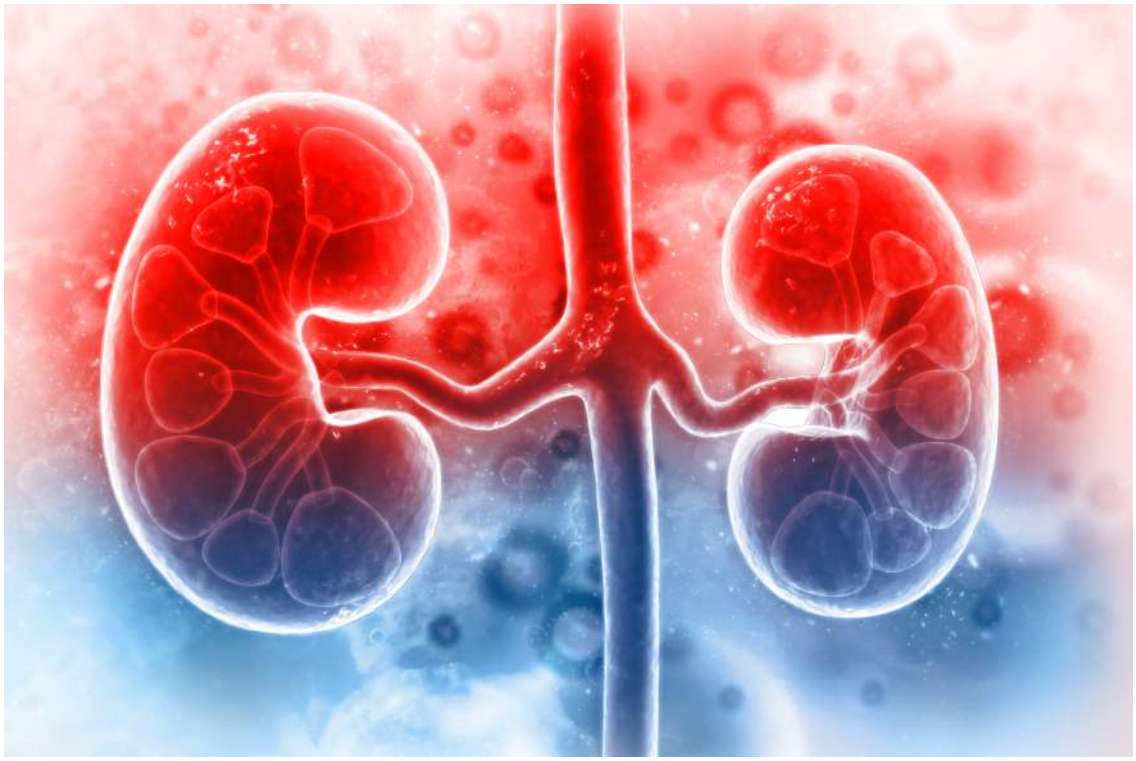
PREVALENCE OF CHRONIC KIDNEY DISEASE IN SEVERELY EXPOSED COHORT POPULATIONS IN BHOPAL



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Prevalence of Chronic Kidney Disease in severely exposed cohort populations in Bhopal

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Introduction:

Chronic Kidney Disease (CKD) is a condition defined as decreased kidney function and/ or kidney damage persistent for at least 3 months[1].. The global prevalence of CKD in general population is reported to be 14.3% (95% CI 14.0 -14.5) of which over 90% are in initial stages of CKD[2]. CKD, even in its earlier stages, is associated with an increased risk of mortality, cardiovascular disease, end stage renal disease (ESRD), fractures, bone loss, infections, cognitive impairment, and frailty. Though sometimes CKD is caused by primary kidney disease, in majority of cases, it is associated with medical conditions, such as diabetes and hypertension which can be controlled effectively with prompt treatment. Therefore, screening for CKD is recommended to reduce complications of CKD and its associated health conditions through timely and prompt treatment[1,3].

In the intervening night of 2/3 December, 1984 about 40 tonnes of mixture of toxic gases leaked out from the pesticide manufacturing plant of Union Carbide India Limited, Bhopal. This accident killed thousands of people and left about 0.5 million population exposed to toxic gases and resultant health problems. ICMR, through Bhopal Gas Disaster Research Centre, Bhopal, carried out a long term population based epidemiological study on health effects of toxic gas exposure (1985-1994) on a cohort of 62,706 exposed and 13,526 unexposed people. The cohort population was surveyed six monthly for morbidity profile and mortality. The findings revealed that a majority of the survivors of gas exposure suffered from multi-system morbidities particularly the respiratory, ophthalmic and gastrointestinal systems[4]. This study later continued under Centre for Rehabilitation Studies, Govt of M.P. (1996-2010) and is still being continued under NIREH since 2011. Results show that gas exposed survivors are reporting higher morbidities compared to unexposed population, especially that of respiratory and ophthalmic systems[5]. The issue of perceived higher prevalence of CKD in the gas exposed survivors has been raised from time to time which needs to be investigated.

The proposed study will investigate the prevalence and associated socio-demographic factors of CKD in Bhopal population and explore correlation, if any, between gas exposure and CKD. Total 215 severely gas exposed from the cohort maintained under the ongoing long-term population based epidemiological study by NIREH will be studied through structured

questionnaire, clinical examination and investigations of urine albumin, urine sugar along with serum creatinine, haemoglobin and random blood glucose. On the basis of estimated glomerular filtration rate (eGFR) and albuminuria findings, prevalence of CKD and its stages will be defined in severely gas exposed individuals along with exploration of socio-demographic determinants of CKD.

Objectives

1. To study the prevalence of chronic kidney disease in the severely exposed cohort population of Bhopal

2. To explore socio-demographic factors associated with chronic kidney disease in Bhopal

Existing knowledge

Bhopal (average height between 472 and 630 meters above the mean sea level; longitude 77º12' – 77º40' E eastern, latitude 23º07' -23º94' N) covers a total area of 2,772 sq. km which is 0.9 percent of the total area of state. The new and old city taken together; the spread of Bhopal city is East-West. As per 2011 census the population of Bhopal was 23,71,061[6,7].

Global CKD prevalence

The known risk factors for CKD include; older age, ethnic origin, hypertension, diabetes mellitus, obesity, high serum cholesterol levels, family history of CKD[1,2]. Worldwide more than 1.4 million individuals with end-stage renal disease require renal replacement therapy with dialysis or transplantation, with 8% annual growth[8]. According to the 2013 Global Burden of Disease study, 956 200 people were estimated to have died from CKD, and reportedly there is 134% increase from 1990, one of the largest rises among the top causes of death[9]. A study carried out by Ene-Iordache *et al*. in 2016, in 12 countries from six regions of the world *viz*. Bangladesh, Bolivia, Bosnia and Herzegovina, China, Egypt, Georgia, India, Iran, Moldova, Mongolia, Nepal, and Nigeria, reported 14.3% (95% CI 14.0 – 14.5) overall prevalence of CKD in general population cohorts (Adjusted for country, ethnic origin and sex). The data was analysed from screening programmes in these countries, matching eight general and four high-risk population cohorts collected in the ISN-KDDC database[2].

Indian CKD prevalence

A study in Delhi and Chennai using random, multistage cluster sampling reported 7.5% prevalence of CKD[10]. More recently, Ene-Iordache et al. (2016) reported the prevalence of CKD in India as 16.8%[2]. Early detection of CKD is important because, the prevalence of CKD is high, CKD has numerous and serious adverse health outcomes and CKD has known risk factors which can be controlled at early stage[1]. On the other hand ESRD requires expensive renal replacement therapy. Because of the scarcity of resources, only 10% of the Indian ESRD patients receive any renal replacement therapy[11]. In Bhopal (MP) Modi and Jha (2006) carried out a longitudinal study for 4 consecutive calendar years (2000-2006) that identified the incidence of end stage renal disease based on 572,029 subjects residing in 36 of 56 wards of

Bhopal. Study reported average crude and age-adjusted incidence rates of ESRD to be 151 and 232 per million populations, respectively. Diabetic nephropathy was found to be the leading cause of ESRD. This study provided the first population-based ESRD incidence data from India revealing it to be higher than previously estimated[11]. Another study In India, representing major centers, both form the public and private sectors, from all parts of the country, was carried out by Rajpurkar *et al*. in 2011. The study concluded that diabetic nephropathy was the commonest cause (31%), followed by CKD of undetermined etiology (16%), chronic glomerulonephritis (14%) and hypertensive nephrosclerosis (13%). About 48% cases presented in Stage V were younger than those in Stages III-IV[12].

Morbidity profile of gas exposed survivors in Bhopal

Bhopal gas tragedy in Dec 1984 exposed nearly 63% (about 6 lakhs individuals) of the then population of Bhopal residing in 36 wards to varying degrees of adverse effects of toxic gases and immediately killing over 3,000 people.. ICMR carried out a long term population based epidemiological study on health effects of toxic gas exposure (1985-1994) under the ambit of erstwhile Bhopal Gas Disaster Research Centre (BGDRC) to document the immediate and long term effects on the exposed population[5]. The findings revealed that a majority of the gas exposed survivors suffered from multi-system morbidities belonging particularly to respiratory, ophthalmic and gastrointestinal systems. The immediate morbidity was about 96-99% for both pulmonary and ophthalmic involvement in the three areas while 74%, 48% and 14% persons suffered with gastrointestinal symptoms in severely, moderately and mildly exposed areas respectively. Any morbidity was observed to be consistently higher in affected areas as compared to control areas. The death rates were higher, especially in persons above 45 years of age, in the exposed areas than in control areas throughout the 10 years period of observation. The higher mortality observed in the initial years in the severely affected areas gradually declined and nearly touched the local/national level subsequently[5].

Subsequently, this population based long term study was continued (1996-2010), using the same methodology, under the Centre for Rehabilitation Studies (CRS), Government of Madhya Pradesh by following a cohort of 34,480 exposed (10,816 persons from severely affected areas, 14,137 persons from moderately affected areas and 9,527 persons from mildly affected areas) individuals and 7,990 unexposed persons from control areas which were the

part of the original cohort[4]. The study revealed a decreasing trend in mortality rate with the passage of time and was below the national urban death rate between 2002-2009 across all age groups. The main cause of mortality among gas exposed as well as unexposed population was respiratory. Morbidities in affected areas were found to be higher than the control areas throughout. Any morbidity though recorded a decreasing trend in affected areas yet remained always above the control area fluctuating under 23%, 20%, 17% in severely, moderately, and mildly affected areas respectively and 8% in control areas since 1999. Similarly, respiratory, and ophthalmic morbidities remained below 20% in affected areas since 1988 compared to below 4% in control areas while GIT morbidities remained below 6% in affected areas in comparison to 2.4% in control areas[4].

Looking in to the gap of availability of incidence and prevalence rates of the morbidity related to chronic kidney disease in gas exposed survivors, there is a need to investigate this aspect. Hence the proposed study will establish the prevalence of CKD and its associated socio-demographic factors in severely gas exposed population in Bhopal

Preliminary work done by the Investigator on this problem:

- Localities and households falling under gas exposed and un-exposed area has been identified from the registered cohort of the ongoing long-term population based epidemiological study, of NIREH.
- Study instrument has been prepared.

Methodology

Study subjects

Study subjects (severely exposed) were among the individuals registered under the currently maintained cohort of the Long-Term Epidemiological Study On Health Effects Of Toxic Gas Exposure who were followed up during the 51st survey (July-Dec 2015). Currently maintained cohort size comes to about 30,981 individuals (24,461 gas exposed and 6,520 unexposed)

Sample size

The sample size has been determined on the basis of 16.8% prevalence of CKD in India reported by Ene-Iordache *et al* (2016)[2]. The sample size has been calculated by considering the prevalence as 16.8 % with margin of error 5% with desired confidence level of 95%.

$$\text{Sample size } n = \frac{_{1-\alpha/2}Z^2 \quad P(1-P)}{d^2} = 215$$

Random sample of 215 severely exposed survivors need to be studied.

Sampling frame

List of individuals borne before December 1984, covered in the 51st round of morbidity survey under the long-term epidemiological study on health effects of toxic gases NIREH during December 2015 was used to select study subjects. As per the data of 51st round of morbidity survey under NIREH long term epidemiological study the population cohort comprises of 8,274 severely exposed survivors in 1751 families.

Sampling technique

Family was treated as a sampling unit and only one individual (borne before December 1984) in the selected families were recruited in the study. To achieve the required sample size of 215 severely exposed survivors the families were selected from the cohort using systematic random sampling. In severely exposed cohort every 8th family will be included to achieve the required sample size.

Data collection

All eligible members of the original cohort in the identified families were included in the survey after obtaining their written informed consent. Each member will be subjected to a semi-structured questionnaire survey, clinical examination, and collection of urine and blood samples as detailed below.

Socio-demography survey

A semi-structured pretested questionnaire was used by the surveyor to collect socio-demographic information for each subject. Questionnaire was included their socio-demographic status (e.g., age, sex, income and education, occupational history), personal and family health history (e.g., hypertension, diabetes, arthritis and kidney disease) and lifestyle behavior (e.g., smoking, liquor consumption), history of medications with renal side-effects (e.g., corticosteroids, non-steroidal, anti-inflammatory drugs) etc.

Clinical Examination

Clinical examination included general and systemic examination (including hypertension, anemia, edema) along with anthropometric measurements (height, weight) according to standard guidelines. Weight was measured in kg. Subject was asked to step up back ward on to the weighing scale and stand still over centre of the scale to minimum cloths and bare feet. Height was measured in cm. by using stadiometer. Subject will be asked to stand erect against the board. Scapula and buttocks must be connected with vertical individual will be asked to inhale deeply and maintain head and body in same position. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by using a digital sphygmomanometer by taking mean of the three readings taken at an interval of 5 minutes.

Collection of biological samples

Urine sample

Mid stream fresh sample of urine was collected in sterile container from each participant for detection of urine albumin and sugar using multi-sticks on the spot. A person having history or evidence of CKD, hypertension, diabetes or a family history of hypertension,

diabetes and CKD and negative for urine albumin with conventional multi-sticks were also be subjected to semi quantitative urinary micro albumin test using Micral urine strip.

Blood sample

Venous blood (4-6 ml) from each subject was collected in a vacutainer under aseptic condition, by a trained technician for estimation of random blood sugar, serum creatinine and haemoglobin. The sample was collected in plain vacutainer for creatinine, in EDTA vacutainer for haemoglobin and sodium fluoride vacutainer for random blood sugar. The samples were transported to lab in an ice box at 2-8^{o}C) and processed in an IDMS standardized biochemical autoanalyzer (creatinine and sugar) and haematological analyzer (haemoglobin) within 4-5 hours of collection.

Estimation of e-GFR and albuminuria

Kidney dysfunction is indicated by reduced glomerular filtration rate (GFR), while kidney damage is manifested as increased urinary albumin excretion. Estimated GFR or eGFR will be calculated using the following abbreviated MDRD equation[13]

eGFR (ml/min/1.73 m^2) = 175 × standardized Scr−1.154 × age−0.203 × 1.212 [if black] × 0.742 [if female]

Value of e-GFR, thus, obtained will be used for staging the kidney disease as given below[13],[14]

Stage	Description	eGFR (ml/min/1.73 m^2)
G1	Kidney damage with normal or increased eGFR	≥90
G2	Mildly decreased e-GFR	89 – 60
G3a	Mildly to Moderately decreased e-GFR	59 – 45
G3b	Moderately to severely decreased e-GFR	44 – 30
G4	Severely decreased e-GFR	29 – 15
G5	Kidney failure or End Stage Kidney Disease	<15 or on dialysis

Albuminuria will be categorized using the dipstick readings as mentioned in the KDIGO guidelines [14] and given below:

Category	Description	Albumin-creatinine ratio (mg/g)	Corresponding Dipstick reading
A1	Normal or mildly increased	< 30	Nil or Traces
A2	Moderately increased	30-300	+
A3	Severely increased	>300	++ or greater

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuria category (CGA)[13, 14]. Kidney disease will be defined as either decreased eGFR (e-GFR <60 mL/min per 1.73 m^2 i.e. stage G3a and above) or albuminuria category A2 and above (i.e. Albumin creatine ratio > 30mg/g)[2,14]. Subjects found to have kidney disease would again be contacted after approximately 12 weeks to reconfirm low e-GFR and high albuminuria to define chronicity of kidney disease. If there is sustained decreased e-GFR or increased albuminuria after 3 months in the absence of reversible factors, CKD will be diagnosed. The person found to have CKD will be referred to a nephrologist / hospital for further investigations and management.

Data entry and analysis

Field survey data was entered in the computer using Visual fox pro software on the same day. Data analysis was done using IBM SPSS 25.0 (SPSS Inc, Chicago, USA). For all the continuous variables, the results are given in Mean±SD, and for categorical variables as frequency and percentage. To obtain the association of various categorical factors such as socio-economic status, male to female ratio, morbidity patterns according to toxic gas exposure between CKD, chi square test was applied. To determine the risk factors for CKD, multivariate backward conditional Binary logistic regression analysis was used. A p value of ≤0.05 was considered as statistically significant.

Ethical considerations

Patient Information sheet were provided to each subject and informed written consent will be obtained (Annexure). Ethical clearance obtained from Institutional Ethical Committee of NIREH.

Results

The present study was undertaken among 215 participants from the severely gas exposed areas of Bhopal. The age and gender wise distribution of study participants is depicted in Table 1. It can be observed that there were 126 (58.6%) females and 89 (41.4%) males. Most of the males as well as females were in the age group 56-65 years. The mean age of male participants was 55.29 ± 12.3years while that for female participants was 59.07 ± 11.7 years.

Table 1: Age and Gender-wise distribution of study participants

Age Groups	Male		Female		Total	
	Number	%	Number	%	Number	%
30-45	24	26.96	17	13.49	41	19.06
46-55	19	21.34	31	24.60	50	23.25
56-65	29	32.58	48	38.09	77	35.81
66 & Above	17	17.10	30	23.80	47	21.86
Total	89	41.4	126	58.6	215	

Table 2 shows the education al status of study participants according to the gender. It can be observed that 28(31.46%) male were illiterate while 90(71.42%) females were illiterate. Thus, most of the study participants (54.88%) were illiterate. Similarly, only 3.25% study participants were having educational status of graduation or above.

Table 2: Educational status of the study participants

Educational status	Male		Female		Total	
	Number	%	Number	%	Number	%
Illiterate	28	31.46	90	71.42	118	54.88
Primary school	44	49.43	21	16.66	65	30.23
Secondary school	04	4.49	04	3.17	08	3.72
Higher Secondary school	09	10.11	08	6.34	17	7.90
Graduate and above	04	4.49	03	2.38	07	3.25
Total	89	41.4	126	58.6	215	

Table 3 depicts the occupational status of the study participants. Most of the male participants were either casual labourers (41.7%) or unemployed (34.8%) while majority of the females were housewives (85.7%). Overall, 20.46% participants were labourers and 18.13% were unemployed.

Table 3: Occupational status of study participants

Occupation	Male		Female		Total	
	Number	%	Number	%	Number	%
Unemployed	31	34.83	08	6.34	39	18.13
Seller/shopkeeper	16	17.97	03	2.38	19	8.83
Labour	37	41.57	07	5.55	44	20.46
Govt. Employee	03	3.37	-	-	03	1.39
Private employee	02	2.24	-	-	02	0.93
Housewife	-	-	108	85.71	108	50.23
Total	89		126		215	

Table 4 illustrates the marital status of study participants. 96.6%of males and 91.3% of females were married while only 3.4% males were unmarried and 6.5% females were unmarried. Overall, 93.5% study participants were married and 6.5% were unmarried.

Table 4: Marital status of study participants

Marital status	Male		Female		Total	
	Number	%	Number	%	Number	%
Married	86	96.6	115	91.3	201	93.5
Unmarried	03	3.4	11	8.7	014	6.5
Total	89		126		215	

Table 5 depicts the dietary habits of the study participants. Overall, 70.7% study participants were having mixed type of diets which included 24.5% males and 32.5% females while 29.3% were strict vegetarians.

Table 5: Dietary habits of study participants

Dietary habits	Male		Female		Total	
	Number	%	Number	%	Number	%
Vegetarian	22	24.7	41	32.5	63	29.3
Mixed	67	75.3	85	67.5	152	70.7
Total	89		126		215	

Table 6 shows the personal habits of the study participants. More than half of the participants did not have any addition. Among females only one female was current tobacco smoker while 43(34.1%) were tobacco chewers. Among male 22(24.7%) were current tobacco smokers, 34(38.2%) were tobacco chewers while only 1(1.1%) had alcohol drinking habit.

Table 6: Distribution of study participants according to personal habits

Personal habits	Male		Female		Total	
	Number	%	Number	%	Number	%
No addiction	28	31.5	82	65.1	110	51.2
Tobacco smoking	22	24.7	01	0.8	23	10.7
Alcohol habit	1	1.1	-	-	1	0.5
Chewing tobacco	34	38.2	43	34.1	77	35.8
Tobacco smoking as well as alcohol habit	1	1.1	-	-	01	0.5
Tobacco chewing as well as alcohol habit	2	2.24	-	-	02	0.9
All (2+3+4)	1	1.1	-	-	01	0.5
Total	89		126		215	

Figure 1 shows that grading of eGFR among the study participants done in the first stage. None of the participants was in the GFR stage 4 and GFR stage 5 severity of eGFR category. 40(18.6%) participants were in Grade 1 GFR stage which included 23(25.8%) males and 17(13.5%) females. Majority participants (64.7%) were in GFR stage 2 which included 57(67.0%) and 82(65.1%) females. 14.3% participants were in GFR stage 3 which included 8.9% males and 23(18.3%) females. Only 5 (2.3%) participants were in GFR stage 3b which

included one male and four females. Thus, the prevalence of chronic kidney disease was 16.7%. Women had a higher prevalence of chronic kidney disease than did men.

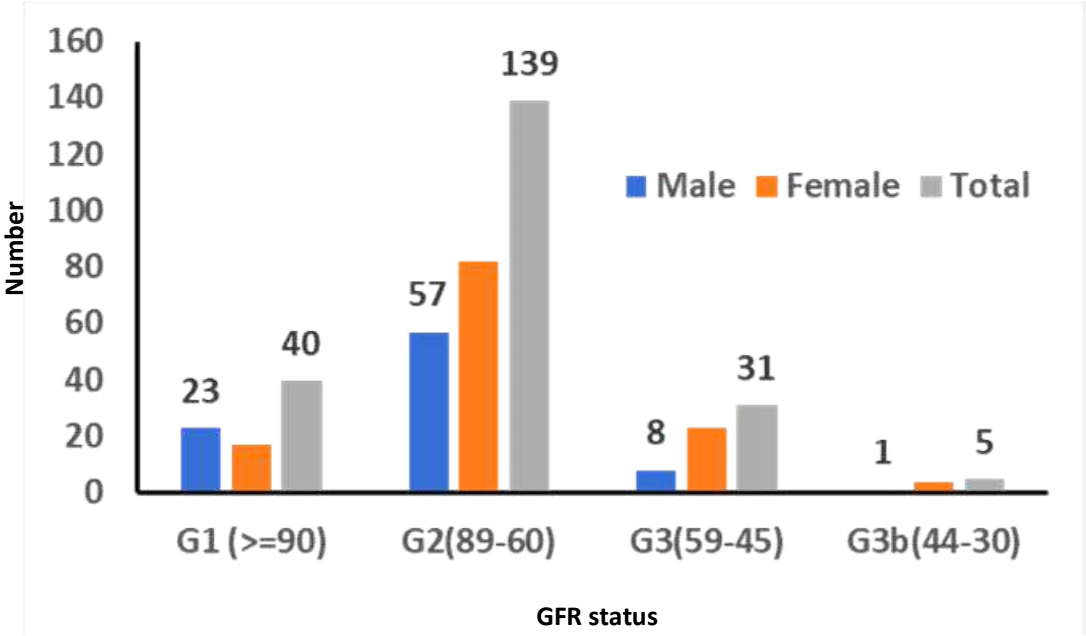

Figure 1: Distribution of study participants according to GFR status done in the first phase

Table 7 describes age wise distribution CKD as per the GFR among the study participants. It can be observed that most of the >65 years age group had higher grades of CKD based on GFR while in the 30-35 years age group majority had milder form of CKD.

Table 7: Age -wise distribution of CKD among study participants

GFR Stage	Age groups (in years)							
	30-45		46-55		56-65		>65	
	N	%	N	%	N	%	N	%
G1 (≥90)	11	26.8	10	20.0	15	19.5	4	8.5
G2(89-60)	26	63.4	37	74.0	50	64.9	26	55.3
G3(59-45)	3	7.3	3	6.0	11	14.2	14	29.8
G3b (44-30)	1	2.4	-	-	1	1.3	3	6.4
Total	41		50		77		47	

Table 8 describes the dietary habit wise distribution of CKD as per the GFR. It can be observed that 18.1% had mild CKD as per GFR out of which 32(82.1%) were on mixed diet while17.9% had vegetarian diet. On the other hand, those having moderate CKD 40% were on mixed diet while 60% were on vegetarian diet.

Table 8: Diet-wise distribution of CKD among study participants

GFR Stage	Dietary habit					
	Vegetarian		Mixed		Total	
	Number	%	Number	%	Number	%
G1 (>=90)	7	11.1	32	21.1	39	18.1
G2(89-60)	45	71.4	94	61.8	139	64.7
G3(59-45)	7	11.1	24	15.8	31	14.4
G3b (44-30)	3	4.7	2	1.3	5	2.3
	63		152		215	

Figure 2 shows the distribution of albuminuria among the study participants. None of the study participant had severe albuminuria. All the males had mild albuminuria while only four females had moderate albuminuria. In the screened populations of albuminuria in phase I was 1.4%.In phase –II, it increased to 1.9%.

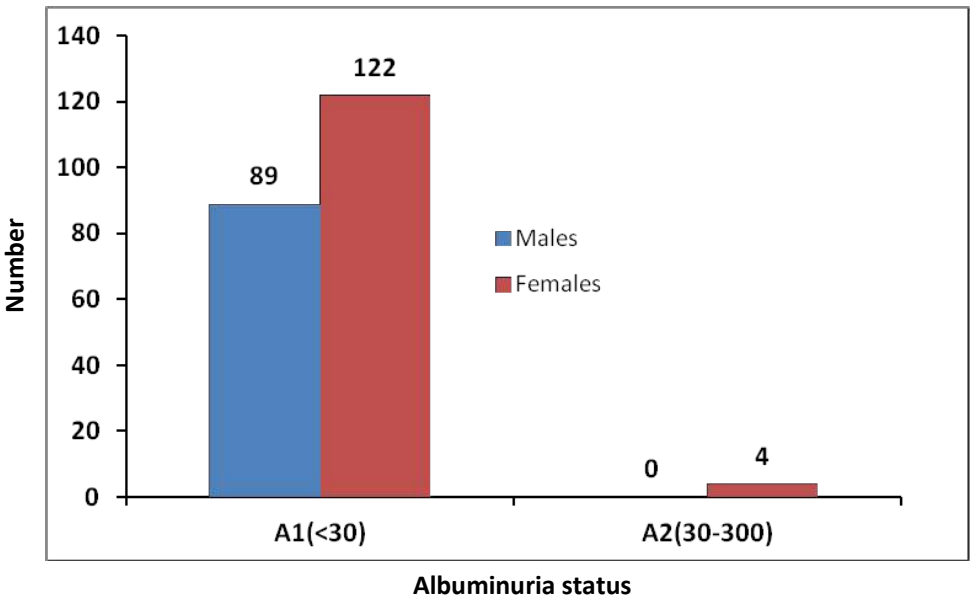

Figure 2: Distribution of albuminuria among study subjects done in the first phase

Figure 3 shows the distribution of GFR status of the study participants done in the second phase. Eight study participants had mildly decreased e-GFR which included six females and two males. Eleven participants had mildly to moderately decreased e-GFR which included seven females and four males. Only one male and seven female participants had moderately to severely decreased e-GFR. The overall prevalence of e-GFR (<60 Ml/min per 1.73 m^2) and albuminuria (≥30 mg/g/litre) was 16.2%. It is statistically insignificant (χ^2=0.58, df=1, p>0.05).

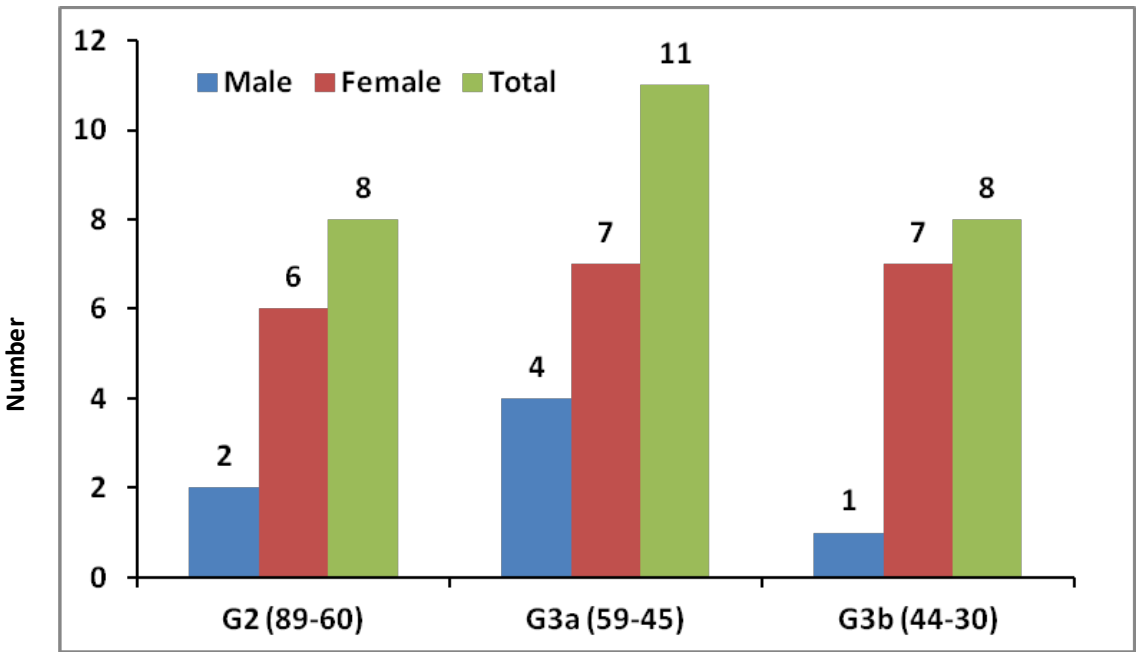

Figure 3: Distribution of GFR status among study subjects done in the second phase

Table 9 shows the distribution of first phase GFR status with albuminuria status as done in the first phase. It can be observed that only four study participants who were in G2 stage of CKD had moderately increased albuminuria while all other study participants who had decreased GFR were either having no or mildly increased albuminuria.

Table 9: GFR vs Albuminuria (Phase –I)

GFR Stage/Category	A1(<30)	A2(30-300)
G1 (≥90)	40	-
G2(89-60)	135	04
G3(59-45)	31	-
G3b(44-30)	05	-

Table 10: Determinants of CKD (n=215) [Univariate Analysis]

Variables	CKD Absent n (%)	CKD Present n (%)	Un adjusted OR (95% CI)	P-Value
Gender				
Male	80 (89.9)	09 (10.1)	Ref	**0.029***
Female	99 (78.6)	27 (21.4)	2.424 (1.08, 5.45)	
Mean age (SD) in years$	56.2 (11.2)	64.2 (13.9)	1.059 (1.03,1.09)	**0.01***
Age group in Years				
35-50	47 (90.4)	5 (9.6)	Ref	
50-65	93 (86.1)	15 (13.9)	1.52 (0.52,4.43)	0.446
> 65	39 (70.9)	16 (29.1)	3.86 (1.29, 11.47)	**0.015***
Education				
Illiterate	92 (78.0)	26 (22.0)	Ref	**0.022***
Literate	87 (89.7)	10 (10.3)	0.407 (0.18, 0.89)	
Occupation				
Unemployed	116 (78.9)	31 (21.1)	Ref	**0.012***
Employed	63 (92.6)	5 (7.4)	0.297 (0.11, 0.81)	
Dietary habits				
Vegetarian	55 (88.7)	07 (11.3)	Ref	0.173
Non-Vegetarian	124 (81)	29 (19.0)	1.838 (0.76, 4.45)	
Smoking				
No	159 (83.2)	32 (16.8)	Ref	0.991
Yes	20 (83.3)	4 (16.7)	0.994 (0.32, 3.11)	
Tobacco (Chewable)				
No	112 (83.6)	22 (16.4)	Ref	0.869
Yes	67 (82.7)	14 (17.3)	1.064 (0.51,2.22)	
BMI				
Underweight	34 (82.9)	07 (17.1)	1.493 (0.57, 3.92)	
Normal	116 (87.9)	16 (12.1)	Ref	0.417
Overweight	26 (72.2)	10 (27.8)	2.788 (1.13, 6.84)	**0.025***
Obesity	03 (50.0)	03 (50.0)	7.250 (1.34, 39.1)	**0.021***
Hypertension				
No	85 (90.4)	9 (9.6)	Ref	
Yes	94 (77.7)	27 (22.3)	2.713 (1.21,6.01)	**0.013***
Diabetes Mellitus				
No	147 (85.5)	25 (14.5)	Ref	0.083
Yes	32 (74.4)	11 (25.6)	2.021 (0.91,4.52)	

*Statistically significant (p<0.05), OR=Odds ratio, CI= Confidence Interval, $ Independent sample t-test

Table 10 shows the univariate analysis of the factors of CKD. It revealed that factors such as gender, age, educational status, occupation, BMI and hypertension were significantly associated with CKD.

Table 11 depicts the individual effect of these factors on CKD after adjusting for other confounders, multiple logistic regression (MLR) was done. Factors with a p-value ≤ 0.1 were included for multivariate analysis. MLR revealed BMI and level of education to be significant predictors of CKD in our study population. Being literate reduced the risk of CKD development by 65% (adjusted OR=0.347, 95% CI=0.13-0.93) when compared with illiteracy. A high BMI increased the likelihood of CKD development as there was a 3.6 times higher risk of CKD development among overweights and 9.3 times higher risk among obese compared to participants with normal BMI. The R2 (Nagelkarke) value of the final model was 0.212, thereby explaining about 21.2% variation of CKD in the study population.

Table 11: Determinants of Chronic Kidney Disease (N=215) [Multivariate Analysis]

Variables included in MLR	**Adjusted OR**	**95% CI**	**P-value**
Gender			
Male	Ref		
Female	1.425	0.463,4.392	0.537
Age group in years			
35-50	Ref		
50-65	0.842	0.260, 2.730	0.774
> 65	1.675	0.488, 6.121	0.435
Education			
Illiterate	Ref		
Literate	0.347	0.13,0.934	**0.036***
Occupation			
Unemployed	Ref		
Employed	0.530	0.135,2.08	0.362
Hypertension			
No	Ref		0.254
Yes	1.684	0.688,4.117	
Diabetes Mellitus			
No	Ref		
Yes	1.528	0.602, 3.877	0.373
BMI			
Normal	Ref		
Underweight	0.995	0.349, 2.833	0.992
Overweight	3.61	1.282, 10.15	**0.015***
Obesity	9.34	1.232, 58.725	**0.030***

*Statistically significant (p<0.05), OR=Odds ratio, MLR=Multivariate Logistic Regression, CI=Confidence Interval

Table 12: Significant determinants of CKD (N=215) [Multivariate Analysis]

Variables	Categories	aOR (95%CI for OR)	P value
Age	Elder (Ref Younger)	4.011(1.714, 9.385)	0.001
Literacy	Illiterate (Ref Literate)	2.647(1.087, 6.445)	0.032
BMI	Under weight (Ref Normal)	1.035(0.394, 2.722)	0.944
	Over weight (Ref Normal)	3.619(1.372, 9.544)	0.009

Developing of CKD was significantly higher in elder (OR=4.011, 95% CI=1.714, 9.385), illiterate (OR=2.647, 95% CI=1.087, 6.445) and overweight (OR=3.619, 95% CI=1.372, 9.544) population.

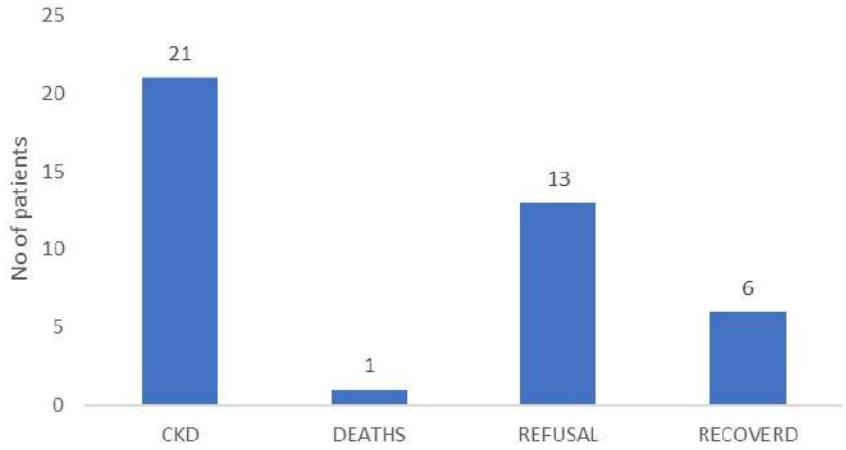

Fig 4: Follow-up details of CKD patients after 3 Months

The cases earlier diagnosed to have CKD were again followed up after a period of three months. It was found that one patient died, 6 had recovered, 13 had refused from the study and 21 are the same from the first follow-up.

Discussion:

CKD is main reasons of global mortality and morbidity. In surveyed population, the overall prevalence of chronic kidney disease was 16.7%. The study has answered the prevalence of CKD in the severely toxic gas exposed cohort population in Bhopal and explores the associated risk factors of this disease. We also detected a high prevalence of smoking (24% -male) and non-Veg diet (70.7%) in covered population which is known as the risks factors for development of CKD.

An earlier cross-sectional study covering 6120 subjects across various Indian cities including Bhopal, reported in 2013nearly similar prevalence (17.2%) of CKD among Indian adults using similar definition and equation used in our study.[15] Further, Ene-Iordache et al.[2] In their cross-sectional study, carried out in 12 lower and middle income countries from six regions of the globe to assess the prevalence and awareness of chronic kidney disease and its risk factors, reported 16.8% prevalence of CKD in India which matches with the prevalence reported in our study.

In our study population, age, BMI and level of education were found significant independent predictors of CKD. The mean age of the study participant in the present study was found to be 57.51±12.072 yrs. A study conducted in Karnataka rural population stated a mean age of 52.73±17.08 yrs, and in our population was 65.03±13.748 yrs[16]. It was observed that higher age group escalated the chances of CKD because of its associated factor as compared to lower age group.

It was seen that having some sort of formal education significantly reduced the likelihood of CKD development as compared to illiterate individuals. Consistent with our findings several studies in western countries[19-23]and in India [17,24,25]reported increased risk of CKD and its outcomes associated with lower level of education. In an observational cohort of 61,457 participants of the Kidney Early Evaluation Program (KEEP) study, it was found that higher educational level was associated independently with a lower prevalence of CKD and lower mortality in those in the cohort who had chronic diseases including CKD.[20]

We found a relationship with BMI and CKD i.e., as the BMI increases the risk of development of CKD also increases. Compared to normal BMI individuals, the likelihood of developing CKD among overweight and obese individuals was 3 times higher. This finding is in

agreement with many studies across a diverse population.[18,26,27]Overweight and obesity results in a wide range of metabolic abnormalities which may affect renal function.[28,29]

Summary and Conclusions

The finding of the current study indicating a 16.7% community-based prevalence of CKD among the severely gas exposed cohort population in Bhopal is, by and large, similar to the national prevalence. This fact should put at rest the concern of perceived higher prevalence of kidney diseases in gas exposed survivors. Though the higher prevalence of diabetes and hypertension may largely be responsible for CKD prevalence in this group of population, it would be prudent to explore the role of gas exposure, if any, in causing CKD or increasing vulnerability to CKD through a well designed case-control study with adequate sample size. There is also a need for primary prevention programmes targeting weight reduction and increasing physical activity at the individual as well as the community level to reduce the burden of CKD and other NCDs. Further, a secondary prevention programme (early screening of renal disease in the at-risk population) with appropriate regional specific guidelines needs to be developed and implemented.

Recommendation

It is recommended that newer study on remaining cohort of gas victims may be undertaken so that they can impart guidelines for health research and treatment.

Limitations of the study

The MDRD equation that we used to estimate GFR has its inherent limitations. It is opined that this equation underestimates GFR among healthy individuals[37]. Moreover, MDRD formulae have not been validated on the Indian population and no correction factor has been derived to modify the equation to suit the Indian population[10,39]. However, the accuracy of the MDRD equation is widely accepted to estimate GFR based on creatinine value in population-based studies[10]. We used spot urine analysis to assess the prevalence of proteinuria which is less sensitive than ACR (albumin to creatinine ratio) or AER (urine albumin excretion)[2,18]. Further, in the present study, the assessment of renal function and damage in participants diagnosed with CKD initially was repeated after 3 months to discriminate between acute and chronic renal disease. However, around 44% (16/36) of subjects with reduced GFR and/or proteinuria, refused to give consent for second-time investigation when contacted after 3 months; these individuals were classified as having CKD based on the results of their initial investigation and this is a major limitation of the study. However, this limitation would have resulted in overestimation rather than underestimation. Moreover, the small sample size was a limitation in ascertaining the risk factors of CKD through logistic regression analysis, as our study did not have enough power to pick up many predictors including proven risk factors such as age, diabetes, hypertension, etc.

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प्रतिभागी सूचित स्वीकृति पत्र (पीआईसीएफ)

(हिन्दी)

प्रोटोकॉल / अध्ययन सं..... प्रतिभागी आई.डी. सं.....

परियोजना का शीर्षक : अत्यधिक गैस प्रभावित व्यक्तियों में चिरकालिक गुर्दा रोग की दर ज्ञात करने के लिए अध्ययन ।

प्रधान अन्वेषक का नाम : डॉ. किशोर कुमार सोनी,

वैज्ञानिक 'बी' (आई.सी.एम.आर.) भोपाल

फोन 0755 2533106 मोबाईल 09425026889

इस सूचना पत्र की सामग्री दिनांक..... को प्रदान की गई थी. मैंने इसे सावधानीपूर्वक पढ़ लिया है / मुझे इस भाषा मे विस्तार से समझा दिया गया है जो मुझे समझ में आती है और मैंने पूरी सामग्री को अच्छी तरह समझ लिया है। मैं पुष्टि करता हूँ कि मुझे प्रश्न पूछने का अवसर दिया गया है। अध्ययन का प्रकार और प्रयोजन तथा इसके संभावित जोखिम / लाभ और अध्ययन पूरा होने की अनुमानित अवधि तथा अध्ययन के अन्य संगत विवरण मुझे विस्तार से समझा दिया गए है।

मुझे बताया गया है कि मेरी भागीदारी स्वेच्छानुसार है और मैं कोई कारण बताए बिना किसी भी समय वापस जाने के लिये पूरी तरह स्वतंत्र हूँ और इस पर मेरी चिकित्सा देखभाल या कानूनी अधिकारों पर कोई प्रभाव नहीं पड़ेगा ।

मुझे पता है कि इस अनुसंधान मे मेरी भागीदारी के बारे में जमा की गई जानकारी सिर्फ / के जिम्मेदार व्यक्तियों द्वारा देखी जाएगी जहां इस अनुसंधान मे मेरे भाग लेने को संगत पाया जाए। मैं इन व्यक्तियों को अपने अभिलेख देखने की अनुमति देता हूँ।

मैं उपरोक्त अध्ययन में भाग लेने के लिये सहमत हूँ।

..... दिनांक : .....

(हस्ताक्षर / बाएं अंगूठे का निशान) स्थान : .....

प्रतिभागी का नाम .....

पुत्र / पुत्री / जीवन साथी .....

डाक का पूरा पता .....

यह प्रमाणित किया जाता है कि उपरोक्त स्वीकृति मेरी उपस्थिति में प्राप्त की गई है।

..... दिनांक : .....

(प्रधान अन्वेषक के हस्ताक्षर) स्थान : .....

(1) गवाह – 1

हस्ताक्षर .....

नाम .....

पता .....

(2) गवाह – 2

हस्ताक्षर .....

नाम .....

पता .....

NIREH, Bhopal

Prevalence of Chronic Kidney Disease in Toxic gas Severely exposed cohort population in Bhopal

A. Individual Proforma

1. LO .No. ☐☐ 2. ICMR No. ☐☐☐☐☐☐ 3. ID ☐☐

4.. Name of the Subject/Participant ..……

……

5. Age ☐☐ 6. Sex ☐ M-1, F-2, T-3

7. Residental Address: ……..

Marital Status	Monthly income	Literacy status	Occupation	Dietary habits	Addiction	Since when (Years)
☐	☐☐☐☐☐	☐	☐	☐	☐	☐☐
Yes - 1 No - 2		No - 1 (Ill Literate) Yes- 2 (Primary) 3 (Secondary) 4-(Hsc.10+2) 5-(UG/PG)	1- Un Employee 2- Seller/Shop keeper 3- Labour 4- Govt. Employee 5- Private Employee 6- House Wife	1- Veg. 2- Non Veg.	1- No Addiction 2- Smoking 3- Alcoholic 4- Gukka/Tobacco 5 - 2+3 6- 3+4 7- All	

Phone number ☐☐☐☐☐☐☐☐☐☐☐

Mobile number ☐☐☐☐☐☐☐☐☐☐

8 . Date of Interview ☐☐☐☐☐☐☐☐

9. Signature of Interviewer……

B. HISTORY OF DISEASE

HISTORY

A. KIDNEY DISEASE ☐

Yes – 1
No – 2

B. Present Morbidity ☐

Yes - 1
No- 2

(Months)

Hypertension ☐☐☐

Diabetes ☐☐☐

Dialysis/RT ☐☐☐

Joint Pain ☐☐☐

Analgesic intake ☐☐☐

Ayurvedic Medication ☐☐☐

C. Physical Examination

A. Height (in cm) ☐☐☐

B. Weight (in kgs) ☐☐☐

C. BP sitting (mmHg)	First	Second	Third	Mean
a) Systolic	☐☐☐	☐☐☐	☐☐☐	☐☐☐
b) Diastolic	☐☐☐	☐☐☐	☐☐☐	☐☐☐

Any other information (not mentioned above) Specify……

D . Laboratory Investigations

A. Urine

1. **Albumin** | | | | | | |
2. **Sugar** | | | | | | |
3. **Microalbumin** | | | | | | |

B. Blood

1. **Creatine** | | | | |
2. **Sugar (Random)** | | | | |
3. **Hb(g%)** | | | | |

C. GFR ml/mt/1.73 | | | |

DIAGNOSIS ……..……..

Any other comment ……

DOCTORS SIGNATURE……..……

DATE | | | | | | | | |

SIGNATURE PI …… **SIGNATURE CO –PI** ……

Comments and any other point ……

……

Original Articles

Prevalence of chronic kidney disease among severely gas-exposed survivors in Bhopal, India

KISHORE KUMAR SONI*, MADHANRAJ KALYANASUNDARAM*, SUSHIL SINGH, SWASTI SHUBHAM, YOGESH DAMODAR SABDE, ANIL PRAKASH, RAJNARAYAN TIWARI

ABSTRACT

Background. The survivors of the 1984 Bhopal gas disaster frequently express concern of them being at higher risk of developing chronic kidney disease (CKD) as a consequence of the long-term health effects of gas exposure. We aimed to estimate the prevalence of CKD among the survivors of severely gas-exposed cohort assembled in 1985 after the Bhopal gas disaster to study the long-term health consequences of gas exposure.

Methods. We did this cross-sectional study with a sample size of 215 systematically selected participants among the severely gas-exposed survivors in Bhopal to estimate the prevalence of CKD. Sociodemographic and relevant past medical history of the participants was obtained using a semi-structured questionnaire and their blood and urine samples were collected. The estimated glomerular filtration rate (e-GFR) was calculated using the Modification of Diet in Renal Disease equation. Those found with reduced e-GFR and proteinuria, suggestive of CKD, were further surveyed after 3 months to differentiate CKD from acute renal damage.

Results. The prevalence of CKD among the severely gas-exposed cohort survivors in Bhopal was 16.7%. Multiple logistic regression analysis revealed that body mass index and level of education were significant predictors of CKD.

Conclusion. The prevalence of CKD among the severely exposed survivors of Bhopal was at par with the national prevalence, putting at rest the apprehension of gas-exposed survivors of being at higher risk of developing CKD.

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INTRODUCTION

Chronic kidney disease (CKD) has emerged as one of the leading causes of global morbidity and mortality with its global prevalence ranging from 8% to 10%.[1–6] The global burden of disease study estimated a 30% increase in CKD prevalence in 2020 compared to 1990.[4] Despite being a global concern, CKD disproportionately affects people from lower-middle-income countries.[5] In India, the prevalence of CKD has increased to epidemic proportions and population-based studies have reported a 4%–20% prevalence of CKD in India.[2,5–10]

CKD in its early stages is considered as one of the major risk factors for fatal and non-fatal cardiovascular events. When it reaches its last stage, also known as end-stage renal disease (ESRD), the financial burden of treatment through dialysis and renal replacement therapy is enormous.[4,5,7,10] In resource-scarce countries such as India, <10% of patients with ESRD have access to any kind of renal replacement therapy.[2,10] Hence, it is appropriate that efforts are focused on prevention rather than treatment.

The Bhopal gas tragedy in December 1984, considered among the worst industrial disasters in the history of humankind, resulted in mortality of 2500–6000 and debilitating over 200 000 people, causing major morbidity and many premature deaths.[11,12] Various clinical and epidemiological studies undertaken subsequently showed a higher prevalence of chronic illnesses such as pulmonary fibrosis, bronchial asthma, chronic obstructive pulmonary disease, keratopathy and corneal opacities in the exposed population.[11,13,14] The Indian Council of Medical Research (ICMR) launched a long-term, population-based epidemiological study in January 1985 to assess the long-term health effects of toxic gases on a cohort of exposed people assembled according to surrogate exposure intensity, i.e. severely, moderately and mildly exposed and this cohort is still being followed up. Although animal studies show acute histopathological changes in renal epithelial cells upon exposure to methyl isocyanate,[11,15] there is a dearth of population-based studies to show the extent of renal disease in the gas-exposed survivors.

Concern has been repeatedly expressed by the gas-exposed survivors and several civil society groups that the prevalence of kidney-related ailments is too high among this vulnerable group as a consequence of the ill-effects of gas exposure in 1984. To address this concern, we did a cross-sectional study to estimate the prevalence of CKD among individuals belonging

to the severely gas-exposed cohort of the ongoing long-term, population-based epidemiological study in Bhopal.

METHODS

Study population

Subsequent to the gas leakage disaster on the intervening night of 2–3 December 1984, the exposed areas were classified into severe, moderate and mild categories based on the immediate mortality occurring between 3 and 6 December 1984. In January 1985, a long-term epidemiological study was initiated to study the health effects of toxic gas exposure by assembling cohorts of 80 021 exposed persons living in areas severely, moderately and mildly affected.[16] The cohort is being followed up for the past 35 years. As per the 51st round of morbidity survey conducted in 2015 by the ICMR-National Institute for Research in Environmental Health (NIREH), there were 8274 severely gas-exposed survivors living in 1751 households in four localities, namely J.P. Nagar, Kazi camp, Kainchichola, and Railway Colony in Bhopal city. The present cross-sectional study was conducted during June–December 2018 involving a selected sample of consenting individuals from this severely exposed cohort.

Sample size and sampling frame

Taking the Indian population prevalence of CKD as 17.2%,[7] the sample size calculated was 214 for the defined population size of 8274 with 95% confidence level and absolute precision of 5% using OpenEpi. The list of households and exposed survivors (born before 3 December 1984) covered in the 51st round of the long-term, population-based epidemiological survey was considered as the sampling frame. With household as a sampling unit, a total of 215 households were selected using systematic random sampling. From each selected household, one survivor was included in the study. If multiple survivors fulfilled the inclusion criteria in a selected household, then one of them was recruited using the lottery method.

Sociodemography and clinical examination

A team comprising a trained physician, research assistant and nurse was involved in the data collection process. Written informed consent was obtained from all the recruited participants. Participants were interviewed in their homes using a semi-structured questionnaire for sociodemographic details, comorbid illnesses such as diabetes, hypertension, arthritis and chronic renal diseases and the history of substance use such as smoking, chewing tobacco and alcohol intake. This was followed by anthropometric measurements, clinical examination and collection of biological samples, i.e. urine and blood for assessing serum creatinine, random blood sugar level and urine protein.

Anthropometric measurements such as height and weight of the participants were taken as per the standard method. Blood pressure was measured using a digital sphygmomanometer (OMRON-Automatic Blood Pressure Monitor Model HEM-7124) in the sitting position. For each individual, the average of three readings, taken at an interval of 5 minutes, was considered as the final value of blood pressure.

Collection and processing of biological samples

Urine. Mid-stream fresh sample of urine was collected in a sterile container from each participant and albumin was assessed using dipsticks (Erba-Uro-dipcheck240).

Blood. Venous blood (4–6 ml) from each subject was collected in two vacutainers under aseptic conditions. The sample collected in plain vacutainer was used for estimating creatinine and the one collected in sodium fluoride vacutainer for estimating random blood sugar. The samples were transported to the laboratory in an icebox at 2–8 °C and processed in an IDMS standardized biochemical auto-analyser (Transasia-EM 200*)* within 4–5 hours of collection.

Calculation of estimated glomerular filtration rate

A reduced glomerular filtration rate (GFR) was considered as the indicator for kidney dysfunction and increased urinary albumin excretion as an indicator of renal damage. Estimated GFR (e-GFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation.[17] Staging of renal disease based on the e-GFR category and categorization of proteinuria using the dipstick readings was done as per the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.[18]

Definition of study variables

Participants with either sustained decrease in e-GFR (e-GFR <60 ml/minute per 1.73 m^2, i.e. stage G3a and above) or proteinuria of category A2 and above (i.e. albumin-to-creatinine ratio [ACR] >30 mg/g) for at least 3 months were defined as having CKD. Participants with reduced e-GFR and proteinuria were contacted again after 3 months to reconfirm low e-GFR and high proteinuria to ensure the chronicity of kidney disease. If the decrease in e-GFR or the presence of category A2 and above proteinuria persisted at the third month of survey in the absence of reversible factors, then the respective participants were diagnosed to have CKD. Such participants were referred for further investigation and management.

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 the use of antihypertensive medication. Participants were defined as having diabetes mellitus when random blood sugar ≥200 mg/dl was detected in collected blood samples along with the presence of symptoms such as polyuria, polyphagia, polydipsia and weight loss or when participants reported a history of diabetes or use of insulin or other hypoglycaemic medication.

The WHO classification of body mass index (BMI) was used to classify participants according to their BMI category, i.e. BMI <18.5 kg/m^2 was classified as undernutrition, BMI between 18.5 and 24.9 was classified as normal, BMI between 25 and 29.9 was considered as overweight and BMI ≥30 kg/m^2 was classified as obese.

Ethical approval for the study was obtained from the Institutional Ethics Committee of ICMR-NIREH, Bhopal. Participants' confidentiality was maintained.

RESULTS

A total of 215 gas-exposed survivors belonging to the severely exposed cohort of the long-term population-based epidemiological study were assessed for the presence of CKD. The mean (SD) age of the participants was 57.5 (12.07) years with higher participation (58.6%) of females. Nearly half the participants (50.2%) belonged to the 50–65 years age group. About 54.9% of participants did not have any formal education, whereas 30.2% of participants had completed primary level education. About 18% of participants were unemployed, 50.2%

TABLE I. Sociodemographic characteristics of the study population (*n*=215)

Variable	Categories	Frequency (%)
Gender	Men	89 (41.4)
	Women	126 (58.6)
Age group (years)	35–50	52 (24.2)
	50–65	108 (50.2)
	>65	55 (25.6)
Marital status	Married	201 (93.5)
	Single	14 (6.5)
Education	Illiterate	118 (54.9)
	Primary	65 (30.2)
	Secondary	8 (3.7)
	Higher secondary	17 (7.9)
	Graduate and above	7 (3.3)
Occupation	Unemployed	39 (18.1)
	Shopkeeper	19 (8.8)
	Labour	44 (20.5)
	Government employee	3 (1.4)
	Private employee	2 (0.9)
	Homemaker	108 (50.2)
Dietary habits	Vegetarian	62 (28.8)
	Non-vegetarian	153 (71.2)
Substance use	No substance use	110 (51.2)
	Smoking	23 (10.7)
	Alcohol	1 (0.5)
	Tobacco chewing	80 (37.2)
	All three habits	1 (0.5)

Mean (SD) age 57.5 (12.07) years

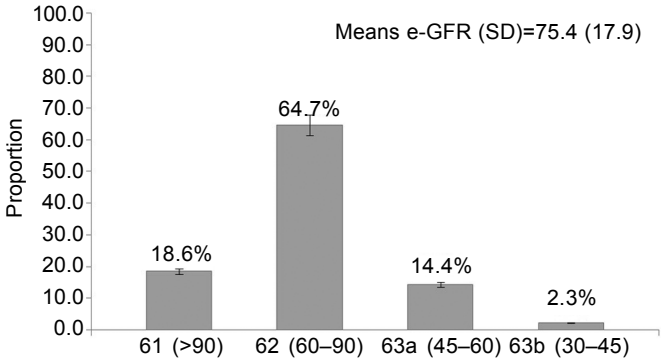

FIG 1. Distribution of the study population according to their estimated glomerular filtration rate category given by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (*n*=215)

were homemakers and 71. 2% were non-vegetarian. Tobacco chewing was the most common (37.2%) substance use among the study participants (Table I).

The prevalence of CKD was found to be 16.7% (95% CI 12.2–22.2). The mean (SD) e-GFR of the participants was 75.4 (17.9) with 14.4% of participants belonging to the G3a category of e-GFR (Fig. 1). Proteinuria was present in 2.7% (6/215) and diabetes and hypertension were present in 20% (43/215) and 56.2% (121/215), respectively.

The mean (SD) age of the participants diagnosed as having CKD (*n*=36) was 64.2 (13.9) years and their mean e-GFR was 53.4 (10.9). Three-fourths (75%, 27/36) of the participants with CKD had hypertension, 30.6% (11/36) had diabetes, 27.8% (10/36) were overweight and 8.3% (3/36) were obese. Of the 36 participants with CKD, 32 did not have any history of renal disease and were newly diagnosed with CKD.

Univariate analysis revealed that factors such as gender, age, educational status, occupation, BMI and hypertension were significantly associated with CKD (Table II). To find out the individual effect of these factors on CKD after adjusting for other confounders, multivariate analysis was done. Factors with $p<0.1$ were included for multivariate analysis. This showed BMI and level of education to be independent predictors of CKD in our study population (Table III). Being literate reduced the risk of development of CKD by 65% (adjusted OR=0.347, 95% CI=0.13–0.93) when compared with illiterate. A high BMI increased the likelihood of development of CKD as there was a 3.6 times higher risk among overweight participants and 9.3 times higher risk among obese compared to participants with normal BMI. The R^2 (Nagelkerke) value of the final model was 0.212, thereby explaining about 21.2% variation of CKD in the study population.

DISCUSSION

Studies conducted after the Bhopal gas disaster documented a high prevalence of several chronic illnesses related to the respiratory, gastrointestinal, neurological, psychiatric and ophthalmic systems.[11,13,14] However, the burden of renal disease among this community remained undocumented. In the past few years, a concern has been voiced that the prevalence of kidney-related ailments is higher in the gas-exposed community compared to the general population as a consequence of the ill-effects of gas exposure. We did not include moderately and mildly exposed cohort survivors in the study primarily due to operational reasons and second, it was assumed that any long-term adverse effect of gas exposure on the renal system resulting in the development of CKD will be maximal in the severely exposed cohort and thus they will have the highest prevalence of CKD among the three cohorts.

We found a 16.7% prevalence of CKD in the severely exposed cohort of gas survivors. An earlier cross-sectional study conducted using similar case definitions and equations as used in our study, which covered 6120 subjects across various Indian cities including Bhopal reported in 2013, found a nearly similar prevalence (17.2%) of CKD among Indian adults.[7] Further, Ene-Iordache *et al*.[5] in their cross-sectional study carried out in 12 lower- and middle-income countries from six regions of the globe to assess the prevalence and awareness of CKD and its risk factors reported a 16.8% prevalence of CKD in India, which matches with the prevalence reported in our study. A current systematic review based on eight Indian studies reported a 10.2% pooled prevalence of CKD in India.[2] Among the studies included in this systematic review, the highest prevalence in India was 17.2% among participants of the Screening and Early Evaluation of Kidney Disease study, which screened 6120 subjects from 13 academic and private medical centres across India[7] and the lowest prevalence of 4.2% was found among ≤20 years old adult residents from Delhi.[19] Thus, the prevalence of CKD estimated in our study was comparable with the national prevalence.

The minor variations in the reported prevalence among different studies from India could be because different definitions of CKD were used, or the difference in the methods/equations adopted in estimating GFR, the difference in the study population, as well as differences in the geographical area studied, etc.[10,19–21] For instance, Agarwal and Srivastava[22] reported a prevalence

TABLE II. Determinants of chronic kidney disease (n=215) (univariate analysis)

Variable	CKD		Unadjusted OR (95% CI)	p value
	Absent, *n* (%)	Present, *n* (%)		
Gender				
Men	80 (89.9)	09 (10.1)	Reference	
Women	99 (78.6)	27 (21.4)	2.424 (1.08–5.45)	0.029*
Age group (years)				
35–50	47 (90.4)	5 (9.6)	Reference	
50–65	93 (86.1)	15 (13.9)	1.52 (0.52–4.43)	0.45
>65	39 (70.9)	16 (29.1)	3.86 (1.29–11.47)	0.02*
Mean age (SD) in years†	56.2 (11.2)	64.2 (13.9)	1.059 (1.03–1.09)	0.01*
Education				
Illiterate	92 (78.0)	26 (22.0)	Reference	
Literate	87 (89.7)	10 (10.3)	0.407 (0.18–0.89)	0.02*
Occupation				
Unemployed	116 (78.9)	31 (21.1)	Reference	
Employed	63 (92.6)	5 (7.4)	0.297 (0.11–0.81)	0.01*
Dietary habits				
Vegetarian	55 (88.7)	07 (11.3)	Reference	
Non-vegetarian	124 (81)	29 (19.0)	1.838 (0.76–4.45)	0.17
Smoking				
No	159 (83.2)	32 (16.8)	Reference	
Yes	20 (83.3)	4 (16.7)	0.994 (0.32–3.11)	0.99
Tobacco (chewable)				
No	112 (83.6)	22 (16.4)	Reference	
Yes	67 (82.7)	14 (17.3)	1.064 (0.51–2.22)	0.87
Body mass index				
Underweight	34 (82.9)	7 (17.1)	1.493 (0.57–3.92)	
Normal	116 (87.9)	16 (12.1)	Reference	0.42
Overweight	26 (72.2)	10 (27.8)	2.788 (1.13–6.84)	0.03*
Obesity	03 (50.0)	3 (50.0)	7.250 (1.34–39.1)	0.02*
Hypertension				
No	85 (90.4)	9 (9.6)	Reference	
Yes	94 (77.7)	27 (22.3)	2.713 (1.21–6.01)	0.01*
Diabetes mellitus				
No	147 (85.5)	25 (14.5)	Reference	
Yes	32 (74.4)	11 (25.6)	2.021 (0.91–4.52)	0.08

*Statistically significant ($p<0.05$) †Independent sample *t* test OR odds ratio CI confidence interval CKD chronic kidney disease

of CKD of 0.79% in India. The prevalence might have been underestimated due to the use of serum creatinine >1.8 mg/dl as the cut-off. On the other hand, Anupama and Uma[10] reported the prevalence of CKD as 6.3% using the MDRD equation in a rural population of southern India. The difference in the CKD prevalence estimated in our study with that of other studies[2,10,22] could partly be explained by the high prevalence of diabetes (20%) and hypertension (56.2%) among the subjects in our study. In 2005, Modi and Jha[23] conducted a large ESRD incidence study among the gas-exposed victims of Bhopal visiting the dedicated tertiary care hospital, and reported that average crude and age-adjusted incidence rates were 151 and 232 per million population, respectively. In our community-based, cross-sectional study conducted among the severely gas-exposed cohort survivors, we found that the prevalence of later stage of CKD (G3b) was 2.3%. There is a need for future community-based prospective studies to ascertain the change in incidence rates in this population. Further, Modi and Jha in their study found that diabetic nephropathy was one of the leading causes of ESRD,[23] which was reflected in our study as well.

In our study, 89% of the subjects diagnosed with CKD were unaware of the status of their renal condition and hence were new cases of CKD identified during the study. This indicates the lack of screening for renal damage among those suffering from other chronic non-communicable diseases (NCDs). Hence, there is a need for designing and implementing country-specific standard guidelines for screening of patients with NCDs for their renal function. A notable finding in our study was the lower prevalence of proteinuria (2.7%), which is at variance to earlier population-based studies on CKD.[10,24] This could partly explain why a higher proportion of patients with CKD were unaware of their renal condition in our study because, at the primary care level, screening of renal function is based on urine protein analysis. This should be considered while planning any screening programme in this population.

In our study population, BMI and level of education were found to be significant independent predictors of CKD. Having some formal education significantly reduced the likelihood of development of CKD compared to illiterate individuals. Consistent with our findings, several studies in western countries[24–28] and India[19,29,30] reported an increased risk of CKD and its outcomes in individuals with a lower level of education. In an observational cohort of 61 457 participants of the Kidney Early Evaluation Program study, it was found that higher educational level was

TABLE III. Determinants of chronic kidney disease (*n*=215) (multivariate analysis)

Variable	Adjusted OR	95% CI	p
Gender			
Men	Reference		
Women	1.425	0.463–4.392	0.54
Age group (years)			
35–50	Reference		
50–65	0.842	0.260–2.730	0.77
>65	1.675	0.488–6.121	0.44
Education			
Illiterate	Reference		
Literate	0.347	0.13–0.934	0.04*
Occupation			
Unemployed	Reference		
Employed	0.530	0.135–2.08	0.36
Hypertension			
No	Reference		
Yes	1.684	0.688–4.117	0.25
Diabetes mellitus			
No	Reference		
Yes	1.528	0.602–3.877	0.37
Body mass index			
Normal	Reference		
Underweight	0.995	0.349–2.833	0.99
Overweight	3.61	1.282–10.15	0.02*
Obese	9.34	1.232–58.725	0.03*

*Statistically significant ($p<0.05$) OR odds ratio MLR multivariate logistic regression CI confidence interval

associated independently with a lower prevalence of CKD and lower mortality in those in the cohort who had chronic diseases including CKD.[26] The educational status of an individual may impact development of CKD and its diagnosis through several factors such as health literacy and knowledge of the impact of comorbid illnesses on renal function, health-related behaviour including healthcare seeking and utilization and access to healthcare delivery systems.[27] Many studies have reported the association of unhealthy behaviours such as consumption of unbalanced diet, smoking and alcohol intake with a lower educational level.[26–28] Similarly, an association has also been observed between lower educational level and diseases such as diabetes and hypertension.[3] A study exploring the socioeconomic disparities in prevalence of CKD revealed that education was associated more closely with the prevalence of CKD and its clinical outcomes as compared to income.[31] Factors such as health behaviour, comorbid illness and health system access that are influenced by lower educational status may lead to higher risk of CKD and thus need to be studied in detail in Indian settings.

We found a dose–response relationship with BMI and CKD. Compared to individuals with normal BMI, the likelihood of developing CKD among overweight individuals was three times higher and for obese individuals, the likelihood increased to nine times. This finding is in agreement with previous studies conducted across a diverse population.[32–34] Overweight and obesity result in a wide range of metabolic abnormalities, which may affect renal function.[35,36] Presumably, some of the harmful effects of obesity on kidneys are mediated through comorbid illnesses such as diabetes and hypertension. Evidence exists about the independent and direct effect of adiposity on kidneys induced by the endocrine activity of adipose tissue.[36,37] However, whether BMI is an appropriate indicator of adiposity is a debatable issue.[37]

Limitations

In our study, GFR was estimated based on the MDRD equation. However, it has been shown that the accuracy of GFR estimation could be improved using the CKD-EPI equation using cystatin C in combination with serum creatinine.[38,39] We could not measure cystatin C due to resource constraints. We calculated the prevalence of CKD-based GFR estimated by CKD-EPI-Cr (creatinine alone) equation and there was minimal variation (<1%) with the prevalence calculated by the MDRD method. The mean GFR calculated by MDRD (75.29 [17.9]) and CKD EPI-Cr (75.34 [18.2]) was similar. The MDRD equation that we used to estimate GFR has its inherent limitations. This equation possibly underestimates GFR among healthy individuals.[39] Moreover, MDRD formulae have not been validated in the Indian population and no correction factor has been derived to modify the equation to suit the Indian population.[10,39] However, the accuracy of the MDRD equation is widely accepted to estimate GFR based on creatinine value in population-based studies.[10] We used spot urine analysis to assess the prevalence of proteinuria, which is less sensitive than ACR or AER (urine albumin excretion).[2,20] Further, in our study, the assessment of renal function and damage in participants diagnosed with CKD initially was repeated after 3 months to discriminate between acute and chronic renal disease. However, around 44% (16/36) of subjects with reduced GFR and/or proteinuria refused to give consent for a second investigation when contacted after 3 months; these individuals were classified as having CKD based on the results of their initial investigation and this is a major limitation of the study. However, this limitation would have resulted in overestimation rather than underestimation. Moreover, the small sample size was a limitation in ascertaining the risk factors of CKD through logistic regression analysis, as our study did not have enough power to pick up many predictors

including proven risk factors such as age, diabetes and hypertension.

Conclusions

Our findings of a 16.7% community-based prevalence of CKD among the severely gas-exposed cohort population in Bhopal is similar to the national prevalence. This should put at rest the perceived concern of higher prevalence of CKD in gas-exposed survivors. The higher prevalence of diabetes and hypertension may largely be responsible for the CKD prevalence. It would be prudent to explore the role of gas exposure, if any, in causing CKD or increasing vulnerability to CKD through a well-designed case–control study with adequate sample size. There is also a need for primary prevention programmes targeting weight reduction and increasing physical activity at the individual as well as the community level to reduce the burden of CKD and other NCDs. Further, a secondary prevention programme (early screening of renal disease in the at-risk population) with appropriate regional specific guidelines needs to be developed and implemented.

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Conflicts of interest. None declared

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