

Non-steroidal anti-inflammatory drugs and the kidneys in health and the risk of progression to kidney disease: A mini review

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Though debated, the use of non-steroidal anti-inflammatory drugs in pain management could be associated with kidney injury, particularly in prolonged and high dose exposures. Therefore other supporting measures are needed to support or rule out nephrotoxicity.

This mini review summarizes available literature in the field. Various studies were reviewed and the weight of argument in support of refusal of NSAIDs nephrotoxicity and it showed no convincing evidence of the nephrotoxicity

of NSAIDs except in acute interstitial nephritis. The risk of developing, and progression of CKD is also assessed but a definitive conclusion seem difficult to make even with higher doses and in prolonged exposures.

While the argument ranges on, and in the interim assuming the nephrotoxicity of NSAIDs, the inclusion of some inflammatory markers that are known to be elevated or depressed in kidney disease could be of significant value in determining the true nephrotoxicity profile of NSAIDs in health, and perhaps in CKD. These markers may also be of value in the monitoring and prognostication of illnesses associated with NSAIDs use.

Key Words: *Non-steroidal anti-inflammatory drugs; Acute interstitial nephritis; Chronic kidney disease; Inflammatory markers, Nephrotoxicity; Kidney function*

INTRODUCTION

Non-steroidal anti-inflammatory drugs are analgesic, anti-inflammatory and antipyretic agents that are readily available, Over-The Counter (OTC) drugs, often inexpensive, and commonly abused drugs [1-3]. Their use is associated with pan-systemic features manifesting as peripheral blood eosinophilia, hypertension, and kidney dysfunction, cardiac and hepatic diseases [4-6]. Despite being anti-inflammatory agents, NSAIDs in exerting their analgesic and antipyretic effects could activate the inflammatory cascade leading to the release of cytokines, reactive oxygen species and other inflammatory mediators [7,8]. Though used worldwide, epidemiological study shows a higher prevalence among manual laborers in Low Income Nations (LINs) compared to the developed nations with consequences on the functions of the kidneys, heart and vasculature [9]. Paulose Ram et al [10] reported that twelve million Americans were chronic users of NSAIDs and 18% of this were taking Ibuprofen while Patino and his group found that 2% of NSAIDs users in the US had to stop due to renal toxicity [11].

The low level of industrialization and mechanized farming in Low Income Nations (LINs) has necessitated a higher percentage of artisan and manual laborers, it would be expected that there would therefore be a higher prevalence of NSAIDs use in these nations compared to the developed nations. Agaba et al. in Nigeria reported a 13% prevalence of NSAIDs use in a community study where they found a cumulative life time dose of 5000 units [9-12]. Another study in Nigeria showed that 22% of frequent NSAIDs users had kidney dysfunction (eGFR <60 ml/min) as against 6% in a healthy population, $P < 0.001$. The use of NSAIDs for more than a month is reported to increase the risk of progression from acute interstitial nephritis to CKD [13-15].

There are still no consensus views on the nephrotoxicity of NSAIDs, but most studies have associated NSAIDs use with Acute Kidney Injury (AKI) but findings about their etiopathologic role and progression in chronic kidney disease are yet not in agreement [16-18]. Albuminuria is a known marker of kidney disease, same with a heightened inflammatory cascade [19,20]. Population based studies have shown that NSAIDs use is associated with both albuminuria and heightened inflammatory response compared to non-users [20,21].

The nephrotoxicity of NSAIDs is reported to be dependent on factors like frequency of use, type, duration and dosage, comorbidities, dehydration and background kidney disease. Gender differences have been implicated in NSAIDs nephrotoxicity [9-22].

LITERATURE REVIEW

NSAIDs in people without kidney disease

This mini review accessed kidney function in the nephrotoxicity of NSAIDs has continue to be a contentious issue as findings from various studies have either supported or refuted NSAIDs' nephrotoxicity. In a large retrospective cohort study on NSAIDs and kidney function, Wan et al followed up the kidney function of 1,982,488 Chinese with GFR >60 ml/min/1.73m² for a median of 6.3 years and found 14% with incident eGFR <60 ml/min/1.73m² and 21% with a $\geq 30\%$ decline in eGFR [23]. The authors reported a significantly higher risk of incident eGFR <60 ml/min/1.73 m² (HR, 1.71; 95% CI, 1.67-1.75) and a $\geq 30\%$ decline in eGFR (HR-1.93; 95% CI, 1.89-1.96) in NSAIDs users compared with non-users. They reported that etoricoxib had the highest risk of renal function decline to GFR<60 ml/min/1.73 m² (HR, 3.12; 95% CI, 2.69-3.62) and a $\geq 30\%$ decline in eGFR (HR, 3.11; 95% CI, 2.78-3.48) while Ibuprofen had the lowest risk of eGFR<60 ml/min/1.73 m² (HR, 1.12; 95% CI, 1.02-1.23) and a $\geq 30\%$ decline in eGFR (HR, 1.32; 95% CI, 1.23-1.41). The authors concluded that the use of any NSAIDs increased significantly the risk of incident eGFR <60 ml/min per 1.73 m² [HR, 1.71; 95% CI, 1.67-1.75) and a $\geq 30\%$ decline in eGFR (HR, 1.93; 95% CI, 1.89-1.96), with composite (HR, 1.88; 95% CI, 1.85-1.91). Though retrospective, this study was strengthened by its large sample size, the relatively long followed up time, its associating NSAIDs use with treatment outcomes and more importantly the fact that the subjects mostly had normal kidney function thereby widening possible treatment outcomes. Many researchers have reported that the withdrawal of phenacetin from the market has led to a marked reduction in the incidence of Analgesic Nephropathy (AN) hence in nations where Phancetin was sold like in Hungary and China, the incidence of AN was higher than in nations with phenacetin withdrawal [5-23].

In the largest study of NSAIDs use and kidney function involving healthy subjects with normal kidney function in Nigeria, a significantly greater risk

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of kidney dysfunction (eGFR <60 ml/min) was found amongst 100 frequent NSAIDs users who were age and sex matched with healthy controls $P < 0.001$.⁹ The study involved subjects without known risk for kidney disease who were grouped according to the duration of drug exposure and reported that the risk of kidney dysfunction was positively correlated with duration of exposure, age of subjects and dosage. The authors found the risk of nephrotoxicity with any single drug to be least with Diclofenac and highest with Ibuprofen. They found a significantly higher cumulative life time dose in NSAIDs users with Kidney Dysfunction (KD) compared to those without KD (2306.4 vs 1292.9). Though a small sized study, with less reliance on the frequency and dosage as reported by researchers assessing in NSAIDs users, the relationship between changes in GFR and, duration of exposure, as well as being an age and sex-matched study strengthened the study.

Aspirin is commonly used by the elderly, in hypertension and diabetes but in healthy population, both normal and higher doses in chronic users is reported not to worsen kidney function [24-26]. In an Belgium prospective controlled trial, the nephrotoxicity of Aspirin was assessed alone, in combination with an NSAIDs, and in non-users and they found that 6% in the NSAIDs group, 1% of non-users had worsened kidney function while none in the Aspirin monotherapy group suffered decline in kidney function (RR, 6.1, 95% CI 1.4-25.9)[27].

Paulose-Ram and his group, in a study of frequent non-opioids analgesic users, found that 14% of American adults were frequent users of non-opioid analgesics with aspirin alone accounting for 57.1% and NSAIDs accounting for 21.4%. The authors found that most users of non-opioid analgesic agents took the drug for at least a year, and their use was common in the elderly population. With prolonged use and a greater involvement of the elderly in their use, coupled with a physiologic decline in kidney function and higher levels of inflammatory markers in them, there could be an increase in the risk for and progression of kidney disease. The possibility of the presence of risk factors for kidney disease may have limited the applicability of the findings [10].

Therapeutic doses of NSAIDs were reported by Nderitu et al not to significantly increase the risk of CKD progression unlike higher doses (OR, 0.96; 95% CI, 0.86-1.07) and (OR, 1.26; 95% CI, 1.06-1.50) respectively [28]. The non-consideration of the comorbid states of the subjects could have limited the study considering the multiple findings of the near non-progression enhancing relationship between NSAIDs use and CKD.

Despite the volume of work on NSAIDs and their effects on kidney function, there is still no consensus opinion concerning their nephrotoxicity or otherwise, although their ability to induce Acute Interstitial Nephritis (AIN), a form of Acute Kidney Injury (AKI) seems to be a widely held view[9-14]. Possible diagnostic features of AIN, apart from known features of AKI, and apart from histologic findings, include Elevated Eosinophil Count (EEC) in Peripheral Blood Film (PBF) a known non-specific finding in AIN [29]. The presence of eosinophilia in a healthy population taking NSAIDs could therefore be a pointer to some degree of nephrotoxicity of these drugs. The progression of AIN to Chronic Interstitial Nephritis (CIN) could be accelerated by NSAIDs use with features of neutrophilia in AIN transforming to mononuclear cells infiltration in peripheral blood and in tissues, and infiltration could lead to organ enlargement from cellular hypertrophy [9-30]. EEC tend to be commoner in CKD than AKI, eosinophilia been a proven marker of an ongoing inflammatory process that is more prevalent in CKD than AKI [29-32].

The application of other supporting evidences of nephrotoxicity of these drugs could add to the panel of evidences of nephrotoxicity or otherwise of these drugs, particularly in people not receiving anti-proteinuric drugs [19-33]. Though anti-inflammatory, the proteinuric effects of NSAIDs are well reported, further studies should therefore including correlations between the changes in kidney function (GFR) and the quantity of proteinuria using Protein Creatinine Ratio (PCR) or Albumin Creatinine Ratio (ACR) which is reported to be the more reliable measure of the two[34-36].

The peripheral blood film could be a reliable investigative tool in determining NSAIDs' nephrotoxicity, with the Neutrophil Lymphocyte Ratio (NLR), being a known inflammatory marker could also be assayed in NSAIDs therapy that is not short term [37]. The NLR may not be a reliable inflammatory marker in CKD due to the background chronic inflammatory process associated with CKD, but its use in healthy population groups could be very useful in determining the overall nephrotoxicity or otherwise of NSAIDs. Apart from the NLR, the platelet count is reported to be elevated in CKD compared to a healthy population [29-38]. Its determination may be of value in long term NSAIDs therapy (>12 months) as a progressive increase could be suggestive of progression to CKD in people with pre CKD conditions like hypertension, diabetes and sickle anemia [39]. Further still, the serum levels of measures such as the C-reactive protein (ESR) and the Erythrocyte Sedimentation Rate (ESR) as inflammatory markers could come handy in healthy population groups and in kidney disease [40-43]. The incorporation of these measures into the investigation panel for NSAIDs user could be of significant step towards deciding the nephrotoxicity or otherwise of NSAIDs.

CONCLUSION

The overall nephrotoxicity of non-steroidal anti-inflammatory drugs is still been debated. Despite this, prolonged and higher doses seem to increase the risk of nephrotoxicity, even as the risk of acute interstitial nephritis from NSAIDs use is less contentious. The determination of the levels of some inflammatory markers known to be elevated in kidney disease, such as urinary albumin, peripheral blood platelets, and eosinophil count, neutrophil lymphocyte ratio, the C-reactive protein and erythrocyte sedimentation rate could further enhance the ability of physicians to classify NSAIDs as nephrotoxic or not.

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