Chronic Kidney Disease (CKD) Meets Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): A Risky Interaction of Toxicity and Impaired Clearance

Anirban Banerjee [1], Samrat Bose[*] [2], Soumita Das [3], Shreya Sarkar [4], Asfakul Islam [1], Shubham Kolay [1], Prasanna Roy [5], Sreetama Moitra [1], Suvasish Mitra [1], Prasit Roy [5], Bipasha Pal [1], Ankit Chatterjee [6], Joyeta Ghosh [1]

[1] Guru Nanak Institute of Pharmaceutical Sciences and Technology, 157/F Nilgunj Road, Panihati, Kolkata, West Bengal-700114
[2] JIS University, 81 Nilgunj Rd, Agarpara, Kolkata, West Bengal-700109
[3] NSHM Knowledge Campus, 124 BL Saha Road, West Bengal-700053
[4] Flemming College of Pharmacy, Balarampur, Beralia, West Bengal-700144
[5] Gandhari College (School of Pharmacy), Garhbari, Nazir Bazar, West Bengal-721655
[6] Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Dr. Meghnad Saha Sarani, Durgapur, West Bengal-713212

Corresponding Author
Mr. Samrat Bose*
Assistant Professor, Department of Pharmacy, JIS University
Email: samratbose09@gmail.com

ABSTRACT

Chronic Kidney Disease (CKD) affects over 850 million individuals globally, posing a significant public health burden with rising morbidity and mortality, marked by progressive nephron loss and impaired renal clearance mechanisms. It substantially alters pharmacokinetics and enhances drug toxicity risk. Nonsteroidal anti-inflammatory drugs (NSAIDs), widely used analgesics, compromise renal hemodynamics through prostaglandin synthesis inhibition, potentiating nephrotoxicity. Evidence from large-scale cohort studies and meta-analyses reveals consistent associations between NSAID exposure and acute kidney injury (AKI), electrolyte disturbances, and accelerated CKD progression. Several guidelines, including the Kidney Disease: Improving Global Outcomes (KDIGO), recommend minimizing or avoiding NSAID use in CKD, especially when the estimated Glomerular Filtration Rate (eGFR) falls below 60 mL/min/1.73 m². While emerging data suggest short-term NSAID use may be permissible under strict supervision in select cases, the prevailing consensus remains conservative. Effective pain management in CKD must balance analgesic efficacy with nephron preservation through a guideline-directed approach. This review critically examines the mechanistic underpinnings and clinical consequences of NSAID use in CKD populations. It evaluates dose-dependent nephrotoxicity, interaction with the renin-angiotensin-aldosterone system (RAAS), and the cumulative burden in patients with comorbid conditions such as hypertension and myocardial infarction.

Keywords: Chronic Kidney Disease (CKD), Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Nephrotoxicity, Clinical Guidelines

ABBREVIATIONS

AA – Arachidonic Acid; ACE – Angiotensin-Converting Enzyme; AKI – Acute Kidney Injury; ALLHAT – Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; Ang II – Angiotensin II; ARB – Angiotensin Receptor Blocker; ATTACK – Aspirin To Target Arterial Events in CKD; CKD – Chronic Kidney Disease; (cTALH) – Cortical Thick Ascending Limb of Henle; cAMP – cyclic adenosine monophosphate; EGF – Epidermal Growth Factor; ER – Endoplasmic Reticulum; ERBP – European Renal Best Practice; ET – Endothelin; COX – Cyclooxygenase; CYP450 – Cytochrome P450 Enzyme System; eGFR – Estimated Glomerular Filtration Rate; ESRD – End-stage Renal Disease; GBD – Global Burden of Disease; hCOX – Human COX; JGA – Juxtaglomerular Apparatus; KDIGO – Kidney Disease: Improving Global Outcomes; MBD – Membrane-Binding Domain; MBF – Medullary Blood Flow; MD – Macula Densa; MI – Myocardial Infarction; MICs – Medullary Interstitial Cells; NSAID – Nonsteroidal Anti-Inflammatory Drug; NF-κB – Nuclear Factor-κB; PGs – Prostaglandins; PGD2 – Prostaglandin D2; PGDS – Prostaglandin D Synthase; PGE2 – Prostaglandin E2; PGES – Prostaglandin E Synthase; PGI2 – Prostacyclin; PGIS – Prostacyclin Synthase; PLA_2 – Phospholipase A_2; PRA – Plasma Renin Activity; TGF – Tubuloglomerular Feedback; TIPS-3 – The International Polycap Study-3;

1. Introduction

CKD is a progressive disorder characterized by a persistent reduction in renal function. It is typically characterized by a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 or albuminuria ≥30 mg/day or evidence of structural kidney damage persisting for at least three months [1][2][3]. CKD has emerged as a significant global health burden, with an estimated prevalence of 8–16% in the general population, affecting approximately 850 million individuals worldwide [3][4][5]. The growing prevalence of diabetes mellitus, hypertension, obesity, and aging populations primarily drives the increasing incidence of CKD. The Global Burden of Disease (GBD) study highlights CKD as one of the fastest-rising causes of mortality, with end-stage renal disease (ESRD) accounting for a substantial proportion of morbidity and healthcare expenditures [6][7]. The pathophysiology of CKD involves progressive nephron loss, maladaptive glomerular hyperfiltration, interstitial fibrosis, and inflammation, leading to a decline in renal function and systemic complications, including mineral-bone disorders, anemia, and metabolic acidosis [8][9][10].

Table 1: Stages of Chronic Kidney Disease (CKD) Based on Glomerular Filtration Rate (GFR) **[11]**

Stage of CKD	GFR (mL/min/1.73 m²)	Description
Stage 1	>90	Normal kidney function or elevated
Stage 2	60-89	Mild reduction in kidney function
Stage 3a	45-59	Mild to moderate decline in function
Stage 3b	30-44	Moderate to severe kidney dysfunction
Stage 4	15-29	Severe loss of kidney function
Stage 5	<15	End-stage kidney failure

NSAIDs represent one of the most widely prescribed pharmacological classes, utilized extensively for their analgesic, antipyretic, and anti-inflammatory properties [12][13][14]. NSAIDs function primarily by inhibiting the cyclooxygenase (COX) enzyme family, which is responsible for converting arachidonic acid into prostaglandins and thromboxanes—key mediators of inflammation, pain perception, and homeostatic functions [13][15][16]. COX enzymes exist in two primary isoforms: COX-1, which is constitutively expressed and involved in maintaining renal perfusion, gastrointestinal mucosal protection, and platelet aggregation, and COX-2, an inducible isoform predominantly associated with inflammation and pain modulation [17][18][19]. In individuals with normal renal function, prostaglandins play a compensatory role in maintaining GFR by countering the renin-angiotensin-aldosterone system (RAAS), particularly in conditions of volume depletion or renal hypoperfusion [20][21][22]. COX-1 inhibition contributes to adverse events, particularly in the renal system. In patients with compromised kidney function or CKD, prostaglandin synthesis disruption may lead to significant hemodynamic and nephrotoxic consequences [23][24].
Despite their efficacy, NSAIDs pose significant risks in patients with CKD due to their nephrotoxic potential. The reductions in prostaglandin-mediated vasodilation by NSAIDs can precipitate acute kidney injury (AKI), accelerate CKD progression, and contribute to electrolyte imbalances (hyponatremia and hyperkalemia), hypertension, and cardiovascular complications (including heart attack, stroke, and heart failure) [25][26][27].

This review comprehensively examines the interaction between NSAID therapy and CKD, emphasizing the mechanistic basis of NSAID-induced nephrotoxicity, alterations in NSAID pharmacokinetics in CKD patients, and the clinical consequences of NSAID use in this population. By synthesizing data from recent clinical studies, mechanistic investigations, and pharmacokinetic analyses, this review aims to critically appraise NSAID therapy in CKD and inform clinical decision-making for healthcare professionals managing this vulnerable patient population.

2. Molecular Structure of COX Protein

The human COX (hCOX) family comprises two primary isoforms: COX-1 and COX-2. These isoforms share approximately 70% sequence identity but differ significantly in their expression patterns, regulatory mechanisms, and physiological roles [28][18][29]**.** COX-1 is ubiquitously expressed in most tissues [*Table 2*] and is involved in maintaining renal function, gastric mucosal protection, and platelet aggregation. The inducible isoform is typically undetectable in most tissues under basal conditions and upregulated in response to pro-inflammatory stimuli, cytokines, and growth factors (such as Epidermal Growth Factor, TGF-β1, and Vascular Endothelial Growth Factor) [18][30][31]. The constitutive COX-2 expression occurs in macula densa (MD), medullary interstitial cells (MICs), and glomerular podocytes, underscoring its crucial role in renal physiology [32][33]. Both isoforms catalyze the oxygenation of arachidonic acid to prostaglandin G_2 (PGG_2), followed by its reduction to PGH_2.

The structural complexity of cyclooxygenase enzymes underpins their functional versatility and interactions with therapeutic agents. hCOX enzymes are homodimers embedded in the endoplasmic reticulum (ER) and nuclear membrane, composed of 576 (consisting of 599 amino acids, with a mature form of 576 residues after signal peptide cleavage) and 581 (contains 604 amino acids, with a mature form of 581 residues, including an 18-residue insertion absent in COX-1) amino acid residues respectively [18][34][35]. Despite their high sequence homology, key sequence variations, including additional glycosylation sites in COX-2, influence their structural dynamics and regulatory mechanisms.

2.1. Domain Organization of COX

Cyclooxygenase enzymes are multi-domain and membrane-bound proteins. The domain architecture is crucial for comprehending these enzymes' catalytic mechanisms, membrane anchoring, and selective drug binding properties. The structural organization of each COX monomer is divided into three primary domains: the Epidermal Growth Factor (EGF)-like domain, the Membrane-Binding Domain (MBD), and the Catalytic Domain [18][36]. The EGF-like domain (residues 34–72) adopts a compact, β-sheet-rich structure, stabilized by disulfide bonds (characteristic of the EGF fold) [18][37][38]. This motif is common in extracellular and membrane-associated proteins, mediating protein-protein interactions. Crystallographic studies reveal that the EGF domain contributes to homodimerization, a prerequisite for enzymatic activity, as it facilitates proper heme incorporation and stabilizes the active site conformation. The C2 axis of symmetry observed in COX dimers is partly maintained by the EGF domain through hydrophobic and electrostatic interactions [39][40]. The EGF domain spatially positions the enzyme relative to the membrane surface. This orientation optimally aligns the MBD and the Catalytic Domain for substrate acquisition and processing [40][41].

The membrane-binding domain (residues 73–116) is an α-helical bundle consisting of 4 amphipathic helices (A–D), oriented parallel to the membrane surface. The helices are arranged such that hydrophobic residues face the lipid bilayer, embedding the enzyme in the membrane, while hydrophilic residues orient toward the aqueous cytoplasmic environment [18][42][43]. The MBD of COX enzymes partially inserts into the ER cytoplasmic leaflet and nuclear envelope membranes. This shallow embedding positions the enzyme optimally to capture AA and other polyunsaturated fatty acids released from phospholipids [40].

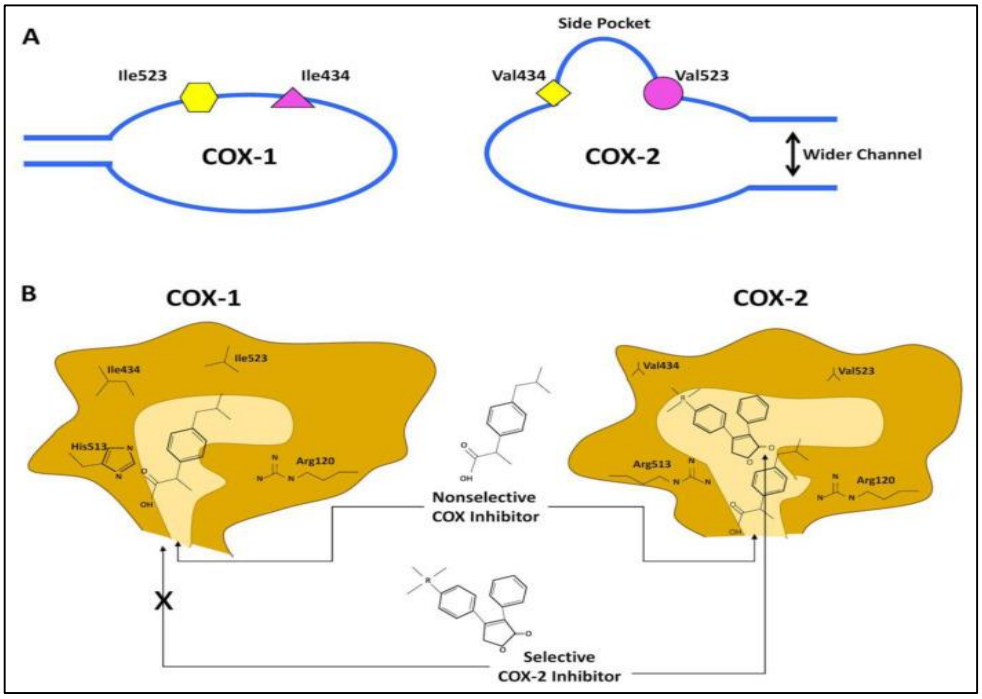

Figure 1: Schematic Illustration of the Structural Variations in the Substrate-Binding Channels of Cyclooxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2). Adopted from [60]

The catalytic domain is a multi-functional region containing a heme cofactor and two distinct active sites responsible for the sequential oxidation of AA to PGH_2, which consists of a seven-helix bundle homologous to other heme peroxidases [29][44][45]. The heme-binding pocket is essential for enzyme function, held in place by conserved histidine residues (His-336 and 388) that coordinate the iron atom [40][46]. The heme iron undergoes cyclical oxidation-reduction, mediating electron transfer between the peroxidase and active sites. The peroxidase active site is near the heme-binding region, reducing hydroperoxides to alcohols, generating radicals essential for cyclooxygenase activity [40]. The active site of COX enzymes is a long, L-shaped (inverted) hydrophobic channel that extends from the membrane-binding domain to the core of the catalytic domain [*Figure 1; B*]. The active site is lined with crucial amino acid residues that facilitate substrate binding and catalysis, including Arg120, Tyr384, Ser530, Val349, Leu352, and Leu359 [28][18][35][47]. The active site volume of COX-2 is approximately 25% larger than that of COX-1, owing to a valine-to-isoleucine substitution (Val-523 in COX-2, Ile-523 in COX-1). This structural difference accounts for the selectivity of COX-2 inhibitors like celecoxib and rofecoxib [28].

2.2. Dimerization and Functional Assembly

COX is an example of an allosteric and cooperative enzyme that possesses an oligomeric state. It exists as homodimers, each monomer contributing to the overall enzymatic activity. Each subunit contains independent active sites, and functional asymmetry arises during catalysis, where one subunit acts as the “catalytic monomer” and the other as the “allosteric monomer” [48][49][50][51]. The dimer interface spans ~20% of the total protein surface area, involving residues primarily from the EGF-like domain and MBD. Hydrogen bonds and salt bridges stabilize the dimer interface of COX enzymes, and Trp-87 and Arg-120 form a critical hydrophobic clamp, anchoring the subunits [18][40][52][53]. Crystallographic and mutagenesis studies suggest that COX dimers are functionally asymmetric; the catalytic monomer binds AA and performs the cyclooxygenase and peroxidase reactions.

Meanwhile, allosteric monomer regulates catalytic efficiency by modulating heme redox states and substrate affinity through long-range conformational shifts [40][54][55]. This half-site reactivity ensures tight regulation of prostanoid synthesis, preventing excessive prostaglandin production and reducing oxidative stress. This dimerization-dependent regulation provides a sophisticated mechanism for spatiotemporal control of inflammatory responses. It highlights potential therapeutic opportunities for targeting the dimer interface to develop allosteric inhibitors with improved selectivity and safety profiles [40].

2.3. Sequence Variations and Structural Distinctions Defining COX Isoform Specificity

COX-1 is a housekeeping enzyme encoded on chromosome-09, involved in baseline prostaglandin production for renal homeostasis, gastroprotection, and platelet function. COX-2 is an inducible enzyme encoded from chromosome-01, upregulated in response to cytokines and pro-inflammatory stimuli [28][56]. Despite sharing ~70% sequence identity, COX-1 and COX-2 exhibit distinct structural features that underlie their divergent physiological roles and differential sensitivity to inhibitors. Unlike COX-1, COX-2 lacks a 14-residue segment near its N-terminus, which may contribute to its looser dimer interface and higher catalytic flexibility. COX-2 contains an 18-residue insertion in the catalytic domain (missing in COX-1), introducing subtle changes to the cyclooxygenase active site topology [29][57][58]. The N-linked glycosylation site (residue Asn-594) of COX-2 influences membrane interactions and enzyme stability [59][44]. COX-1 possesses an inverted L-shaped hydrophobic channel lined by smaller side chains, COX-2 has an enlarged active site due to Val-523 substitution, which introduces greater flexibility and accommodates bulkier substrates like arachidonic acid derivatives and endocannabinoids [28][35][47].

3. COX Enzymes in Kidney Function and Homeostatic Regulation

COX enzymes are indispensable regulators of renal homeostasis, orchestrating complex physiological processes. These isoforms exhibit distinct expression patterns and functional roles within the kidney, influencing basal and adaptive renal responses. COX-1 is constitutively expressed in renal tissues, including the glomeruli, collecting ducts, and renal vasculature [56][61][62]. Unlike COX-1, COX-2 exhibits dynamic, inducible expression, localized primarily to the MD, cortical thick ascending limb of Henle (cTALH), and MICs [61][63][64]. Despite their distinct expression patterns, COX-1 and COX-2 exhibit functional redundancy. The dynamic interplay between COX-1 and COX-2 ensures the kidney can respond flexibly to acute and chronic physiological stressors.

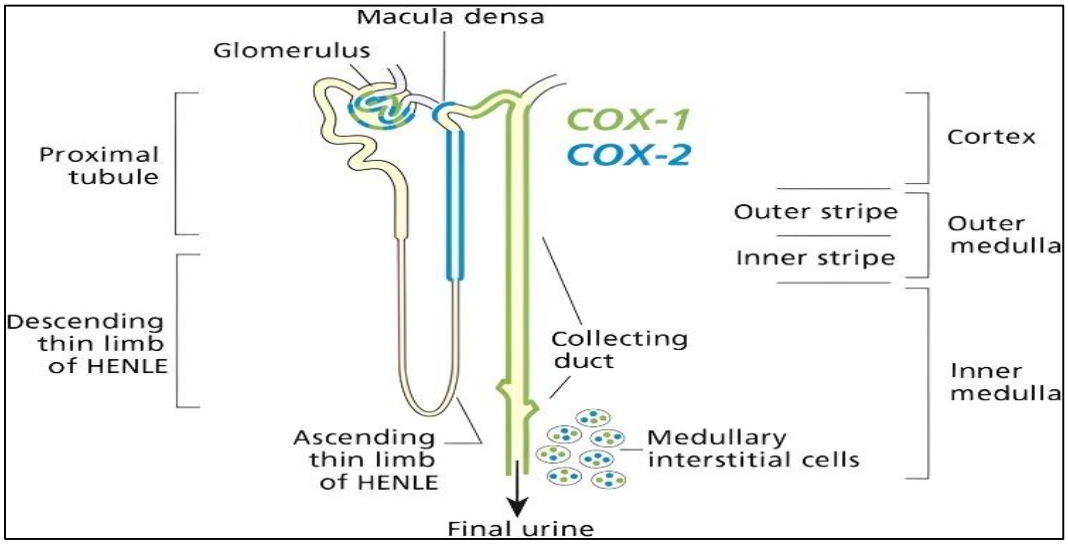

Figure 2: Illustration of COX-1 and COX-2 Localization in the Kidney: COX-1 (green) and COX-2 (blue) expression in various regions of the nephron, including the macula densa, proximal tubule, Henle's loop, and collecting duct.

Table 2: Distribution and functional Roles of COX-1 and COX-2 in Various Tissues

COX Isoform	Location	Function
COX-1	Platelets	Constitutively expressed in most tissues; plays a role in platelet aggregation, gastric protection, renal function, and regulation of vascular tone.
	Stomach	Involved in protecting the gastric mucosa by regulating the production of prostaglandins that maintain mucosal blood flow and bicarbonate secretion.
	Kidney	Participates in the regulation of renal blood flow and filtration.
	Brain	Involved in homeostatic functions such as maintaining blood-brain barrier integrity and modulating cerebral blood flow.
	Endothelium	Contributes to the regulation of vascular tone and platelet aggregation.

COX-2	Inflammatory sites (such as joints, injured tissues)	Induced in response to inflammatory stimuli, it plays a critical role in pain, fever, and tissue repair processes.
	Brain (induced)	Involved in pain processing, neuroinflammation, and neurodegenerative diseases.
	Kidney (induced)	Regulates renal function under stress, including inflammation or injury.
	Endothelium (induced)	Upregulated in response to inflammatory or stress stimuli, contributing to inflammation and blood flow regulation.

3.1. Synthesis of Prostaglandins in the Kidney

PG biosynthesis is a highly regulated, multi-step enzymatic process that plays a fundamental role in physiological homeostasis and inflammatory responses. The COX enzyme family is a central molecule in this cascade, orchestrating AA's pivotal transformation into PGH_2 [*Figure 3*]. This transformation proceeds via a stereospecific radical mechanism, ensuring precise structural fidelity of the final prostanoids [40][60][40][65]. The polyunsaturated ω-6 fatty acid AA (C20) remains esterified (as arachidonate) within membrane phospholipids under resting membrane potential. Its molecular integrity is tightly regulated by phospholipase A_2 (PLA_2), an enzyme that hydrolyzes membrane-bound AA in response to physiological stimuli, including mechanical stress, cytokines, and hormonal signals. The liberated AA serves as the substrate for cyclooxygenases, initiating the prostaglandin synthesis pathway [66][67][68]. The bifunctional heme-containing enzyme COX (COX 1 and 2) catalyzes the oxidation of AA following a tightly orchestrated radical-based mechanism, comprising three fundamental steps: substrate binding, oxygenation, and peroxidase reduction [65][69][70]. AA enters the COX active site via a hydrophobic channel (L-shaped) that accommodates its polyunsaturated tail. The peroxidase domain of COX, containing a heme prosthetic group, facilitates the generation of a tyrosyl radical at Tyr-385 (COX-2 numbering). These radicals abstract the 13-pro-S hydrogen from AA, producing a carbon-centered pentadienyl radical, the reactive intermediate for subsequent oxygenation. This step results in the formation of PGG_2 (a hydroperoxide intermediate) [40][18][71][72]. The structural integrity of the active site dictates the stereoselectivity of these transformations. Particularly in COX-2, restricted binding orientations enforce regio- and stereospecificity. The formation of 15S-hydroperoxide at C15 ensures the correct prostanoid configuration [18][73]. The final step in COX-mediated prostaglandin synthesis involves the conversion of PGG_2 to PGH_2 by the peroxidase domain and is mediated by a heme-dependent electron transfer mechanism. Reducing peroxidase reduces the hydroperoxy group (-OOH) at C15 of PGG_2 to a hydroxyl (-OH) moiety. The resulting PGH_2 is the central prostanoid precursor for downstream enzymatic modifications [18][63][18][74].

3.1.1. Diversification of PGH_2

PGH_2 is an inherently unstable intermediate with an exceedingly short half-life. The immediate enzymatic conversion by tissue-specific isomerases and synthases converts PGH_2 into bioactive prostanoids. This enzymatic diversification ensures the precise regulation of prostaglandin-mediated physiological responses. Prostaglandin E Synthase (PGES) catalyzes the conversion of PGH_2 to PGE_2, a crucial inflammatory mediator that modulates vasodilation and immune responses [22][75][76][77]. Prostaglandin D Synthase (PGDS) facilitates the biosynthesis of PGD_2, a lipid mediator implicated in allergic reactions and sleep regulation [78][79][80][81]. Prostacyclin Synthase (PGIS) generates prostacyclin (PGI_2), a potent vasodilator that plays a critical role in endothelial function and the inhibition of platelet aggregation [82][83]. The tissue-specific expression of these enzymes dictates the functional specificity of prostaglandins, maintaining a delicate balance between hemostatic regulation and vascular homeostasis.

3.1.2. Regulatory Dynamics of Prostaglandin Synthesis

Calcium ion (Ca^{2+}) plays a pivotal role in modulating prostaglandin synthesis by influencing the release of AA and its subsequent enzymatic conversion into bioactive prostanoids.

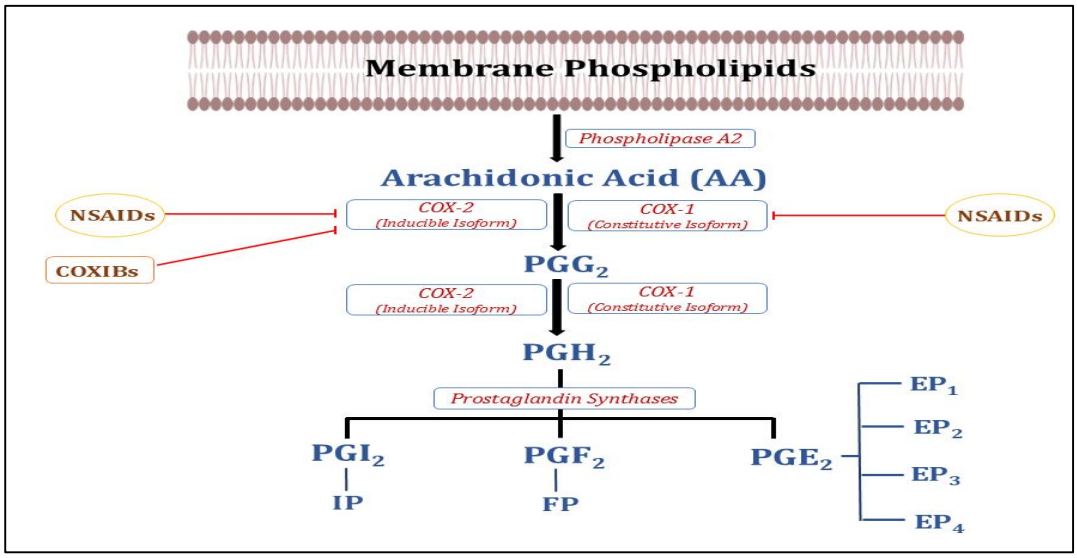

Figure 3: Arachidonic acid metabolism pathway showing COX-1 and COX-2 enzymes, prostaglandin synthesis, and the effects of NSAIDs and inhibitors. Adopted from [77].

Arachidonic acid liberation is the rate-limiting step in prostaglandin synthesis and is catalyzed by cytosolic PLA_2. Ca^{2+} binds to the C2 domain of PLA_2, facilitating its translocation to perinuclear and plasma membranes, enhancing the hydrolysis of membrane phospholipids, and releasing free AA for COX-mediated conversion. The Secretory PLA_2 ($sPLA_2$; Predominantly active in the renal cortex) exhibits a Ca^{2+}-dependent hydrolytic mechanism, contributing to local AA release under inflammatory conditions [84][85][86][87]. Calcium-Independent PLA_2 ($iPLA_2$) indirectly interacts with Ca^{2+} signaling, especially under ischemic conditions, modulating prostaglandin synthesis in the renal medulla [88][89][90].

Although COX enzymatic activity is Ca^{2+}-independent, intracellular Ca^{2+} profoundly influences COX expression and prostaglandin synthesis by regulating AA substrate availability. Under stress conditions (such as ischemia, sodium depletion), predominantly in the macula densa and medullary interstitial cells, COX-2 responds to Ca^{2+}-dependent activation pathways [91]. In glomerular mesangial cells, Ca^{2+} influx via L-type channels enhances COX-2 expression, promoting PGE_2-mediated vasodilation and autoregulation of GFR. The increased intracellular Ca^{2+} activates COX-2 in the proximal tubular cells [63][92]. COX-2-derived prostaglandins modulate afferent arteriolar tone, influencing glomerular filtration rates [93][24].

3.2. Regulation of Renal Blood Flow by COX

COX enzymes are integral to fine-tuning renal blood flow (RBF) and glomerular filtration dynamics due to the generation of bioactive prostanoids. PGs function as critical mediators in balancing vasodilatory and vasoconstrictive forces within the renal vasculature [94][95]. Dysregulation of this system, particularly through pharmacological inhibition of COX enzymes, can compromise renal perfusion and contribute to acute and chronic kidney injuries. The primary function of COX-1 is to sustain basal renal physiology by facilitating the synthesis of vasodilatory PGs (such as PGE_2 and PGD_2). COX–1–derived prostanoids mitigate the vasoconstrictive actions of angiotensin II and norepinephrine on afferent arterioles, preserving RBF and GFR under normal physiological conditions [24][94][96]. COX-2 becomes upregulated in response to volume depletion or high renin states, producing vasodilatory prostacyclin (PGI_2) to safeguard RBF under stress conditions [97][98].

3.2.1. Vasodilatory Actions of COX-Derived Prostaglandins

PGI_2, predominantly synthesized by endothelial COX-1 and COX-2, exerts its effects via IP receptors on vascular smooth muscle cells. It activates adenylate cyclase, increasing intracellular cyclic adenosine monophosphate (cAMP), which ultimately leads to vasodilation and ensures adequate perfusion under both physiological and pathophysiological conditions [95][99][100][101]. PGE_2 is produced via both COX isoforms, depending on the renal compartment, and is notably abundant in the thick ascending limb, collecting duct, and glomerular apparatus. Its vasodilatory actions are subtype-specific, predominantly mediated through EP_2 and EP_4 receptors, which similarly activate cAMP pathways [102][103][104]. Notably, PGE_2 modulates afferent arteriolar tone, safeguarding glomerular filtration during hypovolemia, ischemia, or sympathetic overactivity [105][106].

3.2.2. Vasoconstriction Counterbalance: Antagonism of Angiotensin II and Endothelin-1

The renal circulation is subject to complex neurohumoral control, wherein vasoconstrictors such as angiotensin II (Ang II) and endothelin-1 (ET-1) influence vascular tone. COX-derived PGs function as physiological counter-regulators in this highly regulated system [107][108][109][110]. Ang II induces constriction predominantly of the efferent arteriole, but

also affects the afferent arteriole during heightened systemic activation via AT_1 receptor activation [108][111][112][113]. However, COX-derived PGs (especially PGE_2 and PGI_2) mitigate these vasoconstrictive responses by enhancing local vasodilatory signaling [114][115]. Similarly, endothelin-1 (ET-1; a potent paracrine vasoconstrictor) reduces renal cortical and medullary blood flow through ETA receptors, and PGE_2 blunts the vascular and tubular effects of ET-1 [116][117][118].

3.2.3. Adaptation Mechanisms of RBF by COX

COX-2 is particularly inducible among the two isoforms and exhibits a dynamic expression profile within the renal parenchyma. A key site of its expression under physiological and stress-adaptive conditions is the renal MICs, which play a critical role in modulating medullary blood flow (MBF) and sodium homeostasis. Under high dietary sodium intake conditions, COX-2 expression is markedly upregulated in the inner medulla, particularly within the renal papilla. This phenomenon is believed to be a homeostatic mechanism aimed at promoting natriuresis and preventing volume overload [91][119][120][121][122]. However, COX-2 dynamically responds to fluctuations in sodium intake and osmotic stress, whereas COX-1 primarily maintains baseline electrolyte excretion [62][123].

COX-2 plays a cytoprotective role in the renal medulla during water deprivation or high-salt intake by mitigating hypertonic stress. COX-2 upregulation in response to hypertonicity drives PGE_2 synthesis, activating nuclear factor-κB (NF-κB) and p38 MAPK pathways. This upregulation triggers the transcription of anti-apoptotic genes and hypertonicity-induced cell death [124][125][126][127][128].

3.3. RAAS Modulation and Renin Release by COX

RAAS is a central hormonal cascade that governs renal perfusion, electrolyte balance, and systemic vascular resistance [129][130][131]. COX-derived PGs emerge as critical renin synthesis and secretion modulators, primarily via their autocrine and paracrine actions within the juxtaglomerular apparatus (JGA). The JGA is strategically composed of juxtaglomerular cells (JG cells; *aka* Granular cells), MD cells, and extraglomerular mesangial cells, acting as a sensor-effector interface for renal autoregulation [132][133][134]. Among the prostanoids, PGE_2 is the primary effector stimulating renin release from the JG cell [135][136]. This effect is predominantly mediated through EP_2 and EP_4 receptors (both are coupled to Gs-proteins that activate adenylate cyclase), elevate cAMP levels, and thereby enhance renin gene transcription and exocytosis [137][137][137]. Under physiological stress, such as hypotension, volume depletion, or dietary sodium restriction, tubuloglomerular feedback (TGF) signals via MD lead to upregulation of COX-2 expression, increasing local PGE_2 production. This paracrine signal acts directly on juxtaglomerular cells to stimulate renin secretion, contributing to the compensatory activation of RAAS and restoration of circulatory homeostasis [137][138][139][140].

Evidence from COX-2 knockout mice and pharmacologic inhibition studies underscores the indispensable role of COX-2-derived prostaglandins in renin regulation. Deletion or selective blockade of COX-2 leads to marked suppression of renin mRNA and plasma renin activity (PRA), especially during sodium deprivation. This observation reinforces the notion that COX-2 is a rate-limiting factor in renin biosynthesis under stimulated conditions [62][141][142]. EP receptor knockout models have revealed that EP_4-deficient mice exhibit blunted renin responses, impaired TGF signaling, and alterations in sodium handling, highlighting the PGE_2-EP_4 axis as a molecular determinant of JGA function [143][144][145].

4. Nephrotoxicity and Hemodynamic Consequences of COX Inhibition in Renal Disorders

Renal cyclooxygenases (COX-1 and COX-2) continuously produce PGs that maintain glomerular perfusion and fluid-electrolyte balance. In conditions of reduced circulating volume or renal perfusion, PGs (especially PGE_2 and PGI_2) dilate afferent arterioles to sustain RBF and GFR [24] [25]. COX-derived PGs also modulate tubular transport and counteract potent vasoconstrictors. NSAIDs irreversibly or reversibly inhibit COX, thereby suppressing PG synthesis [17][25]. The four key mechanisms by which COX inhibition exacerbates CKD/AKI are impairment of RBF (GFR regulation), loss of vasoconstrictor buffering, osmotic adaptation, and dysregulated RAAS. COX-2-deficient mice with adenine-induced CKD exhibited exacerbated medullary hypoxia and tubular apoptosis [146].

4.1. RBF and GFR Regulations

COX-generated prostaglandins play an indispensable role in setting renal vascular tone. Under normal and volume-depleted states, PGI_2 and PGE_2-mediated vasodilation raise RBF and sustain GFR when circulating volume or adequate perfusion is low [24][105][147]. Genetic and pharmacologic COX inhibition removes this compensatory mechanism. In experimental models, selective COX-2 blockade blunts the afferent arteriolar vasodilation commonly induced by vasoconstrictors, causing a decline in GFR [123][148][149]. Clinically, NSAID use acutely reduces RBF and GFR, especially in volume-contracted states [123][150][151]. Thus, by impeding COX-mediated PG vasodilation, NSAIDs can precipitate renal hypoperfusion and acute kidney injury, especially in already compromised kidneys [149][152]. In CKD, interstitial fibrosis and hypoxia are prevalent [153][154]; COX-2-derived PGE_2 preserves perfusion in the medullary thick ascending limb and collecting ducts. This is achieved by stimulating vasodilation via EP_2/EP_4 receptors and activating cytoprotective pathways such as NF-κB and MAPK [104][155].

4.2. COX Enzymes in Renal Homeostasis: Counter-Regulation of Vasoconstrictive Pathways

COX-derived prostaglandins act as endogenous buffers against renal vasoconstrictors. PGE_2 and PGI_2 blunt the vasoconstrictor and antidiuretic effects of angiotensin II (Ang II) on the afferent arteriole. Under normal physiological conditions, PGs oppose Ang II–induced afferent

constriction, thereby maintaining GFR. PGs also mitigate the impact of endothelin-1 and sympathetic catecholamines in the renal microcirculation. Inhibition of COX unopposed this vasoconstriction. Experimental studies show that COX-2 inhibition dramatically potentiates the hypertensive response to Ang II by reducing medullary blood flow and sodium excretion [114][138][156][157]. Blockade of PG synthesis by NSAIDs removes the "safety valve" against vasoconstriction [158][159][160]. COX inhibition shifts the balance toward Ang II– and endothelin-mediated afferent arteriolar constriction and AKI.

4.3. Sodium and Osmotic Regulation: Adaptive Mechanisms

Cyclooxygenase pathways are crucial for renal salt and osmotic balance. PGE_2 normally acts as a counter-regulatory factor when sodium reabsorption is high, inhibiting the NKCC2 cotransporter in the thick ascending limb and reducing water reabsorption in collecting ducts. [161][162]. Clinically, selective COX-2 inhibitors consistently decrease urinary sodium excretion in the first days of use, and NSAID use can cause sodium retention and peripheral edema [120][163][164][165]. These effects increase blood pressure and extracellular volume, which is counterproductive, especially in CKD or heart failure. By impairing medullary PG production, COX inhibition also diminishes renal medullary blood flow, further hampering the kidney's ability to concentrate or dilute urine in response to osmotic stress [120][166]. In short, NSAIDs cause inappropriate sodium and water retention and reduce renal concentrating ability, contributing to hypertension and volume overload in susceptible patients.

4.4. Suppression of RAAS Activity

CKD progression involves maladaptive activation of the RAAS [167]. Although localized RAAS activation remains essential for preserving perfusion pressure, systemic RAAS overactivity contributes to hypertension and glomerular injury. COX activity supports RAAS function, where NSAID therapy inhibits this critical mechanism, blunting renin release and destabilizing the delicate hemodynamic balance in CKD [168]. CKD stage 3–4 patients, NSAID administration led to significant reductions in plasma renin activity, correlating with episodes of hypotension, AKI, and fluid overload. Animal models show that COX-1 deletion abolishes Ang II–induced hypertension, whereas COX-2 blockade heightens it [169][25]. Thus, COX inhibition disrupts homeostatic RAAS signaling and can precipitate maladaptive volume and hemodynamic effects.

4.5. Evidence-Based Assessment of NSAID-Associated Renal Adverse Effects

The mechanistic disruptions above manifest as significant nephrotoxicity in patients with CKD or cardiovascular comorbidities. Observational studies consistently link NSAID exposure to higher AKI and CKD progression risk. A meta-analysis of CKD patients estimated a pooled odds ratio of ~1.6 for NSAID-associated AKI [169]. In a large cohort of 1.98 million adults with normal baseline renal function, NSAID use was associated with a 1.71-fold higher hazard of incident eGFR <60 mL/min/1.73m² and a 1.93-fold greater hazard of ≥30% eGFR decline, compared to nonusers [170]. Retrospective analyses report that NSAID use roughly doubles

the odds of AKI or new CKD in elderly and multimorbid populations. For instance, one study found that NSAIDs increased AKI risk by 73% in the general population (OR 1.73) and by 58% in those >65 years (OR 1.58). Combined NSAID and RAAS blocker or diuretic therapy multiplies risk; one analysis showed an OR≈2.5 for AKI in CKD patients on diuretics/RAAS inhibitors who also used NSAIDs [169][25]. These epidemiologic findings align with clinical observations: NSAIDs are a leading cause of drug-related hospitalizations for AKI, especially in patients with CKD, heart failure, or liver disease. So, Cyclooxygenase inhibition disrupts multiple protective mechanisms of renal homeostasis.

5. Clinical implications of aspirin therapy in post-myocardial infarction patients with chronic kidney disease: a case-based evaluation

CKD is a well-established accelerator of atherosclerosis and vascular calcification, substantially increasing the incidence and severity of cardiovascular disease. Patients with CKD are at markedly elevated risk for acute coronary syndromes, including myocardial infarction (MI), due to persistent endothelial dysfunction, dysregulated lipid metabolism, and systemic inflammation. Consequently, the post-MI period in CKD patients is clinically precarious, characterized by higher rates of recurrent ischemic events, arrhythmias, and sudden cardiac death [171][172][173][174][175]. Aspirin, an irreversible COX inhibitor, remains the cornerstone of antiplatelet therapy for secondary prevention of atherothrombotic events [176][177]. However, in patients with impaired renal function, the altered pharmacokinetics and hemostatic fragility necessitate a reevaluation of its efficacy and safety profile. The dual burden of cardiovascular vulnerability and increased hemorrhagic risk complicates the clinical utility of sustained-release aspirin in this population.

5.1. Efficacy of Aspirin in CKD for Cardiovascular Event Reduction

The antithrombotic efficacy of aspirin in CKD patients post-MI is nuanced and highly dependent on the stage of renal dysfunction [178][179]. The International Polycap Study-3 (TIPS-3) trial demonstrated that aspirin (75 mg daily) significantly reduced the composite outcome of non-fatal MI, non-fatal stroke, or cardiovascular death, yielding a hazard ratio of 0.57 (95% CI, 0.34–0.94) in patients with eGFR <60 ml/min/1.73 m², supporting its role in secondary prevention within moderate-to-severe CKD [180]. Conversely, post hoc analyses of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) trial and similar studies failed to identify significant reductions in all-cause mortality or MI recurrence in patients with eGFR <60 ml/min/1.73 m², suggesting a diminishing benefit of aspirin in advanced renal insufficiency [181]. This bifurcation in therapeutic outcomes underscores the need to stratify aspirin use based on CKD stage and individual cardiovascular risk profiles.

5.2. Hemorrhagic Complications and Safety Considerations in Antiplatelet Therapy

CKD is characterized by a paradoxical hemostatic milieu—hypercoagulability coexisting with intrinsic bleeding tendencies [182][183], primarily driven by uremia-induced platelet

dysfunction [184][185][186], vascular fragility [187][188], and impaired prostaglandin-mediated vasoregulation [61][95]. Aspirin, via COX inhibition, exacerbates bleeding risk by suppressing thromboxane A_2 synthesis. Nonetheless, specific observational cohorts have demonstrated no significant increase in major bleeding events across GFR strata, suggesting that when cautiously prescribed, aspirin may maintain a favorable safety margin in secondary prevention [189][190][191]. Notably, low body weight, concurrent anticoagulant use, and uncontrolled hypertension remain critical modifiers of bleeding risk in the CKD-MI subset [192].

The pharmacodynamic response to aspirin is significantly attenuated in CKD due to platelet hyperreactivity and residual thromboxane generation, a phenomenon termed “Aspirin Resistance” [193][194]. This resistance is mechanistically linked to oxidative stress, enhanced platelet turnover, and inflammation-driven non-COX thromboxane synthesis [195][196][197]. Studies using serum thromboxane B_2 assays [198][199] and platelet aggregometry [200][201] have documented persistently elevated platelet activity despite aspirin therapy in CKD, correlating with higher rates of recurrent ischemic events [202][203][204]. These findings reinforce the hypothesis that standard-dose aspirin may be insufficient for effective platelet inhibition in CKD, particularly in sustained-release formulations where bioavailability may be variable.

5.3. Clinical Recommendations

Despite its therapeutic value, aspirin remains the recommended first-line agent for secondary prevention in post-MI CKD patients, conditional upon stringent bleeding surveillance and appropriate dose titration [205][206][207]. Data from coronary care registries indicate a sharp decline in the use of both aspirin and β-blockers as renal function deteriorates. Among patients with creatinine clearance (CrCl) <46.2 ml/min, only 35% received both agents, in contrast to 63.9% among patients with higher CrCl values [108,[209][210]. Clinical variables such as concurrent heart failure, arrhythmias, and hemodynamic instability at admission contributed to therapeutic omission. The role of aspirin in primary prevention is increasingly contested, especially in those with advanced CKD or low thrombotic risk, where the marginal benefit may not outweigh the elevated bleeding potential [207][211]. Ongoing large-scale randomized controlled trials such as ATTACK (Aspirin To Target Arterial Events in CKD) are expected to provide more granular evidence on the net clinical benefit of aspirin stratified by CKD stage and comorbid burden [212]. In the interim, clinical decision-making should prioritize personalized therapy, integrating metrics such as eGFR, hemoglobin levels, platelet function assays, and bleeding risk scores.

6. Current Guidelines and NSAID Management in CKD

NSAIDs remain a cornerstone in the management of pain and inflammation; however, their utility in patients with CKD is met with substantial caution due to their well-documented nephrotoxic potential. By suppressing the COX enzyme (both COX-1 and COX-2) and prostaglandin-mediated vasodilation, NSAIDs compromise renal hemodynamics, particularly

in the afferent arterioles, leading to diminished GFR [13][17][24][97][11]. Epidemiological data underscore these concerns. Longitudinal studies and pooled meta-analyses have identified a statistically significant association between chronic NSAID use and CKD progression. Contemporary clinical guidelines from nephrology and pharmacology societies—including the Kidney Disease: Improving Global Outcomes (KDIGO) and European Renal Best Practice (ERBP)—advocate for stringent restriction of NSAID use in patients with impaired renal function [213][214][169][215]. NSAID therapy is generally contraindicated in individuals with eGFR below 60 mL/min/1.73 m², where renal autoregulation becomes increasingly dependent on prostaglandin-mediated vasodilation [169][123][23]. In stages 3–5 CKD, where structural and functional nephron loss is pronounced, the use of NSAIDs—both selective (COX-2 inhibitors) and non-selective—is discouraged due to heightened risk of glomerular hypoperfusion, sodium retention, hyperkalemia, and acute-on-chronic kidney injury. Particularly in advanced CKD (eGFR <30 mL/min/1.73 m²) and dialysis-dependent patients, NSAIDs are deemed unsafe. [148][170][216]. In scenarios where NSAID therapy is deemed unavoidable, such as refractory inflammatory conditions, guidelines recommend adopting a minimal effective dose strategy for the shortest possible duration. Topical NSAIDs (such as topical diclofenac 1% gel) are often preferred in CKD patients with localized musculoskeletal pain due to reduced systemic absorption and lower nephrotoxicity risk [217][218][219]. Over-the-counter (OTC) NSAID consumption, particularly in CKD patients unaware of their diagnosis or risks, remains a critical concern.

Table 3: Topical Analgesics for Managing Acute and Chronic Pain **[218]**

Topical Analgesics (Formulations)	Common Pain Conditions Tested	Comments
Diclofenac (1% gel)	Minor sports injuries, acute ankle sprains, knee osteoarthritis, and chronic lateral epicondylitis	Topical NSAIDs (especially diclofenac and ibuprofen) are more extensively studied, providing short-term relief for acute injuries and chronic joint conditions like osteoarthritis.
Ibuprofen (5% cream or gel)	Chronic knee pain, chronic leg ulcers, soft tissue injuries, and acute ankle sprains	Effective for managing chronic conditions, especially knee pain and soft tissue injuries.
Ketoprofen (2.5% gel, total daily dose of 250 mg)	Soft tissue injuries	Used for relief in soft tissue injuries.
Salicylates (750 mg aspirin + diethyl ether mixture or 75 mg/mL of aspirin alone)	Acute and postherpetic neuralgia	The combination of aspirin and diethyl ether offers effective relief for neuralgic pain.

Lidocaine (5% medicated patch or plaster)	Postherpetic neuralgia, diabetic neuropathy	Data suggests superior pain control for postherpetic neuralgia compared to oral pregabalin.
Capsaicin (0.025–0.075% cream, 8% patch)	Neuropathic pain, postherpetic neuralgia, acute migraine	Weak evidence, but has shown improvement in neuropathic pain and postherpetic neuralgia.
Amitriptyline (1–5% cream)	Neuropathic pain	Used for neuropathic pain management.
Glyceryl trinitrate (0.72 mg/day)	Lateral epicondylitis, chronic noninsertional Achilles tendinopathy, post-hemorrhoidectomy	Poor data, but has reported improvement in wound healing.
Others (opioids, menthol, pimecrolimus, phenytoin)	Chronic knee pain, vulvar lichen scleroatrophicus, superficial burns, chronic leg ulcers	Scant data, but used for various chronic pain conditions.

6.1. NSAID Interactions and Comorbidities in CKD

The synergistic nephrotoxicity occurs when NSAIDs are co-administered with other medications frequently prescribed in CKD, such as RAAS inhibitors, diuretics [220][129], and calcineurin inhibitors [221][222], resulting in hemodynamic instability and electrolyte imbalances. The simultaneous use of an ACE inhibitor or ARB, a loop or thiazide diuretic, and an NSAID (so-called triple whammy interaction) has been consistently implicated in precipitating AKI [222][223][224]. Furthermore, NSAID-induced sodium retention can exacerbate hypertension, congestive heart failure, and volume overload, all of which are common comorbidities in the CKD population [225][226][227]. In patients with hepatorenal syndrome, cirrhosis, or right-sided heart failure, renal perfusion is highly prostaglandin-dependent. NSAIDs can provoke sudden declines in GFR, precipitating hepatorenal decompensation or exacerbating fluid retention and pulmonary edema [228][229][230]. So, appropriate surveillance and proactive education are critical in mitigating NSAID-associated nephrotoxicity in CKD populations.

7. Discussion and Conclusion

The intersection of chronic kidney disease and nonsteroidal anti-inflammatory drug pharmacology presents a critical clinical dilemma underscored by intricate biochemical, pharmacokinetic, and pathophysiological interdependencies. The widespread utilization of NSAIDs, often without medical supervision, aggravates renal vulnerability, especially in patients with underlying renal dysfunction or comorbidities, such as hypertension and cardiac issues. The nephrotoxic potential of NSAIDs arises primarily from their inhibition of cyclooxygenase enzymes, which are instrumental in the biosynthesis of vasodilatory prostaglandins critical for maintaining renal perfusion. Under normal physiological conditions,

these prostaglandins exert a counter-regulatory effect on vasoconstrictive agents (like Ang II), thereby preserving the glomerular filtration rate. However, in CKD patients, where renal autoregulation is already compromised, NSAID-induced suppression of prostaglandin synthesis severely impairs afferent arteriolar dilation, precipitating acute kidney injury, accelerating fibrotic remodeling, and facilitating a downward trajectory toward end-stage renal disease. The renal expression of COX-2 in the macula densa and glomerular podocytes suggests that selective COX-2 inhibitors are not devoid of renal side effects and may similarly disrupt natriuretic and vasodilatory pathways. From a clinical perspective, the indiscriminate use of NSAIDs in CKD remains a pressing concern, often exacerbated by over-the-counter availability and inadequate risk communication. The evidence collectively advocates for heightened pharmacovigilance, therapeutic individualization, and robust patient education. Regular renal function monitoring, risk stratification based on CKD staging, and exploring alternative analgesic regimens—such as acetaminophen, topical agents, or low-dose opioids—are prudent strategies to mitigate iatrogenic renal injury.

In conclusion, NSAID use in CKD embodies a paradigmatic example of risk amplification through pathophysiological synergy. The interplay between impaired renal excretion, disrupted prostaglandin-mediated hemodynamics, and systemic drug accumulation renders NSAID therapy a double-edged sword in this population. In patients with chronic kidney disease, NSAID use represents a precarious therapeutic choice where the compounded risk of nephrotoxicity often outweighs analgesic benefit.

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Ethical Declaration

The authors declare that the use of Artificial Intelligence (AI) tools in the preparation of this manuscript adhered strictly to the ethical standards outlined by the Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE). AI technologies were employed solely for improving language clarity, grammar, and structural coherence, without contributing to generating novel scientific content, data fabrication, or citation manipulation. Conceptualization, analysis, and interpretations presented in this review represent the original intellectual contributions of the authors. The manuscript was critically

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