Original Article

Association of non-allopathic drugs and dietary factors with chronic kidney disease: A matched case–control study in South India

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Abstract

Background: The multifactorial etiology of chronic kidney disease (CKD) is known to vary with geographical region. Although diabetes and hypertension are the major known contributors for CKD, the role of other risk factors relevant to India needs to be explored. This study was done to find out the role of dietary factors and nonallopathic drugs in CKD. **Materials and Methods:** A hospital‑based individual pair‑matched case–control study was conducted in a tertiary care center in South India. The sample included 80 incident cases of CKD matched with 80 controls. Factors assessed in the study include sociodemographic factors, medical history, dietary factors, nonallopathic drugs, substance use, and other possible confounders. Univariate analysis was performed using McNemar's test and multivariate analysis was done using conditional logistic regression. **Results:** On multivariate analysis, lifetime exposure to nonallopathic drugs increased risk of CKD by approximately five times [odds ratio (OR): 5.15, confidence interval (CI): 1.27–20.87] and chicken intake (two to three times a month to once a week) had an increased risk by approximately four times (OR = 4.23, CI: 1.13–15.80). Fish intake at a frequency of two to three times or more reduced the risk of CKD by 94% (OR = 0.06, CI: 0.01–0.43). **Conclusion:** Chicken intake and lifetime exposure to nonallopathic drugs could increase risk for CKD in South India. Increased fish intake was found to be protective for CKD.

Keywords: Case‑control study, chronic kidney disease, complementary therapies, dietary factors

Introduction

Chronic kidney disease (CKD) has gained public health priority particularly in South‑east Asia in the past two decades. According to the Global Burden of Disease study 2015, global rank for CKD in terms of years of life lost shifted from 25th in 1990 to 17th in 2015.[1] The importance of CKD had not only been due to its contribution of morbidity and mortality but also due to its increasing prevalence. Recent studies in India reported a prevalence of CKD between 8.7% and 16.4%.[2-4]

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Preventive measures focusing on reducing the prevalence of CKD by limiting exposure to risk factors could be cost‑effective in a country like India. But a thorough understanding of risk factors and complex relationship between them is essential for primary prevention. Several studies across the world had contributed to the present knowledge on risk factors for CKD.[5] It is a known complication of diseases such as diabetes and hypertension. Other known causes include chronic glomerulonephritis, immune disorders such as IgA nephropathy, systemic lupus erythematosus, toxins including drugs and heavy metals, and obstructive renal diseases.

Although the list appears exhaustive, there is a considerable gap in the current understanding of CKD etiology in terms

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of unknown causes and interacting risk factors. According to CKD registry of India, in 16% of CKD cases the etiology was undetermined.[6] The etiological profile of CKD was found to vary between regions and among different ethnic groups. A study in Singapore suggested differences in population attributable risk of diabetes and hypertension in CKD for different ethnic groups living in the same region.[7]

In each individual case of CKD, often one particular etiology is considered as the sole explanation. But there has been growing interest in exploring the multifactorial causation of CKD. Few studies conducted outside India had shown the association of dietary factors such as animal protein, animal fat, and red meat intake with CKD.[8-10] Studies in South-east Asia had reported the association of traditional Chinese medicine in CKD.[11,12] Though studies have been conducted worldwide on risk factors of CKD, there persists a need to look for indigenous risk factors relevant to India. The role of factors such as nonallopathic drugs medicine (Indian Systems of Medicine and Homeopathy) and meat intake had not been explored in India. Hence, this hospital-based case–control study was conducted to find out the association of these dietary risk factors and traditional medicine with CKD among patients of a tertiary care center in South India.

Materials and Methods

Study design

An individual pair (1:1) matched case–control study was conducted among adult patients (≥20 years) attending nephrology OPD in a tertiary care center in Puducherry between April 2013 and March 2014.

Sample size

The sample size was estimated as 79 in each group considering the exposure to diabetes mellitus in cases to be 30%[13] and controls to be 10%[14] with an α (Type I error) of 5% and a power of 80% using sample size table for matched pair controlled studies.

Selection of cases and controls

Cases were selected from the outpatients from nephrology department in the institute. Case definition was based on Kidney Disease Improving Global Outcomes (KDIGO) criteria.[15] Cases of CKD confirmed on the basis of KDIGO criteria referred for the first time to nephrology OPD diagnosed within 3 months from the date of interview were recruited. Consecutive cases were recruited to avoid selection bias. Cases of CKD due to known congenital or inherited causes based on physician assessment were excluded from the study.

Respective age- (±5 years) and gender-matched controls were selected from patients admitted in medicine wards. CKD was excluded from in-patients if (1) the estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 (based on CKD-EPI equation) and (2) there is absence of microalbuminuria. Microalbuminuria was defined as urine albumin–creatinine ratio (ACR) ≥30 mg/g estimated by immunoturbidimetry method on a spot urine sample.

Since the control selection process required investigations to be carried out, it was decided to carry it out among in-patients. The in-patients from medicine department were chosen based on similarity to cases in risk profile, feasibility of carrying out anthropometric measurements, and investigations and average duration of stay.

Exposure assessment

A pretested questionnaire was used to obtain information on study parameters for both cases and controls. The questionnaire was reviewed by the faculty for face and content validity. The questionnaire was piloted among five cases and five controls. Based on expert review and pilot testing, necessary modifications were made to the questionnaire. The risk factors studied include sociodemographic factors, exposure to drugs [nonsteroidal anti-inflammatory drugs (NSAIDs) and nonallopathic drugs], and lifestyle factors.

Sociodemographic factors included education, occupation, and income. Occupation was classified as agricultural workers and nonagricultural workers, and per-capita income was categorized into quartiles for analysis.

Self-reported history of diabetes mellitus and hypertension was obtained. History of renal calculi, or history of snake bite or history of admission for dialysis was considered as evidence of acute kidney injury (AKI) and family history of diabetes mellitus, hypertension, and kidney disease among first-degree relatives. The diagnosis at the time of admission for controls was categorized into disease groups based on ICD-10 classification.

Use of nonallopathic drugs in their lifetime and in the past 1 year was assessed. The type of nonallopathic drug use such as Ayurveda, Siddha, Unani, or Homeopathy was recorded. For NSAID use, regular use was defined as taking a tablet for fever or pain at least once a week over a consecutive period of 3 months. Pesticide exposure was assessed using surrogate variables such as proximity of the house to agricultural field, involvement in agricultural work, and involvement of the subject in pesticide spraying.

In the study, a qualitative food frequency questionnaire (FFQ) was used to assess the dietary intake of chicken, fish, and red meat like mutton, pork, and beef.[16] The FFQ had seven frequencies from "never or hardly ever" to "once a day or more." The seven frequencies were later categorized into tertiles based on the distribution of responses. If the tertiles were overlapping, such parameters were classified as dichotomous variables. Alcohol and tobacco use were assessed using WHO-STEPS (WHO STEPwise approach to chronic disease risk factor surveillance) instrument.[17] Body mass index and waist–hip ratio were measured using recommended procedures.[18,19] Ethical approval was obtained from the Institute Ethics Committee.

The patients were interviewed after obtaining a written informed consent.

Among in-patients who were age- and gender-matched, GFR value was estimated based on CKD-EPI equation using serum creatinine value. If GFR >60 mL/min/1.73 m^2, urine ACR was tested.

Statistical analysis

Data were entered into EpiData entry v3.1 and analyzed using IBM SPSSv20 (Armonk, NY). For conditional logistic regression, Stata v12.0 was used.

Association for dichotomous exposures was assessed using McNemar's test for matched-pair studies and strength of association reported using odds ratio (OR) with confidence interval (CI). In this analysis, a matched case and control is considered a pair and a total of 80 matched pairs are analyzed. OR is calculated considering the discordant pairs alone – matched pairs where case is exposed and control is not exposed or vice versa. Univariate analysis for exposures with more than two categories was assessed using conditional logistic regression. Variables that were found significant in univariate analysis ($P < 0.05$) were included in multivariate analysis using conditional logistic regression. Adjusted ORs were reported with 95% CI. Sensitivity analyses were performed for variables such as diabetes, hypertension, obesity, and substance use.

Results

Data were collected from 80 cases and their age- and gender-matched controls. In the study population, the median age of cases was 52 years with a range between 20 and 76 years. More than 50% of the study population in each group was age 50 years or more (cases 60% and controls 55%). The majority of the study population were males constituting 73.8% in each group. Other sociodemographic characteristics are presented in Table 1. A higher proportion of the cases (55%; $N = 44$) did not complete primary level of education compared with controls (46.3%; $N = 37$). Relatively higher proportion of cases belonged to poor socioeconomic status compared with controls.

The majority of patients with CKD (61%; $N = 47$) were classified as stage V based on the eGFR value [Table 2]. Controls were classified based on their diagnosis into major disease groups based on ICD-10. Approximately one-third of the controls suffered from diseases of the circulatory system.

The association of CKD with variables assessed in the study is presented in the form of matched pairs [Table 3]. In univariate analysis [Table 3], history of diabetes (OR = 4.5; CI: 1.67–12.08) and hypertension (OR = 11; CI: 4.29–28.15) emerged as two largest risk factors for CKD in this study.

Lifetime use of nonallopathic drugs showed a significant association with CKD with an OR of 3.4 (CI: 1.2–11.7). Among different types of non-allopathic drugs, Siddha use was commonly reported followed by native medicine.

Table 1: Sociodemographic profile of the study sample

Sociodemographic characteristic	Cases (n=80), n (%)	Controls (n=80), n (%)
Educational status$		
Less than primary level of education	44 (55.0)	37 (46.3)
Completed primary level	36 (45.0)	43 (53.8)
Involvement in agricultural work		
Yes	36 (45.0)	28 (35.0)
No	44 (55.0)	52 (65.0)
Per capita income (₹)$		
First quartile (≤500)	33 (41.2)	24 (30)
Second quartile (501-750)	14 (17.5)	12 (15)
Third quartile (751-1250)	15 (18.8)	24 (30)
Fourth quartile (≥1251)	18 (22.5)	20 (25)

Table 2: Clinical profile of cases and controls*

	n (%)
Staging of disease among cases (n=80)	
CKD stage	
Stage I	1 (1.3)
Stage III	7 (8.8)
Stage IV	23 (28.7)
Stage V	49 (61.3)
Disease classification for controls (n=80)	
ICD-10 major group classified based on diagnosis at admission	
Diseases of the circulatory system	27 (33.8)
Certain infectious and parasitic diseases	19 (23.8)
Neoplasms	17 (21.3)
Diseases of blood and blood forming organs	7 (8.8)
Endocrine, nutritional and metabolic diseases	4 (5.0)
Others**	6 (7.6)

*Classification based on ICD-10 (see annexure), **Others include mental and behavioral diseases, diseases of the skin and subcutaneous tissue, diseases of the nervous system, and diseases of the digestive system. CKD: chronic kidney disease; ICD: International Classification of Diseases

Among dietary factors, chicken intake at a frequency of two to three times or more showed an increased risk for CKD (OR = 3.12; CI: 1.4–6.69). But the third tertile did not show significant association [Table 4]. Fish intake two to three times a month or more not only showed a decreased risk in CKD but also showed a decreasing trend.

Among sociodemographic factors, education and income did not show significant association. Pesticide spraying assessed as involvement in agricultural work did not show any association. Other factors such as history of snake bite, family history of diabetes and hypertension, and regular use of NSAIDs did not show any significant association. Since pork intake was reported among only three subjects, it was not analyzed.

Among dietary factors, beef and mutton intake did not show significant association. Other lifestyle factors such as smoking, alcohol use, and obesity did not show association with CKD.

Table 3: Association of risk factors with chronic kidney disease using matched-pair analysis (*n*=80 pairs)

	Controls		OR (CI)	*P**
	Exposed	Not exposed		
Educational status				
Case exposed (less than primary level of education)	21	23	1.43 (0.72-2.91)	0.337
Case not exposed (completed primary level)	16	20		
Involved in agricultural work				
Case exposed	17	19	1.72 (0.78-4.01)	0.210
Case not exposed	11	33		
Diabetes				
Case exposed	4	18	4.5 (1.67-12.08)	0.004
Case not exposed	4	54		
Hypertension				
Case exposed	5	33	11 (4.29-28.15)	<0.001
Case not exposed	3	39		
History of kidney stones				
Case exposed	0	6	-	-
Case not exposed	0	74		
History of snake bite				
Case exposed	0	3	1	1
Case not exposed	3	74		
Nonallopathic drug use				
Case exposed (ever used)	2	17	3.40 (1.2-11.7)	0.017
Case not exposed (never used)	5	56		
NSAID intake				
Case exposed (regular user)	7	21	2.10 (0.94-4.99)	0.824
Case not exposed (not a regular user)	10	42		
Mutton intake				
Case exposed (once a month or more)	5	14	0.82 (0.37-1.77)	0.719
Case not exposed (never or hardly ever)	17	44		
Beef intake				
Case exposed (once a month or more)	5	12	0.75 (0.32-1.68)	0.571
Case not exposed (never or hardly ever)	16	47		

*McNemar's test. OR: odds ratio; CI: confidence interval; NSAID: nonsteroidal anti-inflammatory drugs

Parameters that showed a significant association in univariate analysis were included in the final multivariate model. In multivariate analysis [Table 5], history of hypertension and lifetime exposure to nonallopathic drugs emerged as independent risk predictors with an OR of 6.71 (CI: 1.72–26.09) and 5.15 (CI: 1.27–20.87), respectively.

Chicken intake at a frequency of two to three times a month to once a week had an increased risk by approximately four times (OR: 4.23, CI: 1.13–15.80). The third tertile did not show any significant association. Fish intake at a frequency of two to three times or more reduced the risk of CKD by 94% (OR: 0.06, CI: 0.01–0.43).

Diabetes did not emerge as an independent predictor in multivariate analysis. Stratified analysis had shown presence of interaction between diabetes and hypertension in this study.

Sensitivity analysis was carried out excluding recently diagnosed cases of diabetes and hypertension. Sensitivity analyses though showed a reduction in the strength of association did not show a change in the direction or significance of results.

Discussion

In a hospital-based case–control study conducted on CKD in Puducherry, four factors – namely hypertension, lifetime exposure to nonallopathic drugs, chicken intake, and fish intake – emerged as independent predictors. Though diabetes showed a significant association in univariate analysis, it did not emerge as an independent predictor in the study.

This study showed a significant association for diabetes in univariate analysis, but multivariate analysis did not show a significant increase in risk. This could be due to interaction between diabetes and hypertension in this study which could be explored in future studies. Though this study did not show significant association, several studies[20,21] established the causative role of diabetes in CKD. Hence, the need for screening CKD among diabetic patients at primary care cannot be overemphasized.

In this study, lifetime exposure to any nonallopathic drug was associated with approximately four times increased risk of CKD (OR = 3.89, CI: 1.08–13.90) after adjusting for other confounders.

Table 4: Association of income, frequency of chicken and fish intake, smoking, and alcohol use with chronic kidney disease using conditional logistic regression

	Cases (*n*=80), *n* (%)	Controls (*n*=80), *n* (%)	OR (CI)	*P***
Per capita income				
Fourth quartile (≥₹1251)	18 (22.5)	20 (25)	1	
Third quartile (₹751-₹1250)	15 (18.8)	24 (30)	0.64 (0.26-1.57)	0.338
Second quartile (₹501-₹750)	14 (17.5)	12 (15)	1.44 (0.53-3.93)	0.472
First quartile (≤₹500)	33 (41.2)	24 (30)	1.83 (0.75-4.43)	0.181
Frequency of chicken intake*				
First tertile	30 (37.5)	44 (55)	1	
Second tertile	48 (60)	29 (36.2)	3.12 (1.40-6.69)	0.005
Third tertile	2 (2.5)	7 (8.8)	0.43 (0.08-2.20)	0.314
Frequency of fish intake*				
First tertile	42 (52.5)	32 (40)	1	-
Second tertile	33 (41.2)	27 (33.8)	0.74 (0.32-1.68)	0.478
Third tertile	5 (6.2)	21 (26.2)	0.13 (0.03-0.49)	0.003
Cigarette smoking				
Never smoked	44 (74.6)	38 (64.4)	1	
Past smoker	13 (22)	18 (30.5)	0.57 (0.23-1.42)	0.235
Current smoker	2 (3.4)	3 (5.1)	0.53 (0.08-3.36)	0.502
Alcohol use				
Never used	39 (66.1)	34 (57.6)	1	
Past user	13 (22)	11 (18.6)	0.86 (0.28-2.64)	0.802
Current user	7 (11.9)	14 (23.7)	0.39 (0.12-1.23)	0.110

**Conditional logistic regression for matched pair studies, *first tertile = never or hardly ever to once a month, second tertile = two to three times a month to once a week, third tertile=two to three times a week or more. OR: odds ratio; CI: confidence interval

Table 5: Multivariate analysis showing independent predictors for chronic kidney disease in the study

Parameter	Exposure level	OR	CI	*P**
Diabetes	No	1	-	0.069
	Yes	5.87	0.87-32.25	
Hypertension	No	1	-	0.006
	Yes	6.71	1.72-26.09	
Nonallopathic drugs	Never	1	-	0.022
	Ever	5.15	1.27-20.87	
Chicken intake	Never or hardly ever	1	-	
	2-3 times a month to once a week	4.23	1.13-15.80	0.032
	2-3 times a week or more	0.38	0.03-4.58	0.450
Fish intake	Never or hardly ever to once a week	1	-	
	2-3 times a month to once a week	0.54	0.15-1.87	0.334
	2-3 times a week or more	0.06	0.01-0.43	0.005

*Conditional logistic regression for matched pair studies. OR: odds ratio; CI: confidence interval

Research on association between non-allopathic drug use and CKD is currently lacking in India. Studies in Thailand and Taiwan[11,12] suggest the role of non-allopathic drug use in CKD. It has been postulated that aristolochic acids (in *Aristolochia indica*) present in Chinese herbal formulations may lead to CKD. *Aristolochia indica* is also a part of herbal preparations in Ayurveda and Siddha medicine.[22] Apart from *Aristolochia*, few other herbal preparations causing nephrotoxicity had been identified.[23] Other possible mechanism could be heavy metal use in non-allopathic drug leading to AKI[24] and such repetitive episodes could culminate in the development of CKD.

Since heavy metals and aristolochic acids are a part of non-allopathic drugs preparations in India, we also postulate heavy metals and aristolochic acids as a possible mechanism. In this study, the lack of recall for the exact name of the drug limits further investigation into the active principle. Hence, further long-term cohort studies are needed to explore the association between use of non-allopathic drugs and CKD. Several studies[25,26] revealed the causative role of NSAIDs in pathogenesis of CKD.

In this study, six cases had a history of renal calculi while none of the controls reported it. Though the study lacks power in detecting an association, it agrees with the results from other studies linking renal calculi with CKD.

This study reveals hypertension as the strongest independent predictor for CKD (OR of 6.71). The association between hypertension and CKD was reported by several studies.[4,21,27,28] The strength of association (OR) in those studies varied between 1.18 and 7.4 due to different methodologies used in assessment of exposure and outcome. Cross-sectional studies in India also reported association between hypertension and CKD with varying ORs of 1.4 and 7.4 in the two studies.[4,28]

But the relationship between hypertension and CKD is complex. While hypertension is considered by some as a marker for CKD, long-standing hypertension could also lead to hypertensive nephrosclerosis manifesting as CKD.[29] Nevertheless, hypertension could be used as an important high-risk criterion to screen for CKD at primary care level.

Increased frequency of chicken intake, that is, two to three times a month to once a week increased the risk of CKD after adjusting for other covariates (OR = 4.23, CI: 1.13–15.80). There was a lack of comparable studies which specifically studied association between chicken intake and CKD. Lin *et al.*[8] found a positive association of animal protein and animal fat with microalbuminuria. Since chicken is an important source of animal protein, increase in its intake could lead to cause CKD. This study, however, lacked sufficient power to detect a dose–response relationship between chicken intake and CKD.

Fish intake two to three times a week or more was found to be protective for CKD with a 94% decrease in risk (OR = 0.06, CI: 0.01–0.43). A cross-sectional study in Australia by Gopinath *et al.*[9] reported a similar reduction in risk of CKD with fish intake in the fourth quartile (OR = 0.68, CI: 0.48–0.97). The protective role of fish was postulated to be due to reduced production of proinflammatory cytokines and nitric oxide by omega-3 fatty acids.[9] Fish is relatively cheaper form of protein and known to have protective role not only in CKD but also in coronary artery disease.[30] Hence, fish intake should be promoted in the community as a replacement for other types of meat.

Since the controls suffered from diseases such as coronary artery disease, association of parameters such as smoking, alcohol, and obesity could have been affected by Berksonian bias. Incidental cases of CKD were included in the study to reduce recall bias. Yet assessment of parameters such as NSAID use could have been subject to recall bias. Social desirability bias could have led to under-reporting of nonallopathic drug use.

The same reference period was used for both cases and controls for different parameters to reduce misclassification bias. To reduce interviewer bias, identical probes were used and effort was made to ensure approximately similar interview time for both cases and controls.

To the best of our knowledge, this is the only case–control study reported from India on CKD. This study also reports for the first time the association between nonallopathic drug use and CKD in India. Though the sample size was low, matching for age and gender increased the power of the study. Appropriate statistical analyses for matched pair studies like McNemar's test and conditional logistic regression were used.

The study lacked sufficient power to detect an association for known risk factors such as renal calculi, AKI, and NSAIDs. Low prevalence of alternative medicine use in the study population was another limitation.

Conclusion

This study, while concluding diabetes and hypertension are the major risk factors for CKD, raises suspicion on factors such as frequent chicken intake and use of nonallopathic drugs. We recommend the screening of diabetic and hypertensive patients at primary care level for CKD. We also recommend promotion of fish intake in the community due to its protective role in CKD.

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Conflicts of interest

There are no conflicts of interest.

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