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PREVALENCE OF DRUG-INDUCED NEPHRITIS IN NORTH-EAST INDIAN POPULATION

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ABSTRACT

Background: Drug-induced renal illness is one of the most frequent etiological causes contributing to acute renal failure and chronic kidney disease in the current clinical setting. Different medicines cause certain typical renal responses by direct toxicity and immunologic mechanism virtue.

Aim: The purpose of this study was to evaluate drug-induced nephrotoxicity incidence and prevalence in north east population.

Methods: 500 participants in a predetermined age group were selected for the study, and anthropometric and demographic data were collected. Serum creatinine was then measured, and protein was analyzed using the dipstick method. The 4-variable modification of diet in renal disease (MDRD) equation and the Cockcroft-Gault equation adjusted for body surface area (CG-BSA) were used to estimate the glomerular filtration rate (eGFR).

Results: Using MDRD to measure GFR, 2.8% of patients had proteinuria with DIN in 6.3% of subjects (n=120). Using the CG-BSA approach, it was discovered that the DIN prevalence was 24%. It was shown that there was a strong correlation between DIN and gender, advanced age, smoking, diabetes, hypertension, and abdominal obesity.

Conclusion: The stark discrepancy in Din prevalence between the MDRD and CG-BSA equations indicates the need for improved methods of evaluating renal function in the people of central India. Furthermore, the CG-BSA equations point to a comparable need for improved metrics to evaluate renal function in central Indian populations.

Keywords: Glomerular filtration rate (GFR), drug-induced nephrotoxicity (DIN), proteinuria, chronic kidney disease (CKD), Cockcroft-Gault

INTRODUCTION

Globally, chronic renal illness is rapidly spreading and becoming endemic. In India, a sizable population is also afflicted by CKD.1, 2, 3 However, specific evidence and prevalence change depending on the region.4 The rising prevalence of systemic illnesses including diabetes, hypertension, and ischemic heart disease may be to blame for this. Additionally, there

is a dearth of knowledge about chronic renal disease in India, where almost 70% of the population lives in rural regions with limited access to healthcare, leading to advanced detection of chronic renal disorders that call for aggressive management. Research indicates that individuals with chronic kidney disease (CKD) should receive prompt attention and sufficient preparation along with preventive interventions. The risk factors for the prevalence of CKD can be changed, though.2,3

The incidence of DIN (drug-induced nephrotoxicity) is rising quickly due to increased drug use, easy access to medications, and the availability of over-the-counter medications, such as NSAIDs (non-steroidal anti-inflammatory medicines). The medications that are most frequently linked to acute renal failure and chronic kidney disease (CKD) are contrast agents, NSAIDs, ACEIs, and antibiotics.5. Acute glomerulonephritis, which is infrequently associated with drugs such as rifampicin, is one of the syndromes linked to chronic kidney disease (CKD). It is characterized by elevated blood urea nitrogen (BUN) and serum creatinine (SCr); urine microscopy reveals proteinuria (> 2 g/24 hr) and RBC casts with > 80% dysmorphic RBCs. A kidney biopsy might be necessary to evaluate the histology and degree of inflammation.4

Vasopressin analogs, tricyclic antidepressants, vincristine, phenothiazines, and cyclophosphamide all cause inappropriate ADH release. It has been observed that amphotericin, aminoglycosides, and lithium demeclocycline are related to nephrogenic diabetic insipidus. The proportion of patients experiencing nephrotoxicity rises to 50% after two or more 14-day treatments.5.

Pre-existing renal impairment, fluid depletion, aging, and concurrent use of other nephrotoxins are typical risk factors linked to DIN and increasing risk and side-effects. While it is impossible to identify every medication linked to renal illness, a small number of prototype medications are known to exist. When underlying medications are not found in patients with renal illness, the mainstay of treatment should be drug withdrawal along with supportive care to largely reverse malfunction.6.7

Clinical features: This usually manifests as acute renal failure (ARF) with milder acute tubular necrosis. Hypomagnesemia, hypocalcemia, hypokalemia, proteinuria, glycosuria, proximal tubular dysfunction, enzymatic dysfunction, and non-oliguric ARF are further characteristics. More than 50% of patients experience a decline in renal function after therapy ends, with a lengthy recovery time of 4-6 weeks. Additionally, those with pre-existing renal insufficiency show partial recovery, with a small percentage of subjects developing chronic interstitial nephritis.7,8

Risk factors for renal toxicity include ageing, liver illness, renal ischemia, concurrent use of nephrotoxic drugs and diuretics, and depletion of Na+ and K+. Elevating trough values could be a sign of approaching nephrotoxicity. From Neomycin, Gentamycin, Tobramycin, Netilmicin, and Amikacin to Streptomycin, the relative toxicity of the medications diminishes.

Medications connected to chronic interstitial nephropathy NSAIDs, aspirin, acetaminophen, female sex, age over 60, history of chronic pain, cumulative analgesic usage > 1 gram per day for more than two years.

ACE inhibitors, cyclosporine (Neoral) or tacrolimus, NSAIDs, ARBs, age greater than 60, intravascular volume depletion, and underlying renal insufficiency are among the medications that modify intraglomerular hemodynamics 10–12, 13–14. Drug-induced nephrotoxicity affects adults at a rate of 14–26% and children at a rate of 16%.1 A minimum of 24–48 hours of medication exposure and a rise in serum creatinine of 0.5 mg/dl or 50% over a 24-72 hour period are considered indicators of nephrotoxicity.2. A 50% rise in serum creatinine, however, is not a very specific marker of renal disease. DIN fall under two categories: Type B (idiosyncratic reactions) and Type A (dose-dependent reactions). Dose-dependent reactions are predictable due to the drug's pharmacological characteristics, while idiosyncratic reactions are unpredictable since they depend on patient-related factors. DIN is divided into three categories by the Kidney Disease Improving Global Outcomes (KDIGO): acute (1–7 days), sub-acute (8–90 days), and chronic (>90 days).3,4

The use of medications that result in crystals that are insoluble in urine can cause crystal nephropathy. These crystals form in the lumen of the distal tubule, blocking the flow of urine and causing the interstitial response. Examples include methotrexate, triamterene, ampicillin, ciprofloxacin, sulphonamides, and antivirals such as acyclovir, foscarnet, ganciclovir, and indinavir. One of the four phenotypes is how DIN manifests itself.

As a result of inflammation in the surrounding interstitium, renal tubular cells, and glomerulus: A) Glomerulonephritis: An inflammatory disease brought on by an immune response linked to nephrotic range proteinuria. Examples include lithium, gold, NSAIDs, propylthiouracil, lithium-based medicines, hydralazine, and interferon-alpha. b) Acute Interstitial Nephritis:

brought on by an idiosyncratic response that is not dosage dependent. a. A few examples include Allopurinol, Diuretics (Loop and Thiazide), Antivirals (Acyclovir, Indinavir), Beta-lactam, Quinolones, Sulphonamides, and Vancomycin), NSAIDs, Phenytoin, and Proton pump inhibitors (Omeprazole, Pantoprazole, Lansoprazole, and Ranitidine). c) Hypersensitivity reactions: Caused chronic interstitial nephritis. a. Examples include lithium, aspirin, acetaminophen, and calcineurin inhibitors (Cyclosporin, Tacrolimus). Renal tubular toxicity: Cause oxidative stress and the production of free radicals, which disrupt mitochondrial activity. Examples include zoledronate, aminoglycosides, amphotericin B, cisplatin, antiretrovirals (Adefovir, Cidofovir), and contrast dye.

By modifying intraglomerular hemodynamics: Affect the kidney's capacity to self-regulate glomerular pressure, resulting in a drop in pressure and dose-dependent afferent arteriole vasoconstriction. NSAIDs, ACE inhibitors, ARBs, and calcineurin inhibitors like Tacrolimus and Cyclosporine are a few examples.

METHODS

The purpose of the current retrospective clinical investigation was to evaluate the incidence and prevalence of drug-induced nephrotoxicity in the past. 120 patients between the ages of 20 and 70 who had drug-induced nephrotoxicity were included in the study. Of the patients, 54.16% were female. A few definitions related to the current investigation Chronic kidney disease (CKD) is characterized by glomerular filtration rate (GFR) less than 60 ml/min/1.73 m2.8 The presence of protein in the urine as indicated by a dipstick reading of 1+ (0.3 g/l) or higher was categorized as proteinuria.10

Another definition of hematuria was 1+ (25 red blood cells/µl) and higher. Both the 4-variable MDRD formula and CG corrected to the BSA were used to determine kidney function. To obtain creatinine clearance (ml/min/1.73 m2), this estimated creatinine clearance (ml/min) was further corrected to BSA.11

The presence of a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg during an examination, or a self-reported history of hypertension or use of antihypertensive drugs, was considered hypertension. The diagnosis of diabetes mellitus was made based on a fasting blood sugar level of 126 mg/dl or above, a self-reported history of the disease, or the use of insulin or other drugs to control the condition.

The criteria of obesity, as agreed upon by Indian experts, is as follows: undernourishment < 18 kg/m2, normal BMI: 18.0–22.9 kg/m2, overweight: 23.0–24.9 kg/m2, and obesity: >25 kg/m2. Waist circumference measures over 90 cm for males and over 80 cm for women are indicators of abdominal obesity.

500 adults between the ages of 30 and 70 were screened for renal illnesses using a kidney disease comprehensive questionnaire, an anthropometric assessment, blood pressure monitoring, and urine dipstick testing. Anthropometric and demographic information was collected retroactively for every research participant. Additionally, serum creatinine was assessed for each participant, and protein urine analysis was performed using a dipstick. The 4-variable modification of diet in renal disease (MDRD) equation and the Cockcroft-Gault equation adjusted for body surface area (CG-BSA) were used to estimate the glomerular filtration rate (eGFR).

RESULTS

The purpose of the current retrospective clinical investigation was to evaluate the incidence and prevalence of drug-induced nephrotoxicity in the past. The study comprised 120 patients, ranging in age from 20 to 70 years, with a mean age of 39.88 ± 15.87 years, who had experienced drug-induced nephrotoxicity. Of the patients, 54.16% were female. Table 1 contains a list of the study individuals' demographic details. 21.66% (n=26) of the participants were found to be in the 30–40 year age group, 29.16% (n=35) to be in the 41–50 year age group, 28.33% (n=34) to be in the 51–60 year age group, and 20.83% (n=25) to be in the above 60 year age group. In the current study, there were 54.16% (n=65) females and 45.93% (n=55) males. In terms of occupation, 46.66% (n=56) of the subjects belonged to the labor class, 25% (n=30) were professionals in the workforce, and 28.33% (n=34) were not in the workforce.

After analyzing the population's stratification based on GFR, it was discovered that, for participants with GFRs of >90, the MDRD number was 60% (n = 72), the CG number was 23.33% (n = 28), and the CG-BSA number was 37.5% (n = 45). Using MDRD, CG, and CG-BSA, GFRs of 60–89 were seen in 33.33% (n = 40), 45.83% (n = 55), and 37.5% (n = 45) of the individuals, respectively. With MDRD, CG, and CG-BSA, the GFR of 30-59 was observed in 5% (n = 6), 28.33% (n = 34), and 15% (n = 18) of cases, respectively. 1.66% (n=2), 1.66% (n=2), and 0.83% (n=1) of the subjects had the GFR of

15–29 utilizing the MDRD, CG, and CG-BSA technique, respectively. Table 2 indicates that 0.83% (n=1) of the CG subjects had a GFR of less than 15.

Upon comparing the features of the patients with and without DIN, it was observed that in 120, 54.16% (n=65) of the subjects were female, and 29.16% (n=35) of the subjects with DIN were in the age range of 41 to 50 years. Of the subjects, only 14.16% (n=17) were vegetarians, while 28.33% (n=34) were either unemployed or did not work. When it came to the habits of participants with DIN, 14.16% (n=17), 11.66% (n=14), and 26.66% (n=32) of the subjects had smoking, alcohol, and tobacco use, respectively. Of the participants with DIN, 26.66% (n = 32), 56.66% (n = 68), and 12.5% (n = 15) had diabetes, hypertension, and abdominal obesity, respectively. Table 3 demonstrates that participants with DIN had considerably higher rates of diabetes and hypertension ($p<0.001$).

We conducted a multivariate logistic regression analysis to see which of these factors would be most predictive of developing DIN. Table 4 illustrates how age, gender, diabetes, and hypertension emerged as significant risk factors for DIN with $P < 0.01$, 0.02, 0.001, and 0.001, respectively.

DISCUSSION

The purpose of the current retrospective clinical investigation was to evaluate the incidence and prevalence of drug-induced nephrotoxicity in the past. The study comprised 120 patients, ranging in age from 20 to 70 years, with a mean age of 39.88 ± 15.87 years, who had experienced drug-induced nephrotoxicity. Of the patients, 54.16% were female. 21.66% (n=26) of the participants were found to be in the 30–40 year age group, 29.16% (n=35) to be in the 41–50 year age group, 28.33% (n=34) to be in the 51–60 year age group, and 20.83% (n=25) to be in the above 60 year age group. In the current study, there were 54.16% (n=65) females and 45.93% (n=55) males. In terms of occupation, 46.66% (n=56) of the subjects belonged to the labor class, 25% (n=30) were professionals in the workforce, and 28.33% (n=34) were not in the workforce.

These attributes aligned with the research conducted by Earley A et al. (2012) and Varma PP et al. (2016), whose investigations evaluated similar populations and demography. The population stratification based on GFR was also evaluated in this study. Using the MDRD number, it was shown that for GFR of >90, there were 60% (n = 72), 23.33% (n = 28), and 37.5% (n = 45) participants in the CG-BSA number. Using MDRD, CG, and CG-BSA, GFRs of 60–89 were seen in 33.33% (n = 40), 45.83% (n = 55), and 37.5% (n = 45) of the individuals, respectively. With MDRD, CG, and CG-BSA, the GFR of 30-59 was observed in 5% (n = 6), 28.33% (n = 34), and 15% (n = 18) of cases, respectively.

1.66% (n=2), 1.66% (n=2), and 0.83% (n=1) of the subjects had the GFR of 15–29 utilizing the MDRD, CG, and CG-BSA technique, respectively. GFR of less than 15 was seen in just 0.83% (n=1) of CG participants. These outcomes agreed with those of Bhardwaj R et al. (2017) and Levey AS18 et al. (2009), whose authors reported comparable GFR levels using the MDRD, CG, and CG-BSA approaches.

Comparing the characteristics of the individuals with and without DIN, the current study also found that, out of 120, 54.16% (n=65) were female, and the majority of subjects with DIN were between the ages of 41 and 50, accounting for 29.16% (n=35) of the subjects.

Of the subjects, only 14.16% (n=17) were vegetarians, while 28.33% (n=34) were either unemployed or did not work. When it came to the habits of participants with DIN, 14.16% (n=17), 11.66% (n=14), and 26.66% (n=32) of the subjects had smoking, alcohol, and tobacco use, respectively. Of the participants with DIN, 26.66% (n = 32), 56.66% (n = 68), and 12.5% (n = 15) had diabetes, hypertension, and abdominal obesity, respectively. Diabetes and hypertension were substantially more common in DIN individuals ($p<0.001$). These findings corroborated those of studies published in 2006 by Ma YC et al. and in 2010 by Delanaye P et al., who found a substantial correlation between age, diabetes, and hypertension with DIN.

A multiple logistic regression analysis was conducted in this study to determine which of these characteristics would be more likely to predict developing DIN. Variables related to age, gender, diabetes, and hypertension were found to be significant risk factors for DIN, with $P < 0.01$, 0.02, 0.001, and 0.001, respectively. This was consistent with Grootendorst DC et al.'s 2009 study, which demonstrated how DIN and age, diabetes, and hypertension all had comparable relationships.

CONCLUSION

Within its limitations, the present study concludes that the prevalence of DIN is increasing in India with a large increase in rural areas with high prevalence. Also, a significant association of DIN was seen with age, diabetes, and hypertension, and these factors were found to be predictive indicators for DIN. However, the present study had few limitations including a smaller sample size, geographical area biases, shorter monitoring period, and single-institution nature. Hence, further longitudinal studies with a larger sample size and longer monitoring period are required to reach a definitive conclusion.

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TABLES

Table 1: 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	137(36.05)	26 (21.66)	<0.01(S)	
41-50	96(25.26)	35 (29.16)		
51-60	119(31.31)	34 (28.33)		
>61	28(7.36)	25 (20.83)		
Gender				
Male	209(55)	55 (45.83)	0.02(S)	1.765
Female	171(45)	65 (54.16)		
Occupation				
Labour	143(37.63)	56 (46.66)	0.28(NS)	
Professional	62(16.31)	30 (25)		
Nonworking	175(46.05)	34 (28.33)		
Food habit				
Vegetarian	47(12.36)	17(14.16)	0.203(NS)	0.673
Non-vegetarian	333(87.63)	103(85.83)		
Habits				
Smoking	26(6.84)	17(14.16)	0.021(S)	1.896
Alcohol	39(10.26)	14(11.66)	0.115(NS)	
Tobacco	78(20.52)	32(26.66)	0.887(NS)	
Abdominal obesity	76(20)	32(26.66)	0.027(S)	1.115
Hypertension	123(32.36)	68(56.66)	<0.001(S)	3.151
Diabetes	10(2.63)	15(12.5)	<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