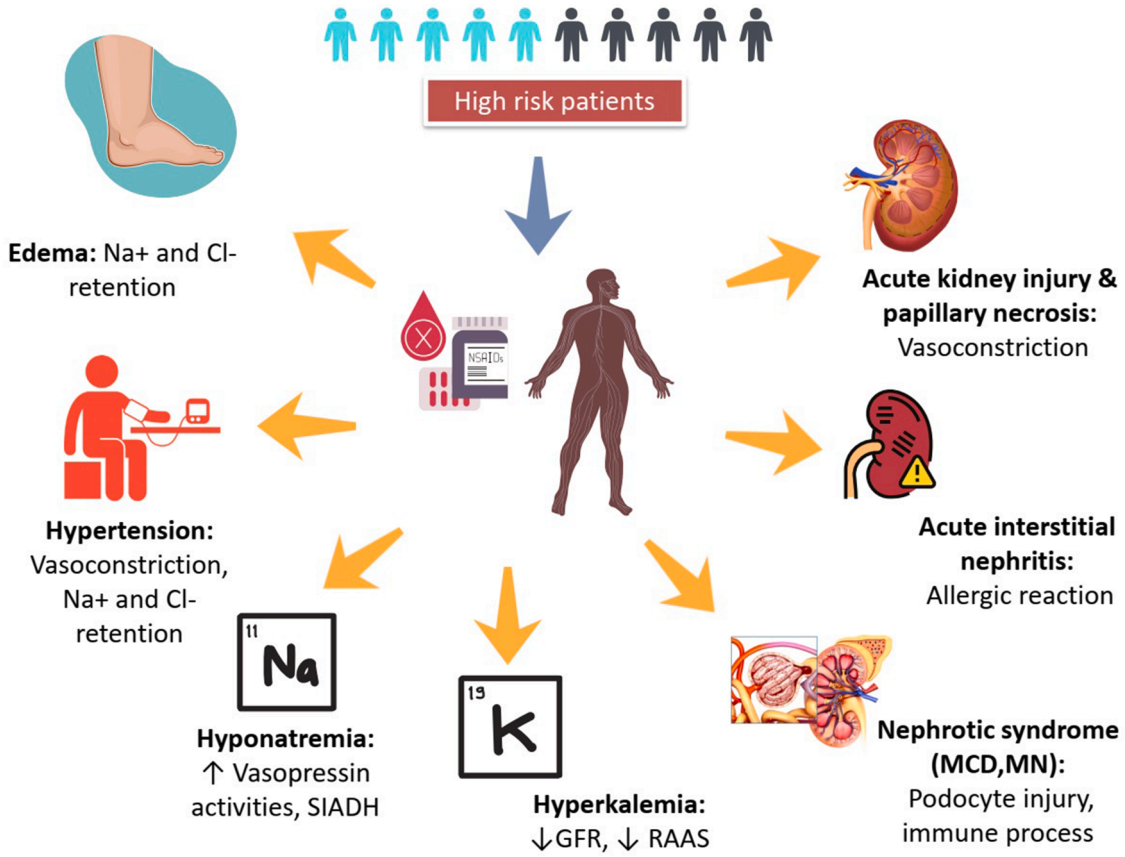

Fig. 3. Spectrum of NSAIDs induced nephrotoxicity. Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate anti-diuretic hormone; GFR, glomerular filtration rate; RAAS, renin angiotensin aldosterone system; MCD, minimal change disease; MN, membranous nephropathy.

2.1. Hypertension

NSAIDs have been shown to elevate blood pressure in both normotensive and hypertensive patients [44]. Earlier studies have shown that indomethacin, naproxen and piroxicam have the greatest effect on blood pressure whereas the least effect is observed in sulindac [44–46]. However, recent studies including a double- blind, randomized multicenter trial have shown that ibuprofen is harboring the greatest effect on blood pressure compared to non-selective and selective COX-2 inhibitors [47]. In fact, COX-2 inhibitors minimally affect BP with only 2.3% blood pressure increase during the use [47]. In general, blood pressure can be increased by 2-5 mmHg in NSAIDs user [44,46]. In hypertensive patients, patients who receive beta-adrenergic antagonist appear to have the highest increase in blood pressure after exposure to NSAIDs compared to those who receive other anti-hypertensive agents [46]. There are several possible mechanisms that can explain the rise of blood pressure, including AKI, vasoconstriction, salt and water retention and vascular endothelial dysfunction [44,47].

2.2. Edema

The incidence of NSAIDs-induced edema is fairly low (<10%) [48]. Patients may have 0.5–1 kg weight gain as a result of NSAIDs exposure [49]. Prostaglandin deficiency (particularly PGE_2) induces reduction in renal blood flow and GFR [48]. It enhances Na+ and Cl- reabsorption via Loops of Henle and up-regulation of vasopressin. Lastly, it can up-regulate endothelin-1 which, in turn, promotes Na+ and Cl- reabsorption. All of these would ultimately result in salt and water retention and edema [44,50].

2.3. Hyponatremia

NSAIDs associated symptomatic hyponatremia is rare [49]. It often occurs in patients with other risk factors of hyponatremia, such as heart failure, cirrhosis, hypovolemia and thiazide diuretic use [6,51,52]. NSAIDs can induce hyponatremia via several mechanisms. They block the PGE_2 inhibitory effect of vasopressin-activated adenylate cyclase in collecting duct, resulting in up-regulation of vasopressin activity [49]. There are several case reports that concomitant use of NSAIDs and desmopressin can generate severe hyponatremia [53,54]. NSAIDs use in marathon runner and other athletes also increases risk of hyponatremia during their performance. In a study of 28 marathon runners, there was a reduction of serum sodium in NSAIDs user whereas serum sodium was increased in non-NSAIDs users [55]. Vasopressin level was noted to be higher in hyponatremic athletes compared to normonatremic group [56]. Hence, potentiation of vasopressin via NSAIDs may explain the observed elevated risk. NSAIDs can reduce medullary blood flow thus increase hypertonicity of medullary interstitium and promotes water absorption [49]. There are also case reports of syndrome of inappropriate antidiuretic hormone (SIADH) after exposure to different NSAIDs, including ibuprofen, indomethacin, piroxicam, sulindac, diclofenac and ketorolac. [57–59] However, other vasopressin stimuli often co-existed with NSAIDs use in these reports [6,58]. Moderate to severe hyponatremia is associated with an increased risk of in-hospital mortality [60].

2.4. Hyperkalemia

PGs can promote renal blood flow, resulting in increased GFR and potassium clearance. They also increase distal Na+ delivery and promote potassium excretion via distal tubule. Furthermore, PGs secreting from macula densa can enhance renin secretion, aldosterone production

and increase kaliuresis [5]. These mechanisms are compromised in NSAIDs users, resulting in diminished potassium clearance. Typically, serum potassium rises by 0.2–0.6 mEq/L. Nonetheless, life-threatening hyperkalemia has been reported [61]. Patients with CKD, diabetes and concomitant RAASi use are at increased risk of hyperkalemia [31,49,62]. Risk of hyperkalemia varies by type of NSAIDs and both non-selective and selective COX-2 inhibitors can cause hyperkalemia [38,63].

2.5. Acute kidney injury

NSAIDs associated AKI does not often frequently in otherwise healthy person. Studies have demonstrated modest increased risk of AKI in the community setting with OR ranging between 1.5 to 2.1 [32,37]. AKI could be seen as early as 1-3 days after exposure depending on NSAIDs half-life [5]. Patients usually present with mild to moderate rise in creatinine and minimal proteinuria although dialysis may be required in rare instances [29]. Renal pathology typically reveals evidence of tubular injury with vacuolated and loss of brush border, leading to simplification of tubular epithelial cells, although biopsy is usually not required in mild to moderate cases [25]. Inflammatory cells infiltration may present [25,64]. In severe case, bilateral renal infarctions may occur [65]. There are also case reports of NSAIDs-induced AKI via massive rhabdomyolysis [66]. Renal function usually improves within 2-7 days after NSAIDs withdrawal [5] and other conservative management, such as fluid resuscitation. [29] However, permanent kidney damages may occur, particularly in patients with more chronic use.

2.6. Acute interstitial nephritis (AIN)

AIN is characterized by inflammatory cell infiltration in tubulointerstitial compartment. Patients often present with AKI and some may have other systemic symptom such as rash, arthralgia, fever and peripheral eosinophilia [67]. Of all AIN cases, drug-induced AIN accounts for more than two-third and NSAIDs are ones of the most common culprits [67]. Renal pathology usually shows cytotoxic T-cell with a paucity of eosinophils, which is notably different from classic AIN from other medications [68]. The median age of patients with NSIADs induced AIN is around 50 years. Patients with NSIADs induced AIN may concomitantly develop nephrotic syndrome but frequently have subnephrotic range proteinuria with median urine protein of 1.1 g/d [69]. About two third of patients developed AKI stage 3 with median peak serum creatinine of 3.6 mg/dl. The median time of exposure is 3 months before the diagnosis. Patients often respond well to steroid therapy and 70% have improved kidney function to near normal [69]. Some studies suggest that early steroid treatment is associated with better outcome [70].

2.7. Nephrotic syndrome

Nephrotic syndrome may occur in NSAIDs users irrespective of their baseline kidney function [28]. It usually occurs between 2 weeks and 18 months after exposure [28]. Minimal change disease (MCD) and membranous nephropathy (MN) are previously thought to be the two most common nephrotic syndromes associated with NSAIDs use [71]. However, a recent large cohort study from the UK has found that membranous nephropathy (39%), focal and segmental glomerulosclerosis (FSGS) (20%) and diffuse crescentic glomerulonephritis (11%) were actually more common than minimal change disease (9%). Nonetheless, it should be noted that only 10% of patients in this cohort underwent a kidney biopsy [72]. They also found that past NSAIDs use (between 2 months and 2 years) as well as current use (2 to 4 weeks) increased odds of nephrotic syndrome with the ORs of 1.24 (1.07–1.43) and 1.34 (1.06–1.70), respectively [72]. Acetic acid derivatives (aspirin) and propionic acid derivatives (ibuprofen, naproxen and fenoprofen) are associated with higher odds [72]. Tip lesion FSGS is also reported in an NSAIDs user [73]. Pathophysiology of NSAID induced nephrotic syndrome remains unclear but it has been postulated that NSAIDs can induce podocyte injury which may incite immune process leading to autoantibodies production [74].

MCD secondary to NSAIDs is often accompanied by severe AKI and may occur with or without concurrent interstitial nephritis [75–77]. Kidney pathology typically demonstrates minimal changes under light microscopy and diffuse foot process effacement under electron microscopy [76]. Treatment involves NSAIDs discontinuation and immunosuppression. Prognosis is generally favorable.

MN is the most common cause of nephrotic syndrome in adults [78]. Prior to the discovery of phospholipase A2 receptor antibody, it has been categorized as primary and secondary MN (in which drug-induced MN belongs to) [79]. Kidney pathology usually reveals mesangial expansion with thickened basement membrane with immunofluorescence displaying IgG granular capillary loop staining. IgG subclass may aid in differentiating primary and secondary MN. Primary MN predominantly has IgG4 deposition whereas secondary MN (such as NSAIDs-induced MN) frequently has IgG1 deposition [74]. However, antigen identification of immune deposits may now become more clinical relevant than the IgG subclass [80]. A study of NSAIDs-induced MN reported the mean age of 55 years old with median onset of 43 weeks (range from 4 weeks to 3 years) after exposure. Most patients had massive proteinuria with mean proteinuria of 10.2 g/day but none required dialysis. Proteinuria usually improved after drug cessation and conservative management without immunosuppression, which is different from primary MN that usually required immunosuppressive treatment [81]. Re-introduction of NSAIDs may result in a relapse of MN [74].

2.8. Papillary necrosis (PN)

PN is a rare kidney disease with reported prevalence of 0.1% and 3–5% in non-diabetic and diabetic patients, respectively,[82] although the prevalence can be as high as 20% in an autopsy series [83]. Risk factors include prolonged NSAIDs use, diabetes mellitus and sickle cell anemia [84,85]. Patients can present with non-specific symptoms such as nocturia, dysuria, pyuria, microscopic hematuria, proteinuria and ureteral colic [86]. Some patients may develop back pain and passing sloughed papillae in the urine [85]. In a severe case, necrotic papillae can clog up ureter resulting in bilateral ureteral obstruction [87]. Kidney imaging may demonstrate calyceal haziness or failure of contrast media filling of minor calyces [86]. Kidney pathology typically reveals coagulative necrosis at renal papilla. Fibrosis and calcification are common in chronic cases [85]. Several animal studies have confirmed the role of NSAIDs in its pathogenesis [88–90]. The anatomical vascular bundles of papillary vessels that only a single or few vessels supplying renal papillae results in over dependency of local PGs in maintaining blood flow to the papillary tip. Therefore, papillary tip is especially vulnerable to severe ischemia in the setting of PGs depletion from NSAIDs [86]. Renal outcome is favorable in PN with less than 2% required dialysis upon diagnosis and 6% during the follow-up period [91].

2.9. Chronic kidney disease progression

The association between NSAIDs use and risk of CKD has not been well-established as earlier studies that demonstrated an enhanced risk of CKD among NSAIDs users suffered from several biases and methodological flaws [92,93]. Nonetheless, more recent studies with better quality appear to show the same result. In a community study, NSAIDs users have a higher odds of developing CKD with OR of 1.63 (95% CI 1.22–2.19) [32]. They are also at increased risk of CKD progression, particularly among high dose users, with the pooled OR 1.26 (95% CI 1.06–1.50) [94,95]. The risk appears to be especially heightened among those with history of hypertension and diabetes [96,97]. Unfortunately, NSAIDs are still prescribed in majority of CKD patients. A recent cross-sectional study showed that nearly two-third of CKD patients were

prescribed NSAIDs and 80% of them were regular users [98].

2.10. Renal cell carcinoma (RCC)

Kidney cancer is one of the most common cancers in the United States with RCC being the most common type accounting for 85% of cases. Studies have suggested that non-aspirin NSAIDs may increase the risk of RCC [99–102]. A recent meta-analysis found that non-aspirin NSAIDs users had a higher risk of incident RCC with the pooled relative risk of 1.25 (95% CI 1.06-1.46). A dose-response relationship was also observed [103]. The pathophysiology remains unclear but may be related to chronic kidney injury leading to DNA damage and carcinogenesis [102].

2.11. Treatment and outcomes

Discontinuation of NSAIDs along with conservative management is generally sufficient for management of renal complications from these drugs. More importantly, avoidance of NSAIDs is crucial especially in high-risk patients. In patients with mild CKD (stage 1-3), only short-term use (≤5 days) with close monitoring is allowed. [6] In CKD stage 4, if it is felt to be necessary and no other alternative agents, short-term and low dose NSAIDs may be considered but with close monitoring for renal toxicity. NSAIDs should be avoided in stage 5 CKD due to high risk of renal complications [6]. AKI secondary to NSAIDs use is typically reversible after discontinuation with a favorable prognosis. Similarly, patients with nephrotic syndrome (MN and MCD) usually respond to NSAIDs withdrawal along with conservative management. However, some patients may require immunosuppression particularly in severe and refractory cases. Similarly, patients with AIN typically responds to NSAIDs discontinuation but often require short course of steroid to ameliorate the inflammation.

3. Conclusion

NSAIDs are ones of the most common prescribed drugs worldwide. They exert their anti-inflammatory action via COX inhibition leading to PGs imbalance. PGs depletion subsequently induces vasoconstriction and impairment of salt and water excretory function. Patients with CKD and upregulated RAAS (heart failure, liver failure or volume depletion) are at increased risk of renal toxicity. AKI from ischemic insult is the most common pattern of renal complications. Hypertension, hyperkalemia, hyponatremia, edema, nephrotic syndrome, AIN and CKD progression are also observed. Discontinuation of NSAIDs along with conservative management is generally sufficient for management of the renal complications. More importantly, avoidance of NSAIDs is crucial especially in high-risk patients.

Financial disclosure

None.

Conflict of Interest

Authors declare no conflict of interest.

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