Original Research Article

Prescription Non-Steroidal Anti-Inflammatory Drugs: Pattern and Nephrotoxicity

ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are very common "over-the-counter" commonly abused drugs used in treating fever, pain and inflammatory conditions. They inhibit prostaglandins and can cause kidney disease and hypertension, particularly in stressed states like dehydration and exercises.

Objectives: To access prescription pattern and effects of common NSAIDs on the kidneys.

Methods: One hundred frequent NSAIDs users (daily use $\geq$ 4 weeks) and 100 healthy controls, who had no known risk factor for kidney disease and gave consent were recruited. Blood samples for serum electrolytes, urea and creatinine, haemoglobin concentration and urine samples for dip strip, and 24 hour protein were collected and analysed.

Results: The mean age of the controls, all NSAIDs users, NSAIDs users without kidney dysfunction (KD) and NSAIDs users with KD were 46.04 $\pm$ 14.21 years, 46.5 $\pm$ 14.2 years, 41.84 years $\pm$ 14.52 yrs and 63.04 $\pm$ 4.21 years respectively, P=0.03. The mean estimated glomerular filtration rate (eGFR) was significantly lower in frequent NSAIDs users than controls, P<0.001. Ibuprofen was the most nephrotoxic and, nephrotoxicity was positively related to combination therapy (P<0.001) and duration of use (P=0.03). Herbal medicines significantly increased the risk of KD, P=0.01. Predictors of KD were advancing age, longer duration of NSAIDs use, Ibuprofen use and combined NSAIDs

Conclusion: Frequent NSAIDs use, common in Orthopaedic units, could be complicated by kidney dysfunction. Ibuprofen, followed by ketoprofen, was the most nephrotoxic. Observed risk

factors for NSAIDs induced nephrotoxicity included advancing age, herbal remedies, Ibuprofen and combination therapy.

Keywords: Non-steroidal anti-inflammatory drugs; Frequent-users; Nephrotoxicity

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are agents commonly used in treating fever, pain, inflammatory conditions and tiredness.[1] They are cheap, often taken without prescription and their use is not regulated by law hence they are commonly abused, defined as use in excessive amount or for purposes different from what they are meant for, for instance, body weakness [2]. The use of these "over-the counter" (OTC) drugs is common among manual labourers and the elderly [2,3]. NSAIDs are broadly classified into eight groups based on their chemical structures and pharmacokinetics [4]. These are: Salicylates (Aspirin), Propionic acids (Ibuprofen, Ketoprofen), Oxicams (Meloxicam), Acetic acid (Indomethacin), Pyrazolones (Phenylbutazole), Cyclo-oxygenase II inhibitors (Celecoxib), Fenamates (Mefenamic acid) and Benzene Acetic Acid Derivatives (Diclofenac).

The duration and frequency of NSAIDs use could be dependent on whether it was prescribed or not.[5] Paulose-Ram et al [6] defined frequent use of an analgesic agent as daily use of up to a month. The authors found a 14% prevalence of frequent users of these drugs in the United States. The prevalence of NSAIDs use in a community survey was found to be 13%, and of this, 22.6% were abusers [2]. Manual labourers often take these drugs for tiredness, pain and aches. In some cases where NSAIDs are prescribed, there isn't sufficient knowledge on the part of some

prescribers concerning possible adverse effects and conditions in which these effects are enhanced [5-7].

In Nigeria, a prevalence of 60% and 70% NSAIDs use is reported among males and females aged over sixty five years respectively. The authors attributed the high prevalence to arthritis and other musculoskeletal conditions that are common in this population.[8] Patino et al [9] reported that about 2% of the population on NSAIDs stopped treatment due to renal complications of these drugs. In 2010, twenty nine million adult Americans (12.1%) were said to be regular users of NSAIDs [10]. About 2.5 million Americans experience kidney dysfunction from NSAIDs use yearly and a new patient is admitted to dialysis every day from NSAIDs use [11].

Outdoor exercises, particularly under the sun, decreases the glomerular filtration rate (GFR) by 19%, dehydration decreases the GFR by 51% [12]. NSAIDs use before, and during exercise is harmful, and worse still, with dehydration and heart failure [13]. Activities of marathoners and manual labourers commonly involves outdoor exposure to the sun and often associated with sweating resulting in dehydration. This explain why the use of NSAIDs by manual labourers and marathoners is associated with an increased risk of hyponatremia, and kidney dysfunction which could progress to kidney disease, and failure [14]. These drugs inhibit prostaglandins actions on the kidneys thereby abolishing prostaglandin-mediated dilatation of the glomerular afferent arterioles, being a vital renal response in stressed states [5, 9, 11].

The use of NSAIDs in orthopaedic units is mostly prescription based unlike OTC use that is common at the community level. Literature is still scanty as it relates to the nephrotoxicity or otherwise of NSAIDs. In this study, we compared the kidney function of frequent NSAIDs users with healthy controls.

Methods

Study design

This was a hospital-based comparative study that lasted 24 months (July 2015-June 2017) at the nephrology unit of Federal Medical Centre, Abeokuta, Nigeria.

Study population

One hundred frequent NSAIDs users without any known risk for kidney disease, and age and sex-matched healthy controls who had no known risk factor for kidney disease, participated. The NSAIDs users were recruited from the orthopaedic outpatient clinics while the controls were healthy hospital staffs. NSAIDs users were shown packets, sachets and containers of the common NSAIDs in the locality to ascertain those used by them alone or in combination.

Exclusion criteria

Participants with hypertension, diabetes, sickle cell anemia, heart failure, chronic liver disease, proteinuria, glycosuria, ultrasound-diagnosed kidney disease and any condition known to impact negatively on kidney function were excluded.

Study protocol

Data was obtained from participants' case notes and from history and entered into a structured interviewer-administered questionnaire.

The height and weight were measured with a standiometer and a weighing scale. The blood pressure (BP) in mmHg, was taken in sitting position (with the back and the arm rested on a support) using a mercury sphygmomanometer (ACCOSON, England) after participants had rested for 5 minutes. Participants were then given a 4-6 litre plastic can treated with tetraoxosulphate VI acid (H_2SO4) for 24 hour urine collection. They were asked to empty their first urine (on walking up in the morning) and discard, and document the time. They collected subsequent urine into the plastic can. Twenty-four hours after the documented time, they emptied

the last urine for the test into the can and immediately brought it to the hospital central laboratory for determination of total protein, electrolytes and creatinine clearance, after which they presented at the clinic for their routine visit. Two on-the-spot urine samples were collected during urine submission, for albumin creatinine ratio (ACR) and dip strip urinalysis.

For the ACR test, a strip with its reagent pad was taken from its container [SIEMENS Microalbustic, REF 2087 (04960872)] which was then capped immediately (to minimise the exposure of the remaining strips to light and air) and immersed almost completely in the urine. It was then removed and the result for the albumin was read after 50 seconds and that of creatinine was read after 60 seconds by matching the colour changes with the corresponding colour on the strip bottle and the values were recorded.

During urine submission, blood was collected into an EDTA containing bottle for estimation of haemoglobin estimation, and into a Lithium heparin bottle for creatinine, urea, sodium, potassium, bicarbonate and chloride. Creatinine based eGFR was calculated using the CKD-EPI formula.[15] Continuous variables were presented as mean with standard deviation which were compared using Student t-test. Categorical variables were presented as proportions with frequencies and compared using Chi-square. Independent predictors of kidney dysfunction were determined using multiple regression analysis. A P-value of < 0.05 was considered statistically significant.

Definition of terms

Frequent NSAIDs users: those that took at least, a unit of the drug (tablet, caplet, capsule, suspension, syrup, patch, cream or ointment) daily for at least 4 weeks [5, 6]

Kidney dysfunction (KD): eGFR of <60 ml/min [16]

Hypertension: $\geq$140/90 mmHg or taking anti-hypertensive drugs. [17]

Diabetes: ≥11.1mmol or taking anti diabetic drugs. [18]

Anemia: Hemoglobin concentration <13g/dL.[19,20]

Metabolic acidosis: serum bicarbonate < 22mmol/L [21]

Dip strip proteinuria: ≥+1 [22]

Microalbuminuria: urine ACR >3.4mg/mmol (>30mg/g) [23, 24]

The study was approved by the Human Ethics Committee of the Federal Medical Centre, Abeokuta, Nigeria with the reference code: NREC/08/04/2010-2015 and FMCA/238/HREC/09/2015.

RESULTS

The frequent NSAIDs users and control group were each made up of 51 females and 49 males. The mean age of the NSAIDs users was 46.54 ± 14.52 years compared with the controls 46.04 ± 14.21 years, P=0.38. A majority of the NSAIDs users (53%) were in the 40-59yrs age group. Thirty eight (38%) NSAIDs users had arthritis, 18 (18%) had low back pain, 12 (12%) had post fracture pain and 10 (10%) had spondylitis.

The mean weight of the NSAIDs users was (71.74 ± 14.92 kg) compared to 67.72 ± 12.54 kg for the controls, P=0.03. The mean BMI and systolic blood pressure of NSAIDs users were significantly higher than controls (Table 1). The mean haemoglobin concentration of NSAIDs users, 12.78 ± 1.20g/dL was significantly lower than controls 13.83 ± 1.49g/Dl, P=0.002. The serum potassium, chloride, creatinine, and 24-hour urinary protein were significantly higher in NSAIDs user than controls while the serum bicarbonate, eGFR (P<0.001) and hemoglobin concentration were significantly lower in NSAIDs users than controls.

The mean age, weight and systolic blood pressure of NSAIDs users with kidney dysfunction (KD) were higher than NSAIDs users without KD, P=0.03, P=0.01 and P=0.04 respectively. The

duration of NSAIDs use was negatively correlated with mean eGFR, P=0.03. NSAIDs users with kidney dysfunction had lower mean haemoglobin concentration but higher proteinuria compared with those without KD. Of the NSAIDs users that took a single NSAID, Ibuprofen users had the lowest mean eGFR, followed by Aceclofenac users while those that took Diclofenac had the highest eGFR. Combined NSAIDs users had lower mean eGFR compared with that of any single NSAID users.

Twenty two (22%) NSAIDs users had kidney dysfunction (GFR <60ml/min) compared to 6% in the controls. Using the ACR, 29.3% of the 41 (41%) NSAIDs users that took combined NSAIDs had kidney dysfunction while 10.2% of the 59 (59%) that took a single NSAID had KD. Participants that used higher doses of NSAIDs had higher urine ACR (Table 3).

Multiple regression analysis (Table 4) showed advancing age, longer duration of NSAIDs use, Ibuprofen, and use of combination drugs, as predictors of kidney dysfunction.

DISCUSSION

The prevalence of kidney dysfunction in NSAIDs users was 22% and was positively related to the number, dose and duration of NSAIDs use. The most common reason for NSAIDs use was arthritis. There was a positive relationship between the eGFR and serum levels of bicarbonate and haemoglobin. The higher prevalence of NSAIDs use in this study compared with the 13% found in a community study in Nigeria and the 14% reported in the United States, could be attributed to the study's (hospital-based) design and participants' NSAIDs-requiring conditions. [2, 6] Another study in Nigeria also attributed NSAIDs use to the treatment of painful conditions and found a prevalence of NSAIDs use among males and females aged over 65 years to be 60% and 70% respectively, in a population that included diabetics and hypertensives, (groups that were both excluded from our study).[8] Though the authors, did not assess kidney function in

their study, they reported a poor response to anti-hypertensives among hypertensives who used the two drug groups concurrently. An implication of this is a higher prevalence of complications of poorly treated hypertension like kidney disease in this population group.[25]

The prevalence of KD in this study is close to 19% reported by Schwarz et al [26] in people that took these drugs daily for more than 4 weeks, and had progressed from acute kidney injury (AKI) to chronic kidney disease (CKD). The CKD-EPI equation used in this study is found to be more reliable than the MDRD when GFR is greater than 60mls/min as it does not overestimate the GFR. Some of the participants used in studies that used MDRD would have been classified as having KD using the CKD-EPI formula.[15, 27]

The positive correlation between participants' age and KD mirrors findings from other studies that found increasing age as a risk factor for kidney disease. [28] The renal insults from exogenous nephrotoxins in the elderly, in whom the renal reserve is often poor, could easily be heightened, and could be overwhelming.[29] The higher risk of nephropathy in females is in agreement with previous studies, and could be multifactorial, with factors like the lower baseline GFR, the higher frequency of NSAIDs use in them, and perhaps, cultural biases that tend to limit relatively, the accessibility of females to healthcare in the local setting.[16, 30-31] Moreover, females, having more body fats with consequent larger volumes of distribution of drugs are expected to carry a higher risk for drug toxicities, particularly in excessive doses. [32] Females, being of smaller body sizes and weights, receive larger drug concentration per unit body tissue, and this could lead to higher toxicities in excess doses, particularly as most adult prescriptions are not weight-based. The lower levels of cytochrome P450 enzyme inducers in females is associated with lower drug degradation in them, resulting in larger serum levels of drugs compared to males. [33]

The negative relationship between the BMI and kidney function agrees with findings that reported an association between higher BMI and risk of new onset kidney disease.[34] Renal hyperfiltration, common in obesity, is associated with nephromegally, higher intraglomerular pressure and kidney damage. The resulting necrosis of the nephron leads to compensatory nephromegally of the remaining nephrons. The interplay of forces relating the kidney size with hyperfiltration, kidney damage and proteinuria is well reported in diabetic nephropathy, obesity, focal segmental glomerulosclerosis (FSGS) and NSAIDs-induced kidney disease. [35, 36]

The association between rising blood pressure (within normal range) and NSAIDs-induced kidney dysfunction in this study mirrors findings by Pirkle et al [37] that established a link between hypertension and kidney disease. This may also give credence to some researchers that favour lower "normal blood pressure" particularly in Africans and African Americans (AA) whom studies have reported to suffer worse consequences of blood pressure increases and hypertension.[38, 39] The higher renal and systemic resistance induced by NSAIDs is consequent upon their inhibition of PGs-induced vasodilatation and this could lead to the activation of the renin angiotensin aldosterone system (RAAS) pathway associated with vasoconstriction, fluid retention, higher effective blood volume (EBV) and, interstitial fluid volume [28, 37]

The higher serum potassium seen in NSAIDs users could result from the inhibition of Na/K/H ATPases which leads to higher potassium extracellular shift with concurrent higher intracellular sodium shift resulting in hyperkalaemia and low sodium, similar to findings by Firestein et al [40] Though NSAIDs induced glomerulopathy is less commonly reported compared to tubulo-interstitial (TIN) injury, secondary glomerular affectation from the progression of a primary TIN disease could lead to lowered glomerular filtration, further worsening the nitrogenous wastes

retention associated with kidney dysfunction. [5,34] The proteinuria in those with KD could be attributed majorly to a more severe form of TIN in them, or a TIN with a glomerular back-leak effect or rarely a primary glomerulopathy which fortunately was less likely considering the fact that nephrotic range proteinuria was not found in any of the participants, unlike in previous studies that reported the contrary.[24, 41] The exclusion of conditions that negatively impact kidney function is most likely responsible for the absence of nephrotic range proteinuria in the participants.[24]

Urinary creatinine clearance has been reported to be an unreliable estimate of the eGFR as the high proximal tubular secretion of creatinine could give falsely elevated urinary creatinine values and therefore higher creatinine clearance. [42] NSAIDs-induced TIN could contribute to glomerular proteinuria that results from glomerular hypertension leading to increased glomerular filtration of normally unfiltered proteins. This is followed by increased tubular absorption and metabolism of these proteins which further damages the tubules leading to tubular epithelial injury and sloughing, obstruction to flow, eventually leading to increased tubular secretion of low molecular weight (LMW) proteins. [23-24, 43] This cascade of events which typifies NSAIDs-induced proteinuria with nephrotic syndrome as a consequences of PG inhibition could explain the positive relationship between proteinuria and KD in this study despite NSAIDs' known anti-inflammatory properties. [44]

The mostly tubular LMW protein loss that complicates tubular and interstitial injury could lead to reduced renal tubular epithelium secretory capacity and the loss of polarity between the apical and basolateral membranes, a form of acute tubular necrosis, similar to findings by Vegal et al. [45] The positive relationship between the systolic BP and nephrotoxicity mirrors findings by Ghosh et al.[46] Proteinuria leads to increased hepatic production of atherogenic lipids and this

increases the risk of plaque deposition, atherosclerotic vessel wall stiffening, increased peripheral resistance and elevated SBP. [47]

The higher frequency of anemia in NSAIDs users compared to healthy controls agrees with previous findings and this could be multifactorial in origin.[20, 48] The congestion involving the hepatic bed and gastrointestinal tract commonly leads to anorexia, early satiety, reduced digestion, absorption and assimilation, factors that contribute to low substrate delivery for erythropoiesis.[49] The predominant interstitial affectation in NSAIDs-induced nephropathy can depress erythropoietin production by the fibroblast cells of the peritubular interstitium. These drugs can cause gastritis and small intestinal mucosal injury with reduction in serum iron, folic acid, B_{12} and other substrates, hence the anaemia that is common in them. [5, 30, 40]

The higher frequency of metabolic acidosis (MA) in NSAIDs users mirrors findings in previous findings that reported higher prevalence of MA from exogenous nephrotoxins. [20, 50] The tubular injury induced by these drugs inhibit the Na/K ATPase, and the intercalated cells disrupting the exchange mechanisms that mediates potassium exchange, with hydrogen ions retention as a consequence.[51]

In this study, the duration of NSAIDs use was directly related to the risk of kidney damage asit was earlier found that NSAIDs use for more than a month increased the risk of progression from AKI to CKD.[26] Prolonged NSAIDs use would prevent the healing process that should follow an episode of AKI as recurrent episodes of injury-repair/healing with reperfusion injury lead to interstitial fibrosis, glomerular sclerosis, tubular wall dilatation, atrophy and scaring. This can indeed progress to severe diminution in kidney function with morphological changes leading to the “sick indented, calcified kidneys” (SICK) seen in long standing NSAIDs abuse. [52] The increased nephrotoxicity associated with Ibuprofen use in this study can partly be attributed to its

multiple dosing in patients thereby increasing the risk of toxicity as subsequent doses are taken by subjects even when blood steady state are attained.[53]

The positive association between NSAIDs doses and nephrotoxicity in the study agrees with previous findings [5, 30, 52] High doses lead to higher plasma drug concentration, greater PG inhibition with its consequences. The more severe nephrotoxicity seen in participants who combined NSAIDs could be related to the multiple pathophysiologic mechanisms involving multiple enzymatic activities leading to the production of endonucleases and disruption of the cytoskeletal frame of the cellular structure, which in the kidneys could compromise the excretory, endocrine and synthetic functions. [5, 52]

Some limitations we encountered included the fact that advance imaging techniques like magnetic resonance imaging or a computed tomography for the determination of SICK were not done on account of cost, as it applies to urine osmolality. With the cross sectional design of the study, kidney function test were not conducted to confirm chronicity of kidney dysfunction. Estimated duration and frequency of NSAIDs use, given by participants may not be very reliable. Patients may occasionally decide to skip, reduce or increase dosage when pain eases or worsen. Information on co-morbid conditions were either self-reported or from participants' case files, undiagnosed diseases that affect results of investigations.

Conclusion

NSAIDs are cheap, very common and often abused OTC drugs and hypertension and kidney disease could complicate their use particularly when used in states of stress, exercises, dehydration, infections, and in prolonged and multiple drug therapy. Prescribers should be more aware of their nephrotoxicity and conditions under which this is enhanced and should therefore consider dosage reduction, single NSAIDs therapy and finding alternatives to "pain killers"

Ibuprofen was the most nephrotoxic while Diclofenac was the least nephrotoxic. Periodic kidney function assessment is needed prior to, during prolonged use, and when nephrotoxicity or the risk for it is increased.

Recommendations

1. More media campaigns, advocacy and net-working should be encouraged to increase awareness of kidney diseases and to institute screening programmes for early detection of disease with prompt referral to the nephrologist.

2. Larger studies involving all races should be carried out to ascertain the sensitivity of screening tools like ACR.

3. Where NSAIDs use becomes inevitable, efforts should be made to reduce the duration, dosages and frequency of use, and combination therapy.

4. Periodic (annual) kidney function test should be conducted on patients on prolonged NSAIDs therapy in conjunction with a nephrologist.

Table 1: Clinical and Laboratory findings in the study participants

Variables	NSAIDs users (Mean ± SD) n=100	Controls (M ± SD) n=100	t-test	P-value
BMI, kg/m^2	27.22 ± 14.43	26.15 ± 5.69	1.11	0.03
Systolic BP, mmHg	127.16 ± 8.67	122.55 ± 10.6	2.01	0.04
Diastolic BP, mmHg	79.16 ± 5.32	74.82 ± 4.44	2.26	0.03
Sodium, mmol/L	134.56 ± 7.62	136.87 ± 1.43	0.06	0.08
Potassium, mmol/L	4.10 ± 2.82	3.82 ± 6.04	2.01	0.03
Chloride, mmol/L	102.67 ± 8.24	96.15 ± 1.88	4.23	<0.001
Bicarbonate, mmol/L	22.56 ± 10.47	23.94 ± 9.01	2.22	0.04
Urea, mmol/L	6.30 ± 2.23	5.34 ± 2.11	2.74	0.04
Creatinine, umol/L	98.12 ± 10.16	77.81 ± 9.88	7.83	<0.001
eGFR, mL/min	87.83 ± 30.72	115.01 ± 26.92	9.84	<0.001
Haemoglobin concentration, g/dL	12.78 ± 1.26	13.83 ± 1.42	2.77	0.02
Serum bicarbonate, mmol/L	21.56 ± 5.52	23.03 ± 6.17	3.24	0.001
24 hour urine protein, (mg/day)	562.52 ± 28.16	212.52 ± 18.16	8.86	<0.001
CrCl, (mL/min)	76.31 ± 11.08	118.18 ± 11.26	9.52	<0.001

NSAIDs-non-steroidal anti-inflammatory drugs, BMI-body mass index, BP-blood pressure, GFR-estimated glomerular filtration rate, CrCl-creatinine clearance

Table 2: Relationship between the duration of NSAIDs use and the eGFR

Variables	Frequency (%)	eGFR	X^2	P-value
1-6 months	23 (23)	96.29 ± 26.30	2.64	0.03
7-12 months	36 (36)	92.45 ± 30.53		
1-5 years	35 (35)	80.98 ± 30.75		
≥5 years	6 (6)	61.51 ± 38.24		

NSAIDs-non-steroidal anti-inflammatory drugs, eGFR-estimated glomerular filtration rate

Table 3: Relationship between the doses and number of NSAIDs and kidney function (ACR >3.4mg/mmol

Variables	Frequency n=100 (%)	ACR <3.4 mg/mmol n=82 (%)	ACR >3.4 mg/mmol n=18 (%)	X^2	P-value
Aceclofenac, mg/day					
100	1 (1.00)	1 (1.22)	0 (0.0)	0.08	0.07*
200	2 (2.00)	2 (2.44)	0 (0.0)		
Diclofenac, mg/day					
50	10 (10.00)	10 (12.20)	0 (0.00)	0.06	0.08
100	14 (14.00)	13 (15.85)	1 (5.56)		

Ibuprofen, mg/day					
600	4 (4.00)	4 (4.80)	0 (0.00)	7.32	<0.001
1200	2 (2.00)	0 (0.00)	2 (11.11)		
Ketovail, mg/day					
100	4 (4.00)	4 (4.80)	0 (0.00)	3.47	0.04
200	6 (6.00)	4 (4.80)	2 (11.11)		
Miloxicam, mg/day					
7.5	5 (5.00)	5 (6.10)	0 (0.00)	0.09	0.06
15	11 (11.0)	10 (12.20)	1 (5.56)		
Combined NSAIDs					
	41 (41.0)	29 (35.36)	12 (66.66)	7.15	<0.001

*ACR=albumin creatinine ratio, *-fisher's exact test*

Table 4: Correlates of kidney dysfunction in NSAIDs users

Variables	NSAIDs users without KD n=78 (%)	NSAIDs users with KD n=22 (%)	OR	95% CI	P-value
Sex					
Males	40 (81.63)	9 (18.37)	2.85	1.78-4.14	0.03
Females	38 (74.51)	13 (25.49)			
Age, years					
<60	76 (84.44)	14 (15.56)	8.65	3.61-12.73	<0.001

≥60	2 (20.0)	8 (80.0)			
Number of NSAIDs					
1	51 (86.44)	8 (13.56)	5.83	5.79-10.96	<0.001
≥2	27 (65.85)	14 (34.15)			
Duration of NSAIDs use, years					
≤1	56 (94.91)	3 (5.09)	6.37	1.38-7.57	<0.001
>1	22 (53.66)	19 (41.34)			
Herbal remedies					
Yes	0 (0.0)	11 (100.0)	9.62	4.82-13.68	<0.001
No	78 (87.64)	11 (12.36)			
Arthritis					
Yes	26 (68.42)	12 (31.58)	4.22	2.49-6.11	<0.001
No	52 (83.87)	10 (16.13)			
Haemoglobin concentration, g/dL					
<13	16 (47.06)	18 (52.94)	7.69	3.66-13.54	<0.001
≥13	62 (93.94)	4 (6.06)			
Serum Bicarbonate, mmol/L					
<22	8 (38.10)	13 (61.90)	8.2	2.99-13.69	<0.001
≥22	70 (88.61)	9 (11.39)			
ACR, mg/mmol					
<3.4	76 (92.68)	6 (7.32)	9.31	2.28-12.85	<0.001
≥3.4	2 (11.11)	16 (88.89)			

KD-kidney dysfunction, OR-odds ratio, CI-confidence interval, NSAIDs-non-steroidal anti-inflammation drugs, ACR-albumin creatinine ratio

Table 5: Multivariate Logistic Regression Analysis

Variables	OR	95% CI	P-value
Age (years)	2.24	1.05-2.45	0.01
Gender	0.62	0.08-0.94	0.09
Duration on NSIADs	2.46	1.32-2.76	0.01
Combination drugs	9.46	1.14-11.28	<0.001
Ibuprofen	1.78	1.81-2.65	0.02
Herbal remedies	0.04	0.03-0.058	0.12

OR=odds ratio, CI=confidence interval, NSAIDs=non-steroidal anti-inflammatory drugs

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