

Nonalbuminuric chronic kidney disease: A dominant presentation in noncommunicable disease population of rural central India

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ABSTRACT

Background: India has largest number of people with diabetes mellitus (DM), and hypertension (HTN) is expected to double in next 25 years, which are common causes of chronic kidney disease (CKD). The focus for prevention of end-stage renal disease has shifted to detection of the iceberg of DM and HTN and its adequate control. Prevalence studies of CKD in India rural community are lacking. **Methodology:** We did community-based cross-sectional study with 3 monthly diagnostic camps in adults ≥ 20 years ($n = 6278$), from 13 villages for early detection of CKD in rural population around Sevagram in a group of noncommunicable disease (NCD) with DM, HTN, ischemic heart diseases (IHD), and stroke in year 2015–2016. **Results:** Study achieved 87% (5440/6278) coverage for albuminuria screening. Prevalence of CKD in NCD population was 19.6% (220/1121) where 86% (181/220) were nonalbuminuric CKD. Prevalence of persistent albuminuria in the study population was 0.8% (45/5440); in NCD population (DM, HTN, IHD, and stroke), it was 2.8% (31/1121). Prevalence of CKD was 19% in HTN and 18.9% in diabetes. The prevalence of nonalbuminuric versus albuminuric CKD was 17.1% versus 1.9% (9 times) in hypertensive individuals and 11.3% versus 7.5% (1.5 times) in individuals with DM. **Conclusion:** Predominance of nonalbuminuric CKD in NCD participants raises suspicion of CKD with undetermined risk factors. Further studies are needed to find the prevalence of nonalbuminuric CKD in overall population and to find out if exposure of pesticides, chemical fertilizers over long duration play an important role in agrarian rural community.

Keywords: Chronic kidney disease, nonalbuminuric chronic kidney disease, noncommunicable disease, rural

Introduction

Noncommunicable disease (NCDs) are estimated to account for 60% of total deaths in India according to the World Health Organization updated overview of the NCD situation.^[1] Chronic kidney disease (CKD) is a key determinant of the poor health outcomes of major NCDs. CKD is associated with an eight- to tenfold increase in cardiovascular mortality and is a risk multiplier in patients with diabetes and hypertension (HTN).

CKD management, end-stage renal disease (ESRD), consumes a disproportionately large fraction of the available resources.^[2] ESRD treatment is very expensive and out of reach of >90% patients in India or the country as a whole.^[3] The intervention strategy, therefore, has shifted to the secondary prevention or the detection of asymptomatic clinical disease. Based on earlier studies, approximately one-third of CKD is due to diabetic nephropathy and one-tenth each due to hypertensive nephropathy and chronic pyelonephritis.^[4] Once detected, management could incorporate aggressive blood pressure control, blood glucose control, and use of angiotensin-converting enzyme inhibitors to delay the progression of CKD. This community-based paradigm

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has been proposed to be the main pillar of a concerted program to prevent CKD.^[4,5] Adopting strategy of prevention would be the best way forward for our country considering the magnitude of problem.^[6]

We undertook study to screen CKD by persistent albuminuria in general population. We also calculated eGFR in all such high-risk subjects with persistent albuminuria and with NCD (diabetes mellitus, HTN, IHD and stroke). NCD were detected from parallel ongoing study. These studies were undertaken with a service motive to establish village clinics for monitoring chronic diseases.

Methodology

The Kasturba Hospital of the Medical College “Mahatma Gandhi Institute of Medical Sciences” Sevagram, Wardha, Maharashtra, has adopted villages under a holistic health-care assurance program from the past 35 years.^[7,8] We adopted a strategy of series of diagnostic camps every 3–6 months in these villages (year 2015–2016) and documented persistent albuminuria by dipstick. NCDs such as DM, HTN, IHD, and stroke in this population were diagnosed by parallel ongoing study.

We surveyed 13 villages with a total population of 9054 around Kasturba Hospital and adults with age ≥ 20 years ($n = 6278$) were included in the study. The demographic data (age, sex, socioeconomic grade, education, physical activity, and tobacco consumption) and history were collected by house-to-house visits. We collected information according to National Family Health Survey-3 (NFHS-3) standard of living index on household ownership of 19 different types of durable goods and four different means of transportation.^[9] Diagnostic village camps held between 6 and 8 am helped us to collect early morning urine sample and fasting blood sugar. We also recorded blood pressure. We withdrew blood for serum creatinine for all study participants who have HTN, DM, stroke, IHD, or persistent albuminuria. If needed, further diagnostic workup was done at Kasturba Hospital, Sevagram. All NCDs were registered in village clinics, and door-step free drug treatment was provided through voluntary village health worker, under supervision of medical team.

CKD is defined as abnormalities of kidney structure or function (manifest either by pathological abnormality or markers of kidney damage including abnormalities in the composition of blood or urine or abnormalities in imaging tests), or GFR < 60 ml/min/1.73 m² present for > 3 months.^[10] Proteinuria was defined as the presence of protein in urine (dipstick) detected $\geq 1+$.^[11] Persistent proteinuria was defined as dipstick test positive for proteinuria of 1+ or more in two separate samples reconfirmed after a gap of at least 3 months. eGFR using four-variable modification of diet in renal disease (MDRD-4) equation.^[12] The eGFR was used to classify participants into kidney disease outcome quality initiative stages of CKD.^[13]

We report here the analysis of albuminuria and eGFR in NCD participants for detection of CKD.

Statistical analysis

All the variables from questionnaire were entered into Microsoft excel sheet and then electronically transferred. Statistical data analysis was done using R, version 3.3.0. (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org/>). Data were summarized in the form of proportions and frequency tables for categorical variables. Continuous variables summarized using mean and standard deviation.

Results

We achieved 87% ($n = 5440/6278$) coverage for proteinuria screening [Figure 1]. The final dataset comprised of 5440 participants (median age 40 years [interquartile range 28–55; range = 20–100 years] [2748 (50.5%) men and 2692 (49.5%) women]). In study population, 14.7% (801/5440) were illiterate, 3.3% (179/5440) reached up to matriculation, and only 0.6% (35/5440) had bachelor degree. Socioeconomic distribution according to NFHS-3 standard of living index in the study population was 7.6% (415/5440) very poor, 24.4% (1331/5440) poor, 53.9% (2933/5440) low middle, 12.5% (681/5440) high middle, and 1.5% (80/5440) high socioeconomic class. The study population is typical bread-earning agrarian rural community engaged in labor-intensive lifestyle.

The prevalence of NCD was found from ongoing parallel studies in the same rural population.

Albuminuric chronic kidney disease

Overall prevalence of albuminuric CKD in rural adult population age ≥ 20 years was 0.8% (45/5440); in NCD population (DM, HTN, IHD, and stroke) was 2.8% (31/1121) and in non-NCD population was 0.3% (14/4319), i.e., NCD population had 8.6 times more risk of albuminuria than in non-NCD population.

Nonalbuminuric chronic kidney disease in NCD population

Table 1 summarizes that the overall prevalence of CKD in NCD participants was 19.6% (220/1121). The prevalence of nonalbuminuric CKD (eGFR < 60 ml/min/1.73 m²) was 16.9% (189/1121) while albuminuric CKD was 2.8% (31/1121). For each albuminuric CKD, there were approximately 6 times more nonalbuminuric CKD in NCD population.

The prevalence of CKD was 19% (169/888) in only hypertensive individuals, 18.9% (10/53) in only DM individuals, and 23.5% (19/81) in individual suffering from both DM and HTN.

The prevalence of nonalbuminuric versus albuminuric CKD in NCD population was 17.1% (152/888) versus 1.9% (17/888)

in lone HTN; 11.3% (6/53) versus 7.5% (4/53) in lone DM and in DM plus HTN was 17.3% versus 6.2%. Overall prevalence of CKD is similar in both DM and HTN, but the prevalence of nonalbuminuric CKD is higher in hypertensive individuals (9 times) compared to individuals with DM (1.5 times).

Table 2 summarizes that, even with the increase in severity of CKD, a significant proportion of patients did not have albuminuria: 84% of Stage 3, 75% of Stage 4, and 50% of Stage 5 CKD.

Discussion

In the community-based cross-sectional study, we found that the prevalence of CKD in NCD population was 19.6% (220/1121), and among these, overwhelmingly 86% (181/220) had nonalbuminuric CKD. Even with increasing severity of CKD, nonalbuminuric CKD persisted in a significant proportion, i.e., 86% in Stage 3, 75% in Stage 4, and 50% in Stage 5 [Table 2]. Prevalence of persistent albuminuria was 0.8% (45/5440) in overall study population, 2.8% (31/1121) in NCD population (DM, HTN, IHD, and Stroke) and 0.3% (14/4319) in non-NCD population. This observation underlines the need for estimating serum creatinine to mop up early kidney disease in non-NCD participants and to prevent progression to ESRD.

In a study from rural South India (March 2011–February 2012) by Anupama and Uma^[14] which involved participants >18 years of age enrolled by random selection in cluster sampling. The study achieved 76.7% coverage (2091/2728) and reported similar findings of predominant nonalbuminuric CKD as in our study. By and domiciliary approach, dipstick proteinuria (≥1+) was tested and eGFR was estimated by MDRD-4 equation to detect burden of CKD. Proteinuria was seen in 2.86% (60/2091) of individuals and eGFR <60 ml/min in 4.35% (91/2091) in overall study population. Among individuals with proteinuria, one-third had eGFR <60 ml/min. Prevalence of CKD considering proteinuria and eGFR <60 ml/min was found to be 6.3% (131/2091). Among these CKD cases, 54.2% were nonalbuminuric and 45.8%

were albuminuric. The study highlights that more than half of CKD patients were nonalbuminuric.

Nonalbuminuric nature of CKD could happen in histopathologically diagnosed tubulointerstitial disease which is known by no significant proteinuria, no clinically evident edema, and no known cause of chronic renal failure (CRF).^[5]

In a country with over 1.2 billion people, a number of ethnicities, widely divergent socioeconomic strata, rural-urban divide, different food habits, exposure to environmental toxins, and pattern of presentation of CKD differs in zones.^[15] In an urban area based study of south zones of Delhi in 2005, Agrawal *et al.*^[16] recruited 4712 participants aged >16 years by cluster sampling, combined domiciliary visit with camp module and achieved 94.77% coverage. They screened for proteinuria and CRF (serum creatinine >1.8). Prevalence of proteinuria was 4.41%, but these participants were not categorized as CKD. CRF was observed in 14.4% albuminuric and 0.15% nonalbuminuric nephropathy. On clinical grounds, diabetic nephropathy accounted for 41%, hypertensive nephropathy for 22%, chronic glomerulonephritis for 16%, and tubule interstitial disease for 2.3% (2/87) of all CRF. Etiological distribution of CRF correlates with predominance of albuminuric CRF.

In screening and early evaluation of kidney disease-India study, inquiry of CKD from 13 various academic medical centers in cities^[17] was done in year 2005–2007. By convenient cohort design sampling, 6120 participants were selected of age >18 years. Ninety-one percent turned up to medical centers and were screened for proteinuria and eGFR using MDRD-3 equation. Proteinuria was observed in 13.7% and prevalence of CKD (Albuminuric and nonalbuminuric) in 17.2% (5.9% with reduced GFR and 11.3% with normal GFR). Overall four fifth of CKD cases had albuminuria.

A observational, cross-sectional study conducted in year 2005–2007 in urban Delhi and surrounding rural area, screened

Table 1: Distribution of albuminuric and nonalbuminuric chronic kidney disease in noncommunicable disease participants

Chronic diseases in NCD population	No CKD (n=901)	Albuminuric CKD (n=31)		Nonalbuminuric CKD (n=189)	Total cases of CKD (n=220) (%)	Total (n=1121)
		eGFR >60 (n=16)	eGFR <60 (n=15)			
Only HTN	719	9	8	152	169 (19)	888
Only DM	43	3	1	6	10 (18.9)	53
Only IHD	8	0	0	1	1 (11.1)	9
Only stroke	15	1	0	0	1 (6.3)	16
Combination of NCDs	116	3	6	30	39 (25.2)	155

NCDs: Noncommunicable disease; HTN: Hypertension; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; DM: Diabetes mellitus; IHD: Ischemic heart diseases

Table 2: Non-Albuminuric state with stages of glomerular filtration rate

Urine albumin tested (n=1121)	Stage 5 (n=4)	Stage 4 (n=20)	Stage 3 (n=49)	Stage 2 (n=132)	Stage 1 (n=557)	Normal (n=359)
Negative (n=1090)	2 (50%)	15 (75%)	42 (85.7%)	131 (99.25%)	547 (98.2%)	353 (98.32%)
Positive (n=31)	2 (50%)	5 (25%)	7 (14.3%)	1 (0.75%)	10 (1.8%)	6 (1.68%)

5252 participants of aged >20 years by multistage cluster sampling method, clinic-based approach and highlighted that the proportion of participants with proteinuria increased as eGFR decreased and almost all participants with eGFR <45 ml/min had evidence of dipstick proteinuria.^[11]

The studies that documented predominance albuminuric CKD belong to diabetic nephropathy, hypertensive nephrosclerosis, and chronic glomerulonephritis category, while nonalbuminuric CKD falls in chronic interstitial nephritis and CKD of unknown (CKDu).^[5] CKDu has also been reported from other parts of South Asia and among South Asians living in the UK.^[18] An association of CKD with herbal medicines has already been established in some parts of the world.^[19,20] The finding presents a challenge for developers of CKD detection program, as these patients do not exhibit the usual parameter that defines high risk for CKD such as HTN or diabetes and does not demonstrate proteinuria.

The other interesting observation was that though overall prevalence of albuminuric plus nonalbuminuric CKD is similar in HTN and DM (19.03% in HTN and 18.86% in diabetes), nonalbuminuric to albuminuric CKD ratio was 9 (17.11%–1.91%) in HTN, whereas it was 1.5 (11.32%–7.54%) in DM. Disproportionately high nonalbuminuric CKD in HTN could mean that CKDu presenting with secondary HTN and may have added to high proportion of nonalbuminuric CKD.

CKDu is the second most frequent cause of CKD after diabetic nephropathy in India has been well documented. It was encountered most frequent in the southern part of the country (20.2%). CKDu presented more frequently with advanced CKD, relatively short history, few symptoms until late in the disease, absent of mild HTN, and little or no proteinuria.^[15]

In Sri Lanka, male paddy farmers of poor socioeconomic status present with progressive nonalbuminuric renal failure.^[21] Suggested etiologies include environmental toxins such as residual pesticides, fluoride, aluminum, cadmium, and cyanobacteria in drinking water.^[15]

Mani^[4,5] proposed a preventive model for decreasing burden of ESRD which has been endorsed by others.^[6] It primarily aimed at preventing progression of kidney disease particularly by detecting iceberg of DM and HTN and to treat them adequately. The strategy screens the community with proteinuria for evidence of kidney injury. In a setting where nonalbuminuric CKD and CKDu are dominating the scene, the proposed strategy will fall short to the expected detection of early nonalbuminuric kidney disease.

The overwhelming use of insecticides, pesticides, herbicides, and chemical fertilizers is a common practice in our rural area. It has been considered as an important risk in preliminary studies.^[22-24] We are not in position to comment about CKDu etiology in non-NCD population as we did not estimate serum

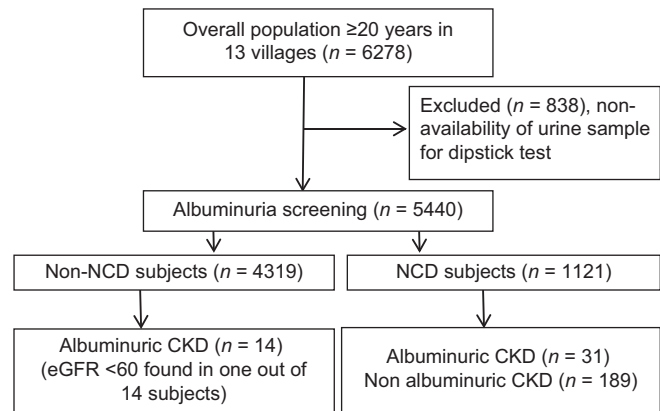


Figure 1: Study profile

creatinine in them. It emphasizes that possibility of missing CKD patients in the early stages is very high when only albuminuria is tested.

There is a need to document the burden of nonalbuminuric CKD in our agrarian community and relate it to insecticide, pesticide, and chemical fertilizer exposure.

Predominance of nonalbuminuric nature of CKD in NCD, DM, and HTN, in particular, is a notable observation in our rural population. There was disproportionately high nonalbuminuric CKD in hypertensive in comparison to diabetes. It is hypothesized that CKD of unknown etiology with secondary HTN may have added to the high proportion of nonalbuminuric CKD. Predominance of nonalbuminuric CKD makes one suspect undetermined risk factor operating. To substantiate it, the study needs to be extended to non-NCD population by serum creatinine estimation in all. If significant prevalence of nonalbuminuric CKD is detected, one needs to ponder whether insecticide, pesticide, and chemical fertilizer exposure over a long duration is culprit as has been suspect in preliminary.^[22-24]

The predominance of nonalbuminuric nature of CKD in NCD demands serum creatinine estimation in rest non-NCD population to diagnose CKDu.

Strength

We screened albuminuria at least twice at the interval of 3 months to establish persistent proteinuria rules out false-positive diagnosis of chronic kidney injury. By voluntary self-help of the people with primary service motive, the study adopted pan village approach and established village clinics for self-care.

Limitations

Nonalbuminuric CKD of undermined etiology could not be judged because we did not estimate serum creatinine in all. Initially, we pleaded for this compromise on account of nonfeasibility. The predominant nonalbuminuric CKD in DM, HTN, IHD, and stroke demands extension of study using serum creatinine as a tool over and above albuminuria in the entire population.

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Conflicts of interest

There are no conflicts of interest.

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