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A RETROSPECTIVE PREVALENCE STUDY OF DRUG INDUCED NEPHRITIS- A HOSPITAL BASED CROSS SECTIONAL STUDY IN CENTRAL INDIAN POPULATION

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Abstract:

Background: Drug-induced kidney disease constitutes an important cause of acute renal failure and chronic kidney disease in present day clinical practice. Different classes of drugs, by virtue of immunological mechanisms or direct toxicity initiate certain stereotyped renal responses.

Objectives: To estimate the incidence and prevalence of drug induced nephrotoxicity, a retrospective study was conducted in the Department of Medicine, Sri Shankaracharya Institute of Medical Sciences, Bhilai, Chhattisgarh, over a period of 6 months from January 2018 to June 2018. The study included 120 determinations of drug induced nephritis between 30-70 years age group. 49.5% of patients were female.

Methods: screening of 500 people aged 30 and above was carried out. Demographic and anthropometric data were obtained, urine was analyzed for protein by dipstick and serum creatinine was measured in all participants. Glomerular filtration rate was estimated (eGFR) using the 4-variable modification of diet in renal disease (MDRD) equation and Cockcroft-Gault equation corrected to the body surface area (CG-BSA).

Results: proteinuria was 2.8%. DIN was seen in 120(6.3%) subjects when GFR was estimated by MDRD equation. The prevalence of DIN was 24% by the CG-BSA method. There was a statistically significant relationship of DIN with gender, advancing age, abdominal obesity, smoking, presence of diabetes and hypertension. The wide difference between the DIN prevalence between MDRD and CG-BSA equations suggests the need for a better measure of kidney function applicable to Indian population. CG-BSA equations suggests the need for a better measure of kidney function applicable to Indian population.

Keywords: Body mass index (BMI), Cockcroft-Gault (CG), Chronic kidney disease (CKD), drug induced nephrotoxicity (DIN), Proteinuria, Glomerular filtration rate (GFR)

INTRODUCTION

Chronic kidney disease (CKD) is rapidly assuming epidemic proportions globally.[1,2,3] In India too, there is a significant burden of CKD although exact figures vary.[4] This has been attributed to the increasing prevalence of diabetes, hypertension and ischemic heart disease. The awareness level among the people is poor. At least 70% of the people live in rural areas with limited access to health care services with the result that CKD is often diagnosed in advanced stages. Studies on the prevalence of diseases help in focusing attention to the magnitude of the burden and planning preventive measures. High-risk characteristics that are associated with such prevalence can be modified.[2,3]

The incidence of drug-induced nephrotoxicity (DIN) has been increasing with the ever increasing number of drugs and with easy availability of over-the-counter medication viz. non-steroidal anti-inflammatory drugs (NSAIDs). Antibiotics, NSAIDs, angiotensin converting enzyme inhibitors (ACEI) and contrast agents are the major culprit drugs contributory to kidney damage.[5]

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Some syndromes include Acute glomerulonephritis (rarely seen with drugs like rifampicin)- Associated with generalized anasarca, hypertension, oliguria; blood urea nitrogen (BUN) and serum creatinine (SCr) elevated; urine microscopy reveals proteinuria (> 2 g/24 hr) and RBC casts with > 80% dysmorphic RBCs. Renal biopsy may be indicated to assess the pathology and to gauge the severity of inflammatory response.[4] Syndrome of inappropriate ADH secretion- seen with phenothiazines, vincristine, chlorpropamide, cyclophosphamide, tricyclic antidepressants, vasopressin analogues. Nephrogenic diabetes insipidus- seen with lithium demeclocycline, aminoglycosides, amphotericin. Number of patients developing nephrotoxicity increases with duration of therapy reaching 50% with 14 days 2 or more of therapy. For most patients suffering from DIN common risk factors which precipitate the adverse effects include: old age, volume - depleted state, pre-existing renal dysfunction and co-existing use of other nephrotoxins. Although it is impossible to present all the drugs causing renal disease, a few prototype drugs are mentioned. In a case of undiagnosed renal disease a possibility of DIN should be kept as the prompt removal of the drug and supportive management can reverse the renal dysfunction to a large extent.[6,7]

Clinical features - Classically it presents as acute tubular necrosis which is generally milder than oliguric ARF. Features include: non-oliguric ARF, proximal tubular dysfunction, enzymuria, proteinuria, glycosuria, hypokalemia, hypocalcemia, hypomagnesemia. In over 50%, renal functions decline after completion of therapy. Recovery is slow and requires 4-6 weeks. Recovery is incomplete if pre-existing renal insufficiency exists. Some patients may progress to chronic interstitial nephritis.[7,8]

Risk factors for AMG toxicity include Na+ and K+ depletion, renal ischemia, increasing age, liver disease, diuretic use and concomitant use of nephrotoxic agents. Rising trough levels may indicate impending nephrotoxicity. Relative toxicites (in decreasing order) Neomycin > Gentamycin > Tobramicin > Netilmicin > Amikacin > Streptomycin.[1,9,10]

Drugs associated with chronic interstitial nephropathy [11,20-23]

Acetaminophen, aspirin, NSAIDs History of chronic pain, age older than 60 years, female sex, cumulative consumption of analgesic > 1 gram per day for more than two years.

Drugs altering intraglomerular hemodynamics [10-12,23,32]

ACE inhibitors, ARBs, NSAIDs Underlying renal insufficiency; intravascular volume depletion; age older than 60 years; concomitant use of ACE inhibitors, ARBs, NSAIDs, cyclosporine (Neoral) or tacrolimus.

The incidence of drug induced nephrotoxicity is 14-26 % in adults and 16% in paediatric cases.[1] Nephrotoxicity is defined as 0.5mg/dl or 50% rise in serum creatinine over 24-72 hour time frame and a minimum of 24-48h drug exposure.[2] But 50% increase in serum creatinine may not be highly specific. DIN can be categorised as Type A- Dose dependent and Type B-Idiosyncratic reactions. Dose dependent reactions are predictable which are based on the pharmacological properties of the drug, whereas the idiosyncratic reactions are unpredictable as they are based on peculiarities of the patient. The Kidney Disease Improving Global Outcomes (KDIGO) classify DIN into acute (1-7 days), sub-acute (8-90 days) and chronic (>90 days).[3,4] Nephrotoxicity caused due to administration of various drugs can be explained by their different mechanisms like,[5,6]

- By altering the Intraglomerular hemodynamics: Interfere with the kidney's ability to auto regulate glomerular pressure, decrease in pressure and cause dose dependent vasoconstriction of afferent arterioles. Examples: NSAID's, ACE inhibitors, ARB's, Calcineurin inhibitors like Cyclosporine and Tacrolimus.
- Renal tubular toxicity: Interfere with the mitochondrial function by increasing the oxidative stress and forming free radicals. Examples: Aminoglycosides, Amphotericin B,

Antiretrovirals (Adefovir, Cidofovir), Cisplatin, Contrast dye and Zoledronate.

- Due to inflammation in glomerulus, renal tubular cells, and surrounding interstitium: a) Glomerulonephritis: Inflammatory condition due to immune mechanism associated with proteinuria in nephrotic range. a. Examples: Gold, Hydralzine, Interferon alpha, Lithium, NSAID's, Propylthiouracil, Pamidronate. b) Acute Interstitial Nephritis: due to non-dose dependent idiosyncratic response. a. Examples: Allopurinol, Antibiotics (Beta lactam, Quinolones, Sulphonamides and Vancomycin), Anti virals (Acyclovir, Indinavir), Diuretics (Loop and Thiazide), NSAID's, Phenytoin, Proton pump inhibitors (Omeprazole, Pantoprazole, Lansoprazole, and Ranitidine) c) Chronic interstitial nephritis: Due to hypersensitivity reactions. a. Examples: Calcineurin inhibitors (Tacrolimus, Cyclosporin), Lithium, Aspirin, Acetaminophen.
- Crystal Nephropathy: Use of drugs which produce crystals that are insoluble in urine. These crystals precipitate within the distal tubular lumen, obstructing the urine flow and eliciting the interstitial reaction. Examples: Antimicrobial agents (Ampicillin, Ciprofloxacin, Sulphonamides), Antivirals (Acyclovir, Foscarnet, Ganciclovir, Indinavir), Methotrexate, Triamterene. DIN presents in one of the four phenotypes.

METHODS

The retrospective study was conducted in the Department of Medicine, Sri Shankaracharya Institute of Medical Sciences, Bhilai, Chhattisgarh, over a period of 6 months from January 2018 to June 2018. An ethical clearance was obtained from the institutional committee prior the study. The study included 120 patients of drug induced nephrotoxicity between 20-70 years age group. 49.5% of patients were female.

Some definitions regarding the present study

- CKD is defined as the presence of either kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2.[8]
- Proteinuria was defined as the presence of protein in urine as detected by 1+ (0.3 g/l) or more on dipstick.[10]
- Hematuria was also defined as 1+ (25 red blood cells/µl) and above. Kidney function was determined by use of both CG corrected to the BSA and the 4-variable MDRD formula.
- This estimated creatinine clearance (ml/min) was further corrected to BSA to obtain creatinine clearance (ml/min/1.73 m^2).[11]
- Hypertension was defined as the presence of systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, on examination or self-reported history of hypertension or use of antihypertensive medications.[12]
- Diabetes mellitus was defined as fasting blood sugar value more than or equal to 126 mg/dl or self-reported history of diabetes or taking insulin or other medications for the control of diabetes.[13]
- Obesity was defined using the Indian consensus definition: malnutrition < 18 kg/m^2, normal BMI: 18.0-22.9 kg/m^2, overweight: 23.0-24.9 kg/m^2, obesity: >25 kg/m^2. Abdominal obesity was defined as waist circumference in men > 90 cm, women > 80 cm.[14]

Screening of 500 people aged 30 and above was carried out for kidney diseases with a detailed questionnaire, anthropometric examination, blood pressure measurement and urine dipstick tests. Demographic and anthropometric data were obtained, urine was analyzed for protein by dipstick and serum creatinine was measured in all participants. Glomerular filtration rate was estimated (eGFR) using the 4-variable modification of diet in renal disease (MDRD) equation and Cockcroft-Gault equation corrected to the body surface area (CG-BSA).

RESULTS

Demographic characteristics: Schematic representation of the study design is shown in table 1. The total number of subjects studied was 500. Mean age was 39.88 ± 15.87 years. The subjects were predominantly adults with more than 70% aged above 40 years. There was

a female preponderance with females constituting (64%) of the population studied. Majority of them (nearly 57%) were labors, unemployed (24%) and less professionals were 19%. Abdominal obesity was seen in 28.90% of subjects.

Co-morbid illnesses: Table 2 showed Stratification of the population according to the GFR (n=120). The prevalence of diabetes in this study was 3.82%. Of the 80 subjects found to have diabetes, only 34 (42.5%) were aware of their diabetic status. Forty-six were newly detected to have diabetes. Hypertension was seen in 702 (33.62%) subjects of whom only 106 (15.07%) subjects gave a history of hypertension indicating that nearly 84.93%% were unaware of their hypertensive status. The prevalence of Ischemic heart disease, stroke and arthritis as reported by the population was 0.87%, 0.76% and 2.4% respectively. Nearly 0.8% gave a history of long-term exposure to painkillers.

Kidney disease indicators: Using the MDRD formula, the prevalence of decreased GFR (<60 ml/min/m^2) was found to be 6.09% in this subgroup of the population whereas the prevalence was as high as 30.85% when the CG formula was applied. Correcting the estimated creatinine clearance to the BSA, the prevalence was found to be 16.11%. Prevalence of CKD taking both decreased GFR and proteinuria into consideration was found to be 6.3% by MDRD criteria and 16.69% by CG-BSA method. (Table 2)

Subgroup analysis was done in the 120 subjects with DIN (MDRD eGFR < 60 ml/min/1.73 m^2. 70 (58.3%) of these were males and 50(40.7%) were females. Majority of DIN subjects were in the age group of 51-60 years i.e. 45 subjects (37.4%) [Table3]. Mean age of the subjects with DIN was 39.46 years. Nearly 60% were in nuclear families and only 12.6% had vegetarian food habits. Nearly 88.8% were either unemployed or were laborers. More than 70% of these subjects were having normal BMI or were underweight. Only 14.5% were obese. However, nearly 30% of the subjects with DIN had abdominal obesity. Proteinuria was present in 60 (45.80%) of DIN subjects while it was absent in 71 (54.20%) of DIN subjects, which indicates that more than one-half of our DIN patients are non-proteinuric. Proteinuria alone without decreased GFR was seen in 40 (30.53%) of DIN subjects.

A multiple logistic regression analysis was performed to see which among these variables would predict higher chances of developing DIN. Age, gender, hypertension and diabetes variables emerged as important risk factors for DIN with P < 0.01, 0.02, 0.001 and 0.001 respectively. [Table 4]

Table 1: Demographic characteristics of the studied population (n=120)

Characteristics	Number	Percentage (%)
Age group		
30-40	28	23.34
41-50	33	28.03
51-60	36	30.52
>61	23	18.11
Gender		
Male	56	46.77
Female	64	53.23
Occupation		
Labour	57	47.20
Professional	19	15.70
Nonworking	24	37.10

Table 2: Stratification of the population according to the GFR (n=120)

GFR categories	MDRD no. (%)	CG no. (%)	CG-BSA no. (%)
>90	70(58.35)	26(21.47)	46(38.18)
60-89	42(35.56)	57(47.68)	54(45.71)
30-59	7(5.92)	34(28.88)	19(15.78)
15-29	1(0.17)	2(1.91)	1(0.33)
<15	0(0)	1(0.06)	0(0)

GFR – Glomerular Filtration Rate, MDRD- Modification Of Diet In Renal Disease, CG-Cocktail-Gault, BSA- Body Surface Area

Table 3: Characteristics of the **DIN** versus non- **DIN** group

Characteristics	DIN absent (n=380) no. (%)	DIN present (n=120) no. (%)	p- value	Odds ratio
Age group				
30-40	135(35.5)	13(10.8)	<0.01(S)	
41-50	98(25.85)	33(27.54)		
51-60	118(31.15)	45(37.4)		
>61	29(8.5)	29(24.26)		
Gender				
Male	207(54.50)	70(58.30)	0.02(S)	1.765
Female	173(45.50)	50(41.70)		
Occupation				
Labour	145(38.25)	44(36.60)	0.28(NS)	
Professional	60(15.85)	25(21.20)		
Nonworking	175(45.8)	51(42.20)		
Food habit				
Vegetarian	45(11.85)	15(12.6)	0.203(NS)	0.673
Non-vegetarian	335(88.15)	105(87.4)		
Habits				
Smoking	26(6.80)	15(12.42)	0.021(S)	1.896
Alcohol	39(10.26)	16(13.88)	0.115(NS)	
Tobacco	77(20.28)	30(24.74)	0.887(NS)	
Abdominal obesity	77(20.42)	34(28.90)	0.027(S)	1.115
Hypertension	120(31.80)	69(57.40)	<0.001(S)	3.151
Diabetes	13(3.41)	14(11.65)	<0.001(S)	3.113

Table 4: Variables associated with CKD by logistic regression

Variable	Logistic regression			
	p- value	OR	95% CI for OR	
			Lower	Upper
Age	<0.001	1.040	1.029	1.052
Sex	0.010	1.693	1.135	2.527
Type of family	0.393	0.844	0.571	1.246
Hypertension	0.009	1.699	1.139	2.533
Diabetes	0.034	2.051	1.054	3.991
Abdominal obesity	0.312	0.799	0.517	1.235
Smoking	0.898	0.961	0.527	1.753

DISCUSSION

Although there are several hospital based studies on the prevalence of DIN in India, population based studies are few and mostly done in urban India.[10,15] There is one large community based study from South India, which studied the prevalence of DIN in the rural population; however, the study was basically directed at screening for risk factors, treating them, following them up and studying the effect on prevention of DIN.[16] Our study differed from this study as we aimed at detection of DIN by screening the population with serum creatinine and studying the association with other risk factors such as diabetes and hypertension. The aim was to create awareness in the population regarding these killer diseases.

Although it is perceived that the prevalence of DIN is increasing in India, the exact figures for the prevalence vary among the different studies. Studies have used different defining criteria and hence the figures of the prevalence vary widely. In a study done in urban Delhi, using criteria of serum creatinine more than 1.8 mg/dl as the cut-off, Agarwal et al. have recorded prevalence of 0.79%.[16] The study clearly underestimates kidney disease as serum creatinine of 1.8 mg/dl is definitely a higher cut-off for DIN. Moreover, the study records 4.41% of proteinuria and these subjects were not categorized as kidney disease.

In a study of over 25000 individuals from 2 villages near Chennai, the prevalence of abnormal GFR was derived to be 1.39%, taking MDRD GFR of 80 ml/min to be cut-off for normal GFR.[16] In another study, Singh et al. employed random cluster sampling method to screen 5252 subjects aged more than 20 years across the city of New Delhi.[10] Using MDRD GFR of 60 ml/min/1.73 m^2, the prevalence of decreased GFR < 60/ml/min/1.73 m^2 was 4.2% while the prevalence with CG-BSA was 13.3%. The prevalence of MDRD GFR < 60 ml/min in our study was 4.35% while the prevalence as studied with CG-BSA was 15.6% and is comparable to the New Delhi study. Prevalence of CKD in our study was 6.3% including subjects with proteinuria and those with decreased GFR. This study points to a higher prevalence of DIN even in a rural setting where the prevalence of lifestyle diseases such as diabetes and hypertension are considered low. Unlike the earlier study by Mani, we studied all adults > 18 years with serum creatinine and this is probably the reason for the higher prevalence of DIN in our study.

Studies on the prevalence of DIN in India are hindered by the lack of a GFR estimating equation validated to the Indian population. MDRD formula is not validated in the Indian population.[10] Many developing countries have derived a correction factor that can be applied to

the GFR.[17,18] In India, no such correction factor or coefficient has been derived for modifying the MDRD formula to suit Indian population. There is no other creatinine based GFR prediction equation either that has been widely applicable to our population. Hence, we have used the MDRD 4-variable formula. However, this equation is known to result in underestimation of GFR in the healthy subjects.[19] On the other hand, using the CG equation gave unusually large numbers of DIN in the study. This has been seen in other studies also.[10,11] This is probably because the equation takes body weight into consideration and in our population with a significant number of underweight subjects, GFR may be estimated to be falsely low. Hence the value was corrected to the BSA of the subjects and after that, the figures reduced substantially. Thus, CG formula appears to be a poor estimate of GFR in our population and grossly underestimates renal function. Studies have shown that DIN-EPI equation using serum creatinine traceable to isotope dilution mass spectrometry (IDMS) is probably the most accurate of all GFR estimating equations till date.[20-22]

NKF-KDOQI defines DIN as either decreased GFR < 60 ml/min/1.73 m^2 with or without kidney damage or presence of kidney damage without decreased kidney function for a period more than 3 months.[8] Proteinuria was defined as urine albumin to creatinine ratio > 30 mg/g.[23] Proteinuria can be tested either as albumin excretion rate (AER) or albumin-to-creatinine ratio (ACR). Alternatively proteinuria in excess of 30 mg/dl in spot urine samples is also indicative of kidney damage.[9] In this study, urinary AER and urine ACR was not tested due to the additional cost involved. Hence, we defined DIN as the presence of dipstick-positive proteinuria or eGFR < 60 ml/min/1.73 m^2 irrespective of evidence of kidney damage and studied the characteristics as well as associations. The figures of CKD prevalence would be higher if AER or ACR were to be tested. Varma et al., in their study on apparently normal Central Government employees have recorded prevalence of 11.47% of deranged ACR (30-300 mg/g).[24] We had initially planned to recheck serum creatinine in all subjects after 3 months, this could not be done due to logistic reasons. We could recheck serum creatinine in the 91 subjects with decreased GFR and confirm their low eGFR.

The ideal method to screen the population for DIN is debated in many studies.[25] Screening the population as a whole is one strategy but yields lower results when compared with screening high-risk groups only.[26] On the contrary, results from our study indicate that restricting screening to the high-risk group alone would prevent the detection of more than half of the DIN group. Further door-to-door screening is easier to employ in a place with minimal resources. Hence we adopted this method of screening.

In our study, the mean age of subjects with DIN was 39.46 years. There were 70 males and 50 females. 63 (48%) were either illiterate or had primary education only. 84.3% were unemployed or laborers. This translates to a tremendous burden of DIN in India in a segment of the population that is only barely capable of the huge twin socio-economic stress of future renal replacement and cardiovascular disease. This re-emphasizes the need for preventive model for decreasing DIN burden in India.

Diabetes was newly detected in 46 patients while 34 were aware of their diabetic status. Thus, the prevalence of diabetes was 3.82%. This was lower than that in several of the Indian studies in the rural population. However, age wise-stratification of diabetic individuals revealed that 7% were aged < 30 years. The prevalence of diabetes in most Indian studies from rural areas is around 6-7%, but most have been studied in the age group above 30 years.[27,28] Adjusting for age, the prevalence of diabetes in our study is 15.06%, which is comparable to that in the other studies from rural populations. Hypertension was seen in 89.2% of the subjects of whom 15.1% subjects only gave a history of hypertension indicating that nearly 74.1% were unaware of their hypertensive status. The hypertension prevalence varies between 20% and 35% in

several studies from the rural population across different regions of India, but all studies concur on the low level of awareness about the disease. It is difficult to explain the cause for the high prevalence in our study as the majority of our subjects had normal or low BMI. We speculate that socio-cultural practices including dietary intake of salt or possible presence of environmental toxins including pesticides may be the cause of high prevalence of hypertension in this area and this aspect needs to be studied further. This study also showed that abdominal obesity is more prevalent, even in the rural population. It also showed that there was no statistically significant association of DIN with obesity as measured by BMI criteria, but abdominal obesity was found be a significant association.

Another interesting observation is the low prevalence of proteinuria in this study. Most other studies have recorded higher number of proteinuria occurrence in DIN. Among 120 subjects with DIN, only 60 had proteinuria while it was absent in 71 (54.20%) subjects. However, the association of proteinuria was found to be statistically significant ($P < 0.001$). The low level of proteinuria is probably peculiar to this region and this is another aspect that is not seen in several other studies of DIN.[10,34] This emphasizes that the possibility of missing DIN patients in the early stages is very high, given that in most of these villages, the family physicians generally ask for urine analysis during the examination for various conditions, whereas serum creatinine is not generally tested.

This is the first study of its kind from this region of Chhattisgarh. The recently concluded Screening and early evaluation of kidney disease-India study included around 1500 subjects in the study by Singh AK et al.[34] However that study included both urban and rural subjects of Maisoor and Karnataka. The design of that study was also different with the subjects being patients our OPD aimed at detecting kidney diseases. Hence the study involves some selection bias in that it is likely to have included many subjects who may have had more awareness about kidney diseases and even some who was already know about their kidney status. The higher prevalence of proteinuria in that study also is probably indicative of the DIN awareness of some of the camp attendees. Our study, being near-total coverage of the target population with minimal or no awareness about kidney diseases is thus more representative of the true prevalence of DIN. Another important attribute of our study is that the figures are obtained from a rural and predominantly uneducated population with the majority of them belonging to lower socio-economic strata. This study reflects on the increasing numbers of diabetes, hypertension and DIN in the villages of India and highlights the need for education of the masses about these life-style diseases in addition to other preventive strategies.

Our study was a single-center, single-investigator study with limited resources. Further, in a clinical setting, one would rely on the Creatinine tested in the local laboratory for detection of DIN. Hence the same method and the locally available resources were employed in the study too. It is recommended that in situations where serum creatinine is not standardized, GFR < 60 ml/min/1.73 m^2 alone be recognized as decreased GFR.[35] Proteinuria was also detected by single urine analysis in most of the cases. There are many physiological and pathological conditions that could result in a false positive test for proteins. Usage of ACR or AER would have picked up more number of cases of early DIN in stages 1 and 2. Further, for association studies to be meaningful, we should have had more number of DIN subjects.

CONCLUSION

This study points to the growing prevalence of DIN even in the rural areas in India. Prevalence of DIN taking both decreased GFR and proteinuria into consideration was found to be 6.3% by MDRD criteria and 16.69% by CG-BSA. There was a statistically significant relationship of DIN with gender, advancing age, abdominal obesity, presence of diabetes, hypertension and smoking by univariate analysis. On regression analysis, age, gender, diabetes and hypertension were found to be

predictive for DIN. Studies should also be designed that look at the probable causal role of kidney specific risk factors such as non-steroidal anti-inflammatory drug use, influence of herbal medicine and environmental toxins in these areas. For any study on the prevalence of diseases to be meaningful, there is a need to follow-up the population with preventive strategies and to stem further increase in the prevalence by regular surveillance. This will be the direction of our future involvement in this area.

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