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Effect of Nonsteroidal Anti-Inflammatory Drugs on Kidney

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

" هوَ الَّذِي أَنْزَلَ السَّكِينَةَ فِي قُلُوبِ الْمُؤْمِنِينَ لِيَزْدَادُوا إِيمَانًا مَع إِيمَانِهِمْ ۗ وَلِلَّهِ جُنُودُ السَّمَاوَاتِ وَالْأَرْضِ ۚ وَكَانَ اللَّهُ عَلِيمًا حَكِيمً ۝"

صدق الله العلي العظيم

سورة الفتح "٤"

DEDICATION

To al- imam al Mahdi .

To the big heart my dear father ,To my great mother .

To my brothers and sisters ,To my family .

To the people who paved our way of science and knowledge .

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Abstract:

This study was done to assess the effect of non steroidal anti inflammatory drug on the kidney

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the isoenzymes COX-1 and COX-2 of cyclooxygenase (COX). Nonsteroidal anti-inflammatory drugs (NSAIDs) are capable of inducing a variety of renal function abnormalities, particularly in high-risk patients with decreased renal blood perfusion who depend on prostaglandin synthesis to maintain normal renal function. Fluid retention is the most common NSAID-related renal complication, occurring to some degree in virtually all exposed individuals; however, clinically detectable edema occurs in less than 5% of patients and is readily reversible on discontinuation of the NSAID. Other electrolyte complications, notably hyperkalemia, are seen infrequently and occur in specific at-risk patients.

The next most worrisome complication is acute deterioration of renal function, which occurs in high-risk patients and is also reversible. Nephrotic syndrome with interstitial nephritis is a rare problem of NSAID use and is reversible. Papillary necrosis is the only permanent complication of NSAIDs and is very rare. Altogether, these renal function abnormalities, with the exception of mild fluid retention, are clinically detectable in approximately 1% of exposed patients. Given the number of patients who take NSAIDs on a prescription or over-the-counter basis, the absolute number of at-risk patients is relatively large. Consequently, an appreciation for the risk factors and pathophysiology of NSAID-induced renal function abnormalities is required for optimal use of these drugs

IV. Chapter one:

1- Introduction

The differential expression and distribution of the 2 COX isoforms implicate them as being involved in the regulation of various physiological functions within the kidney [1] . COX-1 is the dominant isoform to be expressed in glomerular mesangial cells, arteriolar endothelial cells, as well as in cortical and medullary collecting ducts in the kidney of bovine, rabbit, guinea pig, rat, and mouse . In the human kidney, COX-1 has been identified in the collecting duct cells, interstitial cells, and vasa recta . In contrast, basal COX-2 expression is less intense and displays some interspecies variation in localization. COX-2 distribution has been localized in the macula densa of the cortical thick ascending limb of Henle and interstitial cells in rodents, rabbit, and dogs . COX-2 immunoreactivity has also been described in intercalated cells of the cortical collecting ducts in mouse kidney sections . In humans, COX-2 is associated with parts of the renal vasculature, loop of Henle, and podocytes . Furthermore, COX-2 has been detected in macula densa in humans >60 years of age . In general, regarding COX-2 distribution, it is important to be aware that the previously reported expression of COX-2 has only been reported during normal physiological conditions. In response to inflammatory states, however, COX-2 may be expressed in many more cells and different cell types within the kidney

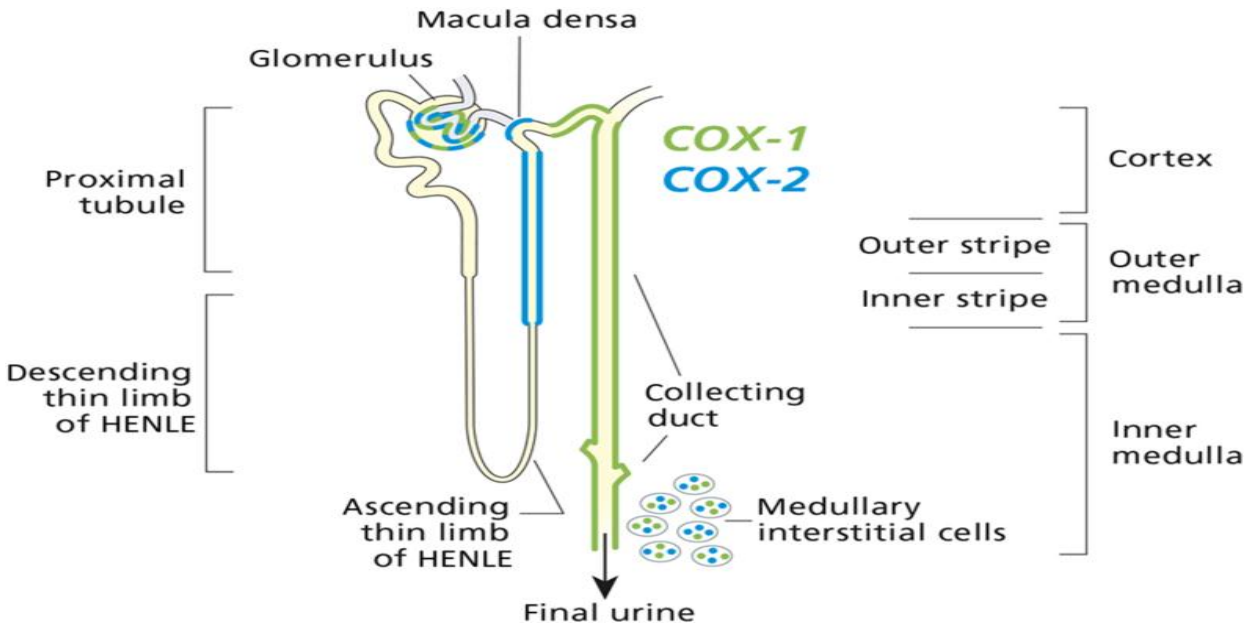


Figure -1- :**Distribution of COX isoforms throughout the nephron**. COX-1 (green) is constitutively expressed in the glomerulus, collecting duct, and medullary interstitial cells. COX-2 (blue) is expressed in the glomerulus, macula densa, thick ascending limb, and medullary interstitial cells.COX, cyclooxygenase. 1

COX-deficient mouse models have provided important information regarding the role of COX-2. Additional investigation into the physiological and pathophysiological effects of these 2 isoforms has also been acquired from COX-deficient mice. Importantly, mice disrupted for COX-1 appear to be generally healthy, and there are no obvious renal defects . In contrast, mice with gene disruption of COX-2 have severe nephropathy, and the kidneys appear pale and smaller than those of the wild-type littermates. In the earlier states, the kidneys show small immature glomeruli in the subcapsular region with enlarged glomeruli outside of this hypoplastic area. With age, the renal pathology develops into more severe states and results in end-stage renal disease. In addition, gender differences in renal phenotype have been reported in COX-2–disrupted mice with a male propensity for kidney injury, increased baseline water turnover, and hypertension . Taken together, it appears that the COX-2 isoform plays a more dominant role in the kidney diseases compared with COX-1.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cox enzyme and represent one of the most common classes of medications used world-wide, with

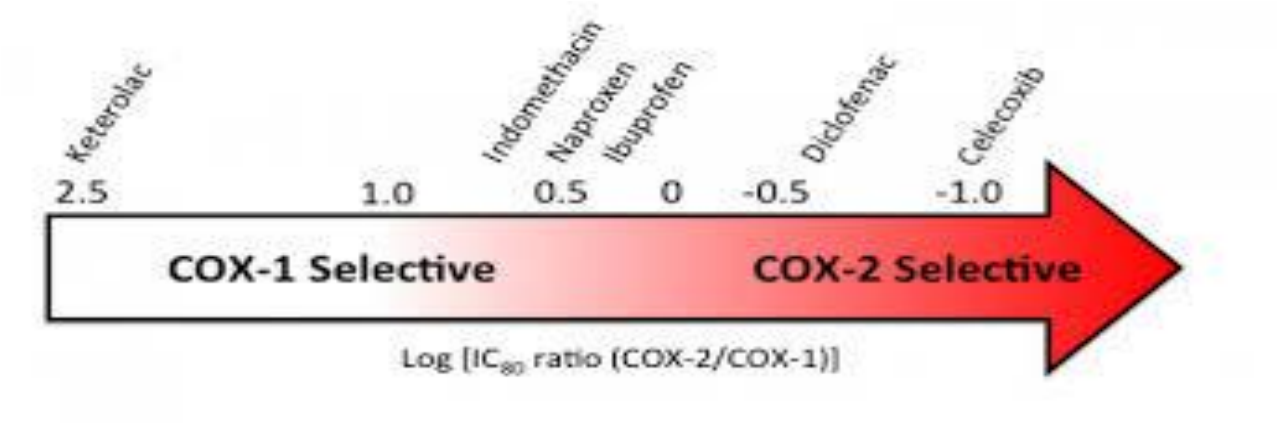
an estimated usage of >30 million per day. Clinically available NSAIDs can be separated into 3 different classes based upon their mechanism of action:**[3]**

- **ASPIRIN:** - Acts to irreversibly inhibit COX 1 & COX-2 by covalent acetylation of serine residues in their respective active sites. Most notably, low doses of aspirin can suppress platelet COX-1 activity , not effect on renal cox , by 95% or more, an effect that is permanent for the lifetime of the platelet, since platelets lack DNA and cannot synthesize new enzyme. All other NSAIDs interact with COX isoforms reversibly and produce variable COX inhibition (ranging from 50% to 95%) in a time-dependent fashion based upon their pharmacokinetic properties.
- **COXIBS:** Selective COX-2 inhibitors were designed and marketed to avoid the GI side effects known to result from suppression protective prostaglandins synthesized by COX-1 in the GI mucosa. Their use led to the first reported incidence of increased cardiovascular events (myocardial infarction and stroke) in 2004. Rofecoxib (Vioxx ®), one of the most selective COX-2 inhibitors was removed from the market because of mounting evidence for significant CV toxicity (Drazen, 2005). Celecoxib (Celebrex ®) is currently the only FDA approved coxib available in the US. It has a 10-20 fold selectivity for COX-2 over COX-1. Etoricoxib (Arcoxia ®) is a second coxib with ~106 fold selectivity for COX-2 over COX-1 that is available outside of the United States.

- **NON-SELECTIVE COX INHIBITORS:** Different non-selective NSAIDs have varying inhibitory effects against COX-1 & COX-2 . The two most commonly used over-the-counter drugs in this group (ibuprofen & naproxen) produce reversible

platelet inhibition ranging from 50 to 95% in a reversible time-dependent manner that may be insufficient to provide cardio-protection throughout a com monly used dosing interval (Reilly & FitzGerald, 1987; Anwar et al, 2015). Ketorolac (Toradol ®), an NSAID most commonly used in a hospital setting, is classified as a non-selective NSAID, although it is arguably very selective for COX-1.

The two most commonly used NSAIDs (ibuprofen & naproxen) are relatively non-selective for inhibiting COX-1 vs COX-2, and therefore can produce unwanted side effects by inhibiting both isoforms.



The gastrointestinal tract and the kidneys are important targets for untoward clinical events associated with the use of NSAIDs[4] .

Nonselective NSAIDs inhibit both COX-1 (expressed constitutively in the kidney) and COX-2 (inducible in most tissues in response to injury or inflammation, but also present at detectable levels in normal adult mammalian kidneys), the rate limiting enzymes for the production of PGs and thromboxane (TX). COX-2 is regulated in response to intravascular volume [5]. COX-1 functions mainly in the control of renal hemodynamics and glomerular filtration rate (GFR), while COX-2 functions primarily affect salt and water excretion [6]. Blockade of either or both of these enzymes can have, therefore, different effects on renal function [7,8]

2- Physiology and Pathophysiology of COX Inhibition

PGs regulate a wide variety of renal functions [9]. PGE_2 is considered to be mainly a tubular PG and PGI_2 a vascular PG. However, renal arterioles, tubules, medullary interstitial cells, and mesangial cells are able to produce both PGE_2 and PGI_2. PGE_2 regulates sodium and chloride transport in the loop of Henle and modulates water transport and renal medullary blood flow. The physiological effects of PG_2 are mediated through the four G-protein-coupled transmembrane prostaglandin receptors EP1, EP2, EP3 and EP4. PGI_2 regulates renal vascular tone, GFR and renin release [10]. Selective COX-2 inhibitors were developed to produce the beneficial effects of NSAIDs, but spare the COX-1-mediated adverse events [11].

In normotensive subjects neither blood pressure nor renal function is significant affected by selective COX-2 inhibitors or nonselective NSAIDs [12,13]. In contrast, inhibition of PG synthesis leads to renal decompensation in situations where renal and systemic hemodynamics are dependent on the availability of PGs [10]. In salt-depleted healthy subjects, selective inhibition of COX-2 causes sodium and potassium retention [14–16]. In elderly patients with compromised renal function, selective COX-2 inhibitors and nonselective NSAIDs may cause reductions in GFR and a reduction in urinary sodium excretion, urinary PGE_2, and 6-keto-$PGF_{1\alpha}$ excretion [17,18]. In elderly subjects with hypertension, treatment with COX-2 selective inhibitors may promote edema formation and elevations in blood pressure [19,20]. Patient groups who are at risk for renal adverse effects from NSAIDs include those with extreme liver dysfunction, or those with nephrotic syndrome and high-level proteinuria, or those with very low renal function [21].

Liver cirrhosis with ascites represents a condition in which kidney function critically depends on PGs. If a decline of renal function in cirrhotic patients is the result of the use of NSAIDs, withdrawal of treatment should usually be sufficient to improve renal function [22]. Animals with carbon tetrachloride-induced cirrhosis and ascites receiving NSAIDs or the selective COX-1 inhibitor SC-506, but not those receiving the selective COX-2 inhibitor celecoxib developed a severe impairment in renal function. These data indicate that COX-1- but not COX-2-derived PGs are involved in the homeostasis of kidney function in advanced cirrhosis [23–26]. treated with celecoxib developed a significant (greater than 20%) decrease in GFR. The reasons for the different findings remain unclear. Previous studies have already shown that the administration of NSAIDs to patients with cirrhosis, ascites, and high plasma renin activity and norepinephrine is associated with a reduction in renal perfusion and GFR and ARF [27–32].

3- COX and the Renin-Angiotensin system

COX-2 activates the renin-angiotensin system, while an increased activity of the renin-angiotensin system inhibits COX-2. PGI_2 and PGE_2 increase potassium secretion primarily by stimulating the secretion of renin and activating the renin-angiotensin-

aldosterone system , inhibition of prostaglandins by NSAIDs can reach life-threatening level hyperkalemia by NSAIDs induce renal insufficiency[33,34]

Macula densa sensing of tubule NaCl concentration at the distal end of the loop of Henle serves as a primary regulatory step in renin secretion and tubuloglomerular feedback (TGF) [35]. Both TGF and renal renin production and release are modulated by PGs derived from the macula densa [36–38]. PG induced juxtaglomerular renin release is mediated via COX-2. In the other hand, COX-2 inhibitors inhibit renin production and secretion [39-44].

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor subtype I antagonists increase the expression of COX-2 in the kidney [45]. The feedback effects of angiotensin II on COX-2 are mediated via nitric oxide synthase-1 (neuronal nitric oxide synthase) [46,47]. In addition, mitogen- activated protein kinases (MAPKs) and, in particular, p38 are important for regulating COX-2 expression in the renal cortex. Low chloride concentrations significantly increase COX-2 and phosphorylated p38 expression [48].

4-COX-2 and Renal Development

CO X-2 is expressed constitutively not only in the adult but also in the fetal kidney [5,49–51]. an increased incidence of oligohydramnios has been observed in women who chronically consumed significant amounts of aspirin or other COX inhibitors during the third trimester of pregnancy. Because the fetal urine is the source of a significant amount of the amniotic fluid, these studies suggested that inhibition of COX led to the suppression of fetal renal function.

COX-2 dependent PG formation is necessary for normal renal development. COX-2 deficient mice exhibit renal dysgenesis [52,53]. In contrast, gene knockout studies showed that COX-1 disruption does not interfere with normal renal development [54]. Administration of a COX-2 selective inhibitor during pregnancy significantly impaired development of the renal cortex and reduced glomerular diameter in both mice and rats, identical to transgenic COX-2 mice, while administration of a COX-1 selective inhibitor did not affect renal development. Prostanoids or other products resulting from

COX-2 activity in the macula densa may act in a paracrine manner to influence glomerular development [55] .

5- COX and Glomerular Diseases

Chemokines such as monocyte chemo-attractant protein-1 (MCP-1) are expressed in glomeruli of animals and humans with glomerulonephritis. MCP-1 is involved in the monocyte/macrophage infiltration into glomeruli and the renal interstitium [56–59]. Mesangial cell production and release of MCP-1 is stimulated by cytokines and growth factors [60–62], while dexamethasone [63] or PGE [64] reduces the glomerular MCP-1 expression, suggesting that endogenously formed PGs can modulate the formation of MCP-1 and influence the clinical outcome of experimental glomerulonephritis. Schneider et al. [65] examined the renal effects of COX-2 selective inhibitors versus indomethacin in two different models of glomerulonephritis: anti-thymocyte serum induced mesangioproliferative glomerulonephritis and anti-glomerular basement antibody induced glomerulonephritis. All NSAIDs augmented the glomerular production of MCP-1 and RANTES suggesting that endogenous PGs normally suppress renal chemokines formation. Increased monocyte/macrophage infiltration was observed only in those animals treated with indomethacin suggesting also a role for COX-1 products in suppressing renal inflammation [65].

Pro-inflammatory agents such as interleukin-1ß [66] and lipopolysaccharide (LPS) [67] induce PGE_2 by COX-2 indicating that COX-2 generated PGE_2 plays an important role in inflammatory processes, such as glomerulonephritis [68–70]. In experimentally induced immune-mediated glomerulonephritis, PGE decreases damage of the kidney through reduction of glomerular immune complex formation, through reduction of inflammatory cell infiltration and through reduction of deposition of extracellular matrix products [71–73]. Prostaglandin EP2 and EP4 receptors modulate the expression of MCP-1 in response to LPS-induced renal glomerular inflammation: Overexpression of EP2 and EP4 decreases MCP-1 expression, while the down-regulation of EP2 and EP4 receptors results in an imbalance in the inflammatory state of mesangial cells.

It was concluded that COX products may participate in the monocyte/macrophage clearing and in the healing process in glomerulonephritis [74].

Certain NSAIDs, such as sulindac, ibuprofen, and flurbiprofen may exert anti-inflammatory effects independently of COX activity and prostaglandin synthesis. Those anti-inflammatory effects are mediated by inhibition of certain transcription factors such as activator protein 1 and nuclear factor-κB and/or by alterations in the activity

of IκB kinase, mitogen-activated protein kinase, and cyclin- dependent kinase [75].

NSAIDs, especially indomethacin, have the potential to attenuate proteinuria in different types of glomerulonephritis [76–78] and nephrotic syndrome [79,80].

In very rare cases, NSAIDs may induce glomerular disease, such as membranous nephropathy which is clinically complicated by nephrotic syndrome. Not only renal transplant patients but also patients with different forms of glomerulonephritis (e.g., membranous nephropathy, focal segmental glomerulosclerosis, steroid-resistant minimal change nephropathy) may be treated with a calcineurin inhibitor. The kidney is vulnerable toward adverse effects of the calcineurin inhibitors cyclosporine A and tacrolimus, including decrease of GFR, tubular dysfunction, glomerulosclerosis, and renal interstitial fibrosis. In Wistar-Kyoto (WKY) rats treated with cyclosporine A (15 mg/kg per day) or tacrolimus (5 mg/kg per day) for seven days each, both drugs markedly lowered renal COX-2 expression while COX-1 expression remained unaltered. Cyclosporine A blunted the increase of renocortical COX-2 expression in response to low salt intake or the combination of low salt-intake with an ACE inhibitor, while renin secretion and renin gene expression were enhanced. These data indicate that calcineurin inhibitors selectively suppress renal COX-2 expression without attenuating the regulation of the renin system [81]. Cyclosporine A may aggravate renal adverse events associated with the use of NSAIDs [82]. Both cyclosporine A and tacrolimus therapy causes afferent renovasoconstriction which is aggravated by NSAIDs resulting in further decline in renal blood flow and GFR. Therefore, in renal transplant recipients on immunosuppression with cyclosporine A or tacrolimus suffering from chronic pain, NSAIDs should be replaced by metamizole, acetaminophen, tramadol and/or steroids.

6-COX and Diabetic Nephropathy

Diabetic nephropathy is a leading cause of ESRD. Renal hyperfiltration is a risk factor for progression of diabetic nephropathy.COX-2 is an important determinant of renal hemodynamic function in subjects with type 1 diabetes. Experimental models of diabetes revealed that COX-2 expression is increased in the macula densa in this condition and is associated with enhanced production of vasodilatory PGs, renin-angiotensin system activation, and renal hyperfiltration. In diabetic rats, hyperglycemia-associated PG production and hyperfiltration were blunted using COX-2 inhibition [83]. In normotensive, normoalbuminuric adolescents and young adults with type 1 diabetes, COX-2 inhibition resulted in a significant decline in GFR in the hyperfiltration group but increased GFR in the normofiltration group [84], indicating that the renal hemodynamic response to COX-2 inhibition is dependent on GFR. Thus, not only the renin-angiotensin system but also COX-2 contributes to the hyperfiltration state in diabetes. COX-2 inhibition decreases proteinuria and retards progressive renal injury in rats [85].

Flow-mediated dilation (FMD) in the brachial artery is significantly higher in normofiltering versus hyperfiltering subjects with type 1 diabetes. In response to COX-2 inhibition during clamped euglycemia, FMD declined significantly in normofiltering but not in hyperfiltering subjects. This effect was abolished by hyperglycemia. It was concluded that systemic hemodynamic function, including the response to COX-2 inhibition, is related to renal filtration status in patients with type 1 diabetes, probably as a results of general endothelial dysfunction [86].

Ibuprofen reduced GFR and albuminuria, while blood pressure was not affected. Both the cortical cyclin-dependent kinase inhibitor p27 (an important regulator of renal and glomerular hypertrophy) and renal fibronectin were increased in the diabetic animals but attenuated by ibuprofen. Thus, chronic low-dose ibuprofen therapy may be beneficial at the onset of diabetic nephropathy [87].[88] examined a model of diabetes and hypertension, in which streptozotocin diabetes was combined with deoxycorticosterone (DOCA)-salt treatment. In this model, glomerular injury progressed at a faster rate than in animals with diabetes or DOCA-salt alone. The renal expression

of COX-2 was increased, along with that of fibronectin, transforming growth factor-beta and plasminogen-activator inhibitor.

7- COX in Ureteral Obstruction and Lithium Nephropathy

COX activity contributes to renal function changes immediately after onset of ureteral obstruction [89–91]. Expression of COX-2, but not COX-1, is markedly increased in the inner medulla in response to unilateral and bilateral ureteral obstruction [89,90,92] .

Ureteral obstruction activates the intrarenal renin-angiotensin-system and increases intrarenal angiotensin II generation [93–95]. Angiotensin II receptor type 1A (AT1R) blockade significantly reduces COX-2 abundance in the postobstructed kidney and also attenuates the angiotensin II- mediated downregulation of aquaporin water channels and key renal sodium transporters in response to urinary tract obstruction [96]. However, AT1R-mediated AQP2 regulation in the postobstructed kidney collecting duct is independent of COX-2 induction [97].

The increased shuttling of APQ2 results in diminished urine volume. The altered urinary concentration ability and body water balance associated with the use of NSAIDs may in part be causally related with the alteration of AQP2 [98]. Lithium treatment is one of the major causes of the acquired form of nephrogenic diabetes insipidus (NDI), a clinical syndrome in which the kidney is unable to concentrate urine despite normal or elevated concentrations of the antidiuretic hormone arginine vasopressin. In lithium-induced NDI rat models, downregulation of AQP2 has been demonstrated. For the treatment of NDI, NSAIDs or coxibs have been useful [99–101]. The upregulation of AQP2 and the Na-K-2Cl inhibition underlies the therapeutic mechanisms by which COX-2 inhibitors enhance antidiuresis in patients with NDI [102].

8- NSAIDs and Blood Pressure

PGs contributed to blood pressure homeostasis via their effects on vascular tone and on renal fluid and electrolyte transport. NSAIDs cause little or no increase in blood pressure in normotensive individuals.

However, NSAIDs and COX-2 inhibitors may increase systemic blood pressure in hypertensive persons and/or undermine blood pressure control with antihypertensive drugs [103,104]. In rodents, COX-1 deletion causes natriuresis and enhances sensitivity to ACE inhibitors. Deficiency of COX-1 reduces blood pressure despite activation of the renin-angiotensin system [105]. Both pharmacological inhibition and genetic deletion of COX-1 abolish the hypertensive response to angiotensin II [106,107]. In contrast, deletion or inhibition of COX-2 reduces renal medullary blood flow and sodium excretion, increases the vasoconstrictive response to angiotensin II [107] and elevates blood pressure [108]. COX-2 deficient mice on a normal diet exhibited systolic hypertension.

COX-2 selective inhibitors have effects on blood pressure that are similar to those of nonselective NSAIDs [109–115]. In contrast, the cardiorenal safety database from the Celecoxib Long-term Arthritis Safety Study (CLASS) indicates that a supratherapeutic dose (400 mg b.i.d.) of celecoxib was associated with an improved cardiorenal safety profile compared with standard doses of either ibuprofen or diclofenac. Celecoxib was associated with a lower incidence of hypertension or edema than ibuprofen. The celecoxib group had significantly fewer initiations of antihypertensives than patients taking ibuprofen. Systolic blood pressure increase >20 mmHg and above 140 mmHg occurred significantly less often with celecoxib as compared to ibuprofen or diclofenac [116]. In a subgroup of patients with prerenal azotemia, significantly fewer patients taking celecoxib exhibited clinically important reductions in renal function (3.7%) as compared to diclofenac (7.3%) or ibuprofen (7.3%). It was concluded that celecoxib may frequently be a more suitable treatment of chronic pain and inflammation than nonselective NSAIDs in patients with compromised renal function [116]. In the study by Sowers et al. [117], patients with hypertension, osteoarthritis, and type 2 diabetes mellitus were randomly assigned to treatment with 200 mg of celecoxib daily (n = 136), 25 mg of rofecoxib once daily (n = 138), or 500 mg of naproxen twice daily (n = 130) for 12 weeks. The blood pressure difference between rofecoxib and celecoxib was 3.78 mmHg ($p = 0.005$), and between rofecoxib and naproxen 3.85 mmHg ($p = 0.005$).

Risk for cardiovascular death is high among patients with rheumatoid arthritis [118]. Because of the increased risk of thrombotic events, the manufacturers of rofecoxib (September 2004) and valdecoxib (April 2005) withdrew their products. However, no selective COX-2 inhibitor is risk free. The Adenoma Prevention with Celecoxib (APC) trial using 400 to 800 mg daily doses of celecoxib had been prematurely terminated owing to a significant excess of cardiovascular death, myocardial infarction, and stroke [119]. Celecoxib in typical 100 to 200 mg daily doses has a lower risk of cardiovascular toxic effects as compared to rofecoxib or valdecoxib. NSAIDs were suggested to have a cardioprotective effect by inhibition of platelet aggregation through inhibition of COX-1. However, inhibition of vascular COX-2 in the presence of inadequate inhibition of platelet COX-1 results in enhanced risk of adverse cardiovascular events including myocardial infarction [120]. In addition, inhibition PG synthesis may cause hypertension, but COX-2 selectivity alone does not define the cardiovascular risk associated with NSAIDs [121]. Dilation of blood vessels and reduction in systemic blood pressure by celecoxib suggest that the reduced work load on the heart may counteract any other deleterious effects of this class of drugs [122].

rofecoxib was more likely to increase the systolic blood pressure than celecoxib [19,20]. Celecoxib (200 mg once a day) caused less development of peripheral edema and less loss of blood pressure control than rofecoxib [107], but invalidity of dose comparison and the imbalance in the number of patients who received ACE inhibitors between both groups of this study have been criticized [45]. In a meta- analysis of 114 clinical trials involving 116,094 patients, rofecoxib treatment was associated with peripheral edema, hypertension, and renal dysfunction, while patients on celecoxib treatment did not differ from controls [123]. The findings suggest that there does not appear to be a class effect in terms of renal adverse events with selective COX-2 inhibitors [124]. In young and elderly normotensive subjects on celecoxib (200mg b.i.d. for 2 weeks), no significant effects on parameters of the renin-angiotensin-aldosterone system, kidney function and blood pressure have been observed [12], while in healthy volunteers with mild volume depletion, COX-2 inhibition caused a 65% decrease in plasma renin activity ($p = 0.008$), which was antagonized by the combined intake of celecoxib and irbesartan. Neither GFR nor renal sodium and potassium

excretion was influenced by a single dose of 400 mg celecoxib intake alone or combined with 150mg irbesartan [125]. Therefore, PGs that increase renin production in response to ACE inhibition are not derived from COX-1 [126].

The incidence rate of renal side effects associated with the use of selective and nonselective COX-2 inhibitors is low in otherwise healthy subjects but can get as high as 20% in high risk patients [127]. In addition, patients who take NSAID, are often afflicted with other disease, need other medications, and may have various risk factors purported to influence the side effects of NSAIDs [128]. In patients with hypertension, increased activation of the renin-angiotensin and sympathetic nervous system may cause subsequent release of vasodilator prostaglandins from the kidney, which act locally to lessen the degree of renal hypoperfusion [129]. In case that this compensatory mechanism is inhibited by NSAIDs, the increase in renal and systemic vascular resistance can cause an elevation of blood pressure [130]. Nonselective NSAIDs may antagonize the blood pressure-lowering effect of antihypertensive medications, including diuretics, ACE inhibitors, and β-blockers [111,131,132].

Decrease in diuretic response was reported when furosemide was simultaneously administered with indomethacin in humans [133]. Indomethacin inhibited the saluretic and diuretic response to furosemide both in adult and newborn rats. Inhibitory interaction between indomethacin and furosemide was achieved at approximately 10-fold lower concentrations in the newborn than in the adult rats, suggesting that the neonate kidney is more sensitive to the action of these drugs than the adult kidney [134]. Indomethacin or meclofenamate blunted the response to furosemide on sodium and chloride transport [135], suggesting that the drugs interact at the Na-K-2Cl cotransporter. Since COX-2-derived PGE_2 is found primarily on the thick ascending limp of the loop of Henle, NSAIDs can lessen response to loop-acting diuretics by as much as 20% (or even more in patients likely to retain sodium, such as in those with congestive heart failure or cirrhosis) [21]. COX inhibition by diclofenac or rofecoxib reduces significantly the hydrochlorothiazide-induced urinary sodium excretion, while urinary potassium excretion is not affected [136].

Cyclosporin attenuates furosemide-induced natriuresis, likely by inhibition of COX-2-mediated natriuresis. A combination of cyclosporine with rofecoxib has no additive effects on PGE_2 formation, natriuresis and diuresis [137]. NSAIDs contribute to resistant hypertension [138]. Interestingly, the increase in blood pressure by selective COX-2 inhibitors can be reduced or even prevented by salt deprivation [139,140].

COX-2-inhibition enhances the pressure effect of angiotensin II [141]. In patients with essential hypertension, even high doses of celecoxib (400 mg/day) did not cause any alteration of the antihypertensive effect of lisinopril [117,142]. ACE inhibitors and angiotensin II receptor blockers are efferent renovasodilators and may cause functional, but reversible, renal insufficiency, which may worsen with NSAIDs by inducing afferent renovasoconstriction. Therefore, lowering of the dose of the NSAIDs as much as possible, lowering of salt intake, retitration of the antihypertensive and calcium channel blockers have been recommended when treating hypertension in a patient taking an NSAID. Another strategy is to use a non-NSAID, such as tramadol or aspirin [6].

In people controlled on verapamil there was no significant rise in blood pressure by ibuprofen or naproxen [143]. In a meta-analysis undertaken by Johnson et al. [144], it appeared that the increase of blood pressure by NSAIDs was greater in people on β-blocking drugs than in those on diuretics or vasodilators. In a group of elderly, normotensive people, ibuprofen elevated blood pressure, while it had no effect in a young group [145]. As discussed before calcium channel blocking drugs are recommended and/or diuretics, if NSAIDs primarily cause a rise in blood pressure due to sodium retention [146]

9- NSAIDs and Acute Renal Failure

Renal prostaglandins function primarily as vasodilators in the kidneys . **In healthy individuals, the impact of prostaglandins on renal perfusion is relatively limited .** However, in the setting of prolonged renal vasoconstriction that develops during settings of advanced age, heart failure, and kidney failure, prostaglandin synthesis is upregulated. Under these conditions when kidney function is compromised , the production of prostaglandins serves an important role to preserve renal blood flow and protect the glomerular filtration rate (GFR) by decreasing pre-glomerular (afferent) arterial resistance

(Figure 2 left). In this setting, even episodic use of NSAIDs can decrease blood flow through the glomerulus, and increase the risk of acute kidney [147]

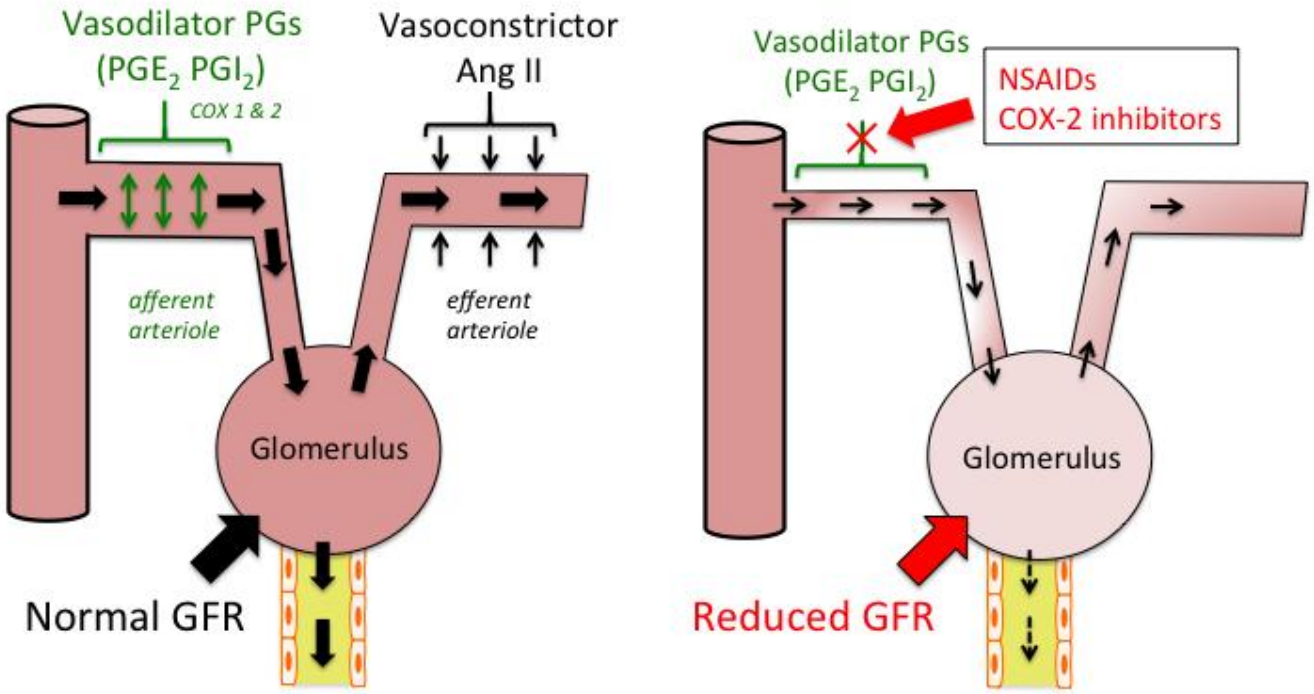


Figure 2. Regulation of renal blood flow & glomerular filtration in the kidney. The glomerular filtration rate (GFR) is optimal when the intraglomerular pressure gradient is maintained at normal levels. A reduction in afferent blood flow or pressure due to hypotension, volume loss (blood loss or excessive diuresis), decreased cardiac output or obstruction (renal artery stenosis) can lower the intraglomerular pressure and result in impaired renal function. **When normal renal function is physiologically impaired, prostaglandin synthesis is increased, such that it plays an increasingly important role in maintaining renal perfusion by causing enhanced pre-glomerular vasodilation (left panel). Under these conditions, NSAIDs & COX-2 inhibitors can adversely affect renal function** by blocking the production of autoregulatory prostaglandins, resulting in a decline in GFR that can ultimately result in acute kidney injury (right panel). Treatment with ACE inhibitors (which reduce the effect of Ang II to produce efferent vasoconstriction) can also further reduce glomerular perfusion and contribute to renal failure. Adapted from Luciano & Perazella (2015).

High acute dose of NSAIDs, have been implicated as causes of ARF, particularly in the elderly [148]. Some reported cases of ARF after initiation of NSAID therapy include apparently healthy subjects [3,4]. Endogenous angiotensin II is an inhibitor of COX-2 expression in the macula densa. Conversely, ACE inhibition and angiotensin II type 1 receptor blockade potently upregulates COX-2 [149] and thus may exacerbate NSAID related renal functions [150].

NSAID treatment is a risk factor for contrast media induced nephropathy (CIN), mostly defined as a relative increase of serum creatinine by ≥25 % or a decrease of GFR by ≥25% within 24–72 hours after contrast media exposure. CIN is a common complication in high risk patients such as those with CKD and diabetes mellitus. Radiocontrast agents

cause vasoconstriction of the vas afferens and may aggravate NSAID induced decrease in renal blood flow, GFR and intraglomerular pressure, particularly in risk patients treated with an ACE inhibitor or angiotensin II blocker. It is, therefore, recommended to discontinue selective or nonselective NSAID therapy 48 hours before administration of radiocontrast agents in those patients. [151] .

Various biochemical abnormalities produced in the kidney in response to the administration of indomethacin include oxidative damage and impairment of structure and function of mitochondria mediated through the production of free radicals [152]. Indomethacin induces also impairment in structure and function of brush border membranes in the kidney mediated by free radicals and the activation of phospholipases [153]. Sepsis and septic shock are important risk factors for acute renal failure due to alterations in glomerular hemodynamics. Endotoxemia causes also a time- and dose-dependent decrease of the renocortical expression of the organic anion transporters OAT1 and OAT3 that paralleled the increased renocortical COX-2 expression and PGE_2 formation. OATs are also downregulated during ischemia/reperfusion-induced ARF and ureteral obstruction, conditions under which renal COX-2 expression is increased. Pretreatment with the COX-2 inhibitor parecoxib attenuates not only OAT1 and OAT3 gene repression in the rat kidney following endotoxin treatment but also the fall in creatinine clearance and para-aminohippurate clearance [154].

As any drug, NSAIDs may cause ARF due to acute interstitial nephritis as a result of allergic hypersensitivity reaction few days after initiation of NSAID therapy. In this case, kidney function usually recover when traditional NSAIDs or coxibs are discontinued. If not, prednisone therapy (1 mg/kg per day) should be considered. Long-term NSAID use may result in chronic interstitial nephritis with interstitial fibrosis and chronic renal dysfunction.

10- NSAIDs and Risk for Chronic Kidney Disease

Analgesic nephropathy is a slowly progressive chronic kidney disease resulting from daily use for many years of preparations containing at least two analgesics (e.g., aspirin, acetaminophen, phenacetin or pyrazolones) in combination with central-acting dependence-inducing substances, such as caffeine, codein, and/or barbiturates.

Analgesic nephropathy is characterized by capillary sclerosis, renal cortical atrophy, chronic interstitial nephritis and/or papillary sclerosis/necrosis/calcifications. In a number of patients with analgesic nephropathy, the uroepithelia can develop transitional cell carcinoma. Analgesic nephropathy can be accurately diagnosed or excluded by computed tomography scanning without contrast media [155]. Even if renal papillary necrosis occurs in patients with analgetic nephropathy, traditional NSAIDs including ibuprofen [156], tolmetin [157], indomethacin [158], benoxaprofen [159], and naproxen [160,161], have been also reported to cause renal papillary necrosis.

No association between regular use of analgesics such as acetaminophen, aspirin, or NSAIDs and chronic renal dysfunction has been observed [162,163], while other studies showed increased risk [164–168]. A case-control study reported a 2-fold increased risk of end-stage renal disease among individuals with lifetime use of more than 1,000 acetaminophen pills and an 8-fold increased risk among those with a lifetime cumulative dose of more than 5,000 NSAID pills [168]. In contrast, multivariable analyses performed in a total of 11032 initially healthy men demonstrated that the relative risks of elevated creatinine level associated with intake of 2,500 or more analgesics pills were

0.83 for acetaminophen, 0.98 for aspirin, and 1.07 for other NSAIDs. No association was observed between analgesic use and reduced creatinine clearance. It was concluded that a moderate analgesic use in this cohort study of initially healthy men was not associated with increased risk of renal dysfunction [169]. A large case-control study found a greater than 2-fold increased risk of newly diagnosed chronic renal insufficiency for regular users of acetaminophen or aspirin but not for those using regularly NSAIDs [170]. In the Nurse's Health Study, acetaminophen use was associated with an increased risk of GFR decline in 11 years, but aspirin and NSAID use not [171]. In contrast, some case-control studies found an association between NSAIDs and the risk of chronic renal dysfunction [168,172].

V. Chapter two

1- Conclusions

NSAIDs inhibit both COX-1 and COX-2, the rate limiting enzymes for the production of PGs and TX. Both isoenzymes are located within the kidney. Blockade of either or both of these enzymes may affect different renal functions. COX-2 derived PGs have profound effects on renal homeostasis suggesting that selective COX-2 inhibitors such as celecoxib may have the same potential for adverse renal effects as traditional NSAIDs, particularly in clinical situations associated with impairment of kidney function such as salt depletion, hypovolemia, liver cirrhosis, congestive heart failure, nephrotic syndrome and CKD. NSAIDs may induce sodium and fluid retention (particularly in the elderly) and increase blood pressure or aggravate an already existing hypertension. Dietary salt restriction, reduction in the NSAID dose, use of non-NSAID analgesics, treatment with calcium channel blocker (in order to reduce renal vasoconstriction) and/or diuretics (even if less effective in the presence of NSAIDs) are possible options for the patients who developed hypertension. Selective COX-2-inhibitor such as celecoxib may affect blood pressure less than traditional NSAIDs. These compounds may dose-dependently increase the risk for ARF, particularly in the elderly with high co-morbidity, and the use of the combination of ACE inhibitors/angiotensin II blockers, diuretics and NSAIDs. Whether regular intake of NSAIDs is a risk factor for end-stage renal disease is controversly discussed in the literature.

2-References

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