The Role of Water Quality in Kidney Stone Disease: A Hospital Based Case-Control Study in Chennai

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Abstract— Around the worldwide, the kidney stone disease (KSD) is common public health problem. In India, 15% of the populations were affected by KSD. The prime objectives of the study was to (i) To assess the role of environmental factors associated with the risk of kidney stones among cases and controls and (ii) To assess the role of water quality and geographic variability on the occurrence of kidney stone. The study showed statistically significant association for renal stones with low socio-economic status, body mass index (BMI) (>25 kg/m2), occupation, source of drinking water, water consumption (<3 L/day), geographic variability, and residence proximity to highways (<500m). The adjusted odds ratios (ORs) were significantly higher for water consumption (<3 liters/day) (OR: 10.58; 95% CI: 5.29-21.18), residence proximity to highways (<500m) (OR: 4.66; 95% CI: 4.46-8.85), drinking of boiling water (OR: 3.22; 95% CI: 1.51-6.88). The study identified the significant role of several modifiable risk factors for KSD among Chennai residents. These risk factors include amount of water intake per day, drinking boiling water, residence proximity to highways. First time stone formers should take extra precaution to avoid recurrence by keeping themselves hydrated in hot condition.

Index Terms— Kidney stone disease, Water quality, Geographic variability, Drinking water,

1 Introduction

Kidney stone disease is the common clinical problem around worldwide. Urinary stone disease is the formation of stone in the kidney, ureter or urinary bladder by the successive physicochemical events of super saturation, nucleation, aggregation, and retention. Kidney stone is formed by the deposition of crystals. Crystal is composed of various components; Such as Calcium oxalate, calcium phosphate, calcium carbonate, magnesium-ammonium phosphate, uric acid and cysteine. Probability of kidney stone formation varies from different countries. KSD poses a major health hazard in both rural and urban societies. In Asia, the stone forming belt has been reported in Sudan, Saudi Arabia, Iran, India, Pakistan (Hussain et al, 1995). In India, the prevalence of kidney stone is 15% (Mitra et al, 2013). Incidence and prevalence of KSD increases significantly because of its tendency to recur within 5 to 10 years. The recurrence rate of kidney stone is high in males than females (Sohgaura et al 2017). The etiology of KSD is multi-factorial and it is influenced by the combination of epidemiological, biochemical, and genetic risk factor (Devuyst et al).

Water quantity and quality plays a major role in KSD and it is agreed that high water intake reduces the risk and recurrence (Briadar et al, 2014). The risk of KSD increases, when urine output is less than 1Liter per day. The recurrence rate of KSD can be prevented when the urine volume exceeds 2 to 2.5Liter per day (Kleiner et al, 1999).In water quality, Water hardness in drinking water from public water supply system is related to kidney stone disease (Haddock et al, 2016). There is a significantly association between high calcium and water hardness in drinking water (Abeywickarama et al, 2015). There are only few studied have been noted in relation between water quality and KSD (Haddock et al, 2016).

Geographic variability is one of the causes for the occurrence of KSD. The geographic variability which indicates the residence proximity to highways, green space cover, living status and built environment. The residence proximity to the highways contributes with the occurrence of KSD (Lue et al, 2013). The study observed that, there is an association between geographic variability and KSD (Soucie et al, 1994). There are only few studies have been noticed for geographical variability and KSD.

1.2 Environmental risk factor associated with kidney stone formation

Risk factors for KSD are often multi-factorial. Major risk factors for kidney stone disease around worldwide are genetic predisposition, metabolic disorders, behavior pattern and environmental factors. As being individual such risk factors can be categorized like age, gender, race, drugs, genetic, diet habit, alcohol consumption and behavior (e.g. hypercalciuria) and environmental factors categorized as occupation, heat stress, water scarcity, and built environment

For kidney stone disease chronic dehydration is the confirmed risk factor (Brenner and Rector, 2008). The study concluded that chronic dehydration is the main cause of kidney stone disease because of the history of exposure to heat (e.g. climate and occupation) (Embon et al, 1990). Water quality also plays a major role in the occurrence of kidney stone disease. The chemical compositions in the drinking water are performed to have an impact on the human health. The water pre-treatment is also linked with the occurrence of kidney stone because of dissolution, precipitation of solution, mixing of different types of water, evaporation, selective removal of ions and resident time of water are major natural factor. Since Chennai is the tropical dry and wet climate, inadequate water facility affects the water quantity.

Other important risk factor for kidney stone occurrence is geographic variability. In the rates of kidney stones, geographic variation has been observed for many years. Many have suggested that the difference may due to variation in built environment, water quality or the prevalence of co-morbid condition that may affect the risk of stones. The study done in US, have observed that highest incidence of the kidney stone occurs in the south than north. This is because of hotter weather in the southern states may lead to dehydration. The residents who live near the major highway roads, they lack from adequate green space, so that they are prone to environmental pollutions, lack from adequate ventilation, low water quality facilities, and noise pollution. The urban populations are mostly affected by such conditions than rural population, because their residents are mostly near the major roadways.

2. LITERATURE REVIEW

This chapter provides a comprehensive review of the past ten year's research on the water quality and geographic variability and the associated environmental risk factor. In addition, PubMed search was undertaken to identify research conducted in India that aimed at identifying risk factors for drinking water quality and geographic variability on KSD. Further, the PubMed search highlights the need to undertake the present research work in India.

In a case-control study, prospectively evaluated 54 patients with whom 78% were males, 63% were in the age range of 26-50, while 32 were in the age range of 51-75. And 82% were had no family history of kidney disease. Interestingly, 98% used natural spring water for drinking purpose. Since the quality of drinking water has heavily influenced the prevalence of certain disease, hydro-geochemical parameters often correlated with disease prevalence (Abeywickarama et al 2015). A hospital based unmatched case-control of 70 cases and 140 controls, was found that genetic predisposition (OR:16.98, CI: 3.02-95.25), frequency of urine per day (OR:5.95, CI: 1.03-34.19) and dietary habit of eating red meat once a week (OR: 32.28, CI: 9.7-143.2) was associated with increased occurrence of kidney stones (Dongre et al 2017). In a cohort study with 1103 Boston area patients, it was found that calculated GFR level is low for the participants whose residential distance is major to roadways (50m to 1000m) which is associated with increased risk factor of cardiovascular disease, but little is known about its impact on renal function (Lue SH et al, 2013). In a case-control study of renal stone disease with 100 study participants (50 cases and 50 control), it was found that consuming soft drink (OR: 8.19; CI: 1.99-33.69), sedentary lifestyle (OR: 10.01, CI: 1.27-78.91), and water consumption <1.5 L/day (OR: 7.73, CI: 2.24-26.69) were significantly higher among cases compared to controls (Mathiyalagen et al 2017). These two studies were from south India and highlight the risk factors common to south Indian population.

A case-control study in India, collected information's related to personal, sources of water, quantity of water through questionnaire, which was found that 53.6% of the patients consumed <3 Liter of water per day. They concluded that quantity of water is more important than the quality (Mitra et al). A study of 666 patients from Chennai city, have concluded that low fluid intake (p=0.000) and high intake of coffee and tea are associated with KSD (Sofia et al 2016).

In a cross sectional study of 11851124 study participants that age, gender, race, geographical among U.S resident associated with prevalence of kidney stone formation by administering the questionnaire to the participants (Soucie et al, 1994). In a case control study of 100 study participants, was found that drinking tea (OR=1.46, CI: 1.03-2.07), history of urolithiasis (2.12, 1.06-90.14), stress and physical inactivity were common risk factors for renal stones occurrence. A case-control study of 2310 study participants, It was found that there is a significant relationship with magnesium in drinking water (R(2)=26%, P=0.05) and they also newly introduced that stone risk index had a strong positive association with urinary calculus (R(2)=28.4%, P=0.04) (Basari et al, 2011). A case-control study in the urban area of Thanjavur showed that drinking less water, intake of high calcium and sodium content in water, intake of non-vegetarian and pH less than 7 and combination of less water intake and non-vegetarian are associated with the formation of kidney stone disease (Ravikumar et al, 2012).

A summary of the literature review on various risk factors including climate change on the prevalence of KSD in the last five years is summarized in Table 3. Further, the relevance of these literature reviews to the design of the current study is provided.

Water scarcity is looming large in urban India. Migration of people from rural to urban cities has resulted in urbanization which is exerting pressure on resource availability. In a prospective study of 1266 kidney stone patients from West Bengal, India, it was found that patients with KSD consumed less than 3L of water daily (Mitra et al 2018). India is facing the dual challenge of water scarcity and climate change that could increase the incidence of KSD. Urbanization, water scarcity and climate change together could put the urban population at greater risk of KSD in India.

2.1 Kidney stones, water quality and environmental risk factor research in India

In recent years, kidney stones become a major public health concern in India. Because of the environmental risk factor such as hot environment, dietary habits, seasonal change. Water quality and geographic variability also plays a major role in the kidney stone disease. Despite the growing public health concern to environmental risk factors and water quality, there has been limited research done on the kidney stone and environmental risk factors compared to research done in our neighboring country China or in the developed countries.

PubMed database search of terms using filters on 'role of water quality and kidney stone disease' and 'geographic variability and kidney stone disease' was undertaken to elucidate the sparse literature available for the role of water quality and geographic variability in KSD in India. This exercise emphasizes the need to address the public health concern of KSD in India through research.

Search term	Number of articles	Summary
Kidney stones in India	728	Primarily focuses on common risk factors in either case-control or longitudinal study designs. Majority of the studies focus on the treatment schemes including alternative medicines such as Siddha and Ayurveda.
Risk factors for kidney stones in India	56	Identifies the risk factors commonly faced by Indian subpopulation in hospital based case-control studies.
Role of water in kidney stone disease in India	6	Primarily focuses on the quality, quantity and the sources of water in either case-control or cross sectional study design. There are only less studies have been done for the role of water in kidney stone disease in India.
Geographic variability in kidney stone disease in India	3	They focus on the location of population residents, sunlight, ambient temperature and green spaces in living area in either cross-sectional or case-control study. There only few studies have been noticed on geographic variability with KSD in India.

3 STUDY RATIONALE, AIM and OBJECTIVES

The prevalence of kidney stones was on the rise in India. Environmental factors including water quality and quantity, geographic variability have been found to increase the incidence of KSD. However, there is limited evidence about the role of water source and its quality on the occurrence of kidney stones. Therefore, the proposed study aims to identify the role of water quality and geographic variability on the incidence of kidney stones using a hospital based case-control study design.

3.1 Study Objectives

1. To assess the role of environmental factors associated with the risk of kidney stones among cases and controls.

2. To assess the role of water quality and geographic variability on the occurrence of kidney stone among select cases.

4 METHODOLOGY

4.1 Study design and subjects

The study was a hospital based case-control study design that included a total sample size of 250 (100 cases and 150 controls) participants. Study participants were recruited from Sri Ramachandra hospital and MIOT, from the Urology OP clinics to capture both urban and rural population. The age matched controls was recruited from General Medicine and ENT op clinics. Personal history, medical history, socio-economic status, occupational, water quality, geographical variability, physical activity and environmental factors related information's was collected using a questionnaire. In addition, a water sample was collected from selected 30 cases to assess the quality of water. Both the fresh and recurrent stone formers were included in the study. The inclusion and exclusion criteria for the study subjects were as follows:

Inclusion criteria:

- Kidney stone patients (both first and recurrent stone formers)
- Paediatric subject aged 2-18years
- Adult subjects aged above 18 years

Exclusion criteria:

- Family history of kidney stone

4.2 Sample size

Using Open Epi (version 3.01d) software the sample size was calculated. An odds ratio (OR) of 2.47 for renal stone occurrence was considered with power set at 80% and 95% confidence interval for sample size calculation based on Vigneshvar et al 2017 work. For a better statistical confidence, Case-control ratio of 1:1.5 was setup and 40% of exposure among controls was assumed. Sample size was calculated to be 80 cases and 80 controls. A conservative sample of 100 cases and 150 controls was selected for the proposed study.

Case definition: A case is defined as subjects (paediatric and adults) who were diagnosed or taking treatment for kidney stone (USG confirmed); they were enrolled in the study after getting informed consent.

Control definition: A control is defined as those subjects who are not having kidney stone issues or any other kidney related problems. They were chosen as controls after getting informed consent. Patients with any co morbidities or genetic predisposition were included.

4.3 Selection of patients

Patients admitted in the urology department, in Sri Ramachandra Institute of Higher Education and Research (Chennai), India, 2019 were recruited as the study participants. The study proposal was approved by institute committee of SRIHER and informed consent of study participant was obtained. By plain x-ray KUB, renal ultrasound and CT scan the diagnosis of kidney stone is confirmed. Information about age, gender, location, source of water quality and quantity, geographic variability were collected from the study participants through Questionnaire. Subjects with family history of kidney stone disease were excluded from the study.

4.4 Collection of water sample

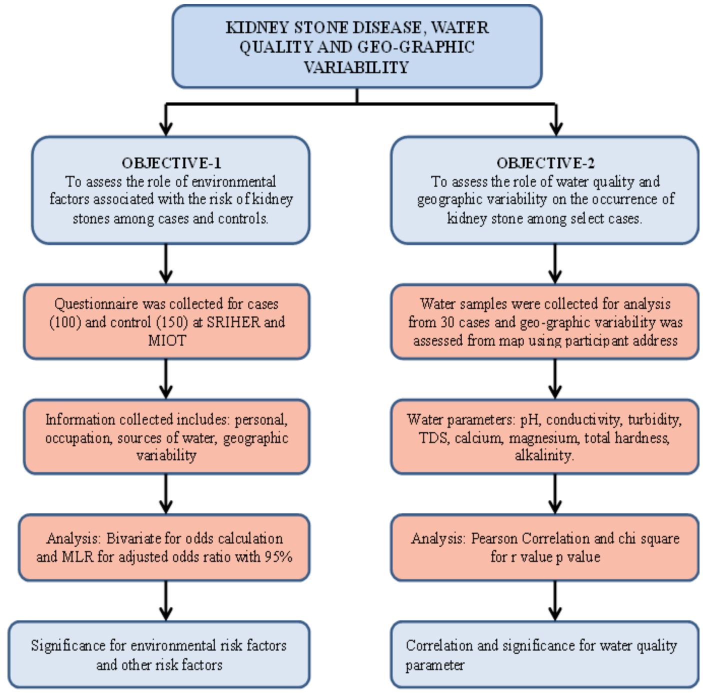
Water samples were collected from the subjects, that they have been using for drinking purpose at least 10 years. Water was collected in sterile polyethylene container which contains 100ml from selected subjects based on the selection criteria. Before a sample collection, the water was initially released to ensure fresh water and filled in 100ml polyethylene container and capped immediately to protect from contamination. The water samples were labeled properly and stored in the refrigerator and were analyzed in the laboratory.

4.5 Water sample analysis

Water samples were collected from the selected cases (n=30) to assess the water quality parameters which includes pH, water hardness, electrical conductivity, turbidity, total dissolved solutes and major ions such calcium, magnesium, water hardness and alkalinity. A subject who consuming water from Aqua guard or any other purifiers fitted in their house was excluded. pH was studied because it represents the acidic of water. The mineral content and salinity of the water were studied from the EC. The total amount of inorganic (e.g., calcium, magnesium) and organic minerals present in the water was studied from TDS. By the titration method using sulfuric acid and ethylene diamine tetraacetic acid, the total alkalinity and hardness were analyzed.

4.6 Study questionnaire

All study participants consenting to participate in the study were administered a questionnaire either at the time of recruitment in Urology OP clinics or in Hospital wards. The study questionnaire was developed based on literature review. The questionnaire was designed to collect participant's information about personal and medical history, socio-economic status, occupational assessment, environmental risk factors, water quality, quantity and geographic variability. Each questionnaire administration took about 10-15 min. A copy of the study questionnaire is attached in the appendix.



Figur1. Flow-chart of the study methodology describing participant recruitment, Questionnaire collection and Data analysis

4.7 Ethical consideration

The study objectives and methods were explained to participants and those who provided a voluntary consent were enrolled in the study. A copy of the informed consent used is attached in the Appendix. Throughout the study period, strict ethical code of practice was followed as prescribed in the National *Ethical Guidelines for Biomedical and Health Research involving Human Participant (ICMR 2017).*

4.8 Data analysis

4.8.1 Case-control data analysis

Data were collected from the questionnaires are entered in the Excel and analysis was performed using either R software or SPSS 20.0 software package. The descriptive statistics on background characteristics of *cases* and *controls* are presented as percentages. Associations between renal stone as 'dependent' variable and each of the 'independent' variables such as age, sex, occupation, socioeconomic status, religion, addictions, the source of drinking water and geographic variability were carried out using bivariate analysis. The information was collected under various sources of water and geographic variability. The association between a dependent variable and each independent variable was measured as Odds Ratio (OR) with 95% Confidence Intervals (CI). Finally, multinomial logistic regression using enter method was carried out to get the final model of risk factors for renal stones by adjusting the confounders. All the variables used for bivariate analysis were pulled for multivariate analysis. The multiple coefficient of determination (r^2) was used as the goodness-of-fit for the model. The $p<0.05$ was considered significant. There are three methods to adjust for confounding (matching, stratification and multivariate analysis). Out of these three methods, matching (age,-matched) was used in multinomial regression to adjust for confounders. Results were expressed by adjusted odds ratio, 95%CI and *p* value.

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5 RESULTS AND DISCUSSION

5.1 General description of cases and controls

A total of 290 (120 cases and 170 controls) study participants were screened out of which 250 (100cases, 150controls) study participants voluntarily consented to participate in the study. Approximately 14-17 cases per day were visited in Sri Ramachandra hospital and MIOT, from urology OP clinic. Increased rate of KSD patients in urology specialty from these two hospitals allowed for the convenient recruitment process. On both weekdays and weekend, study participants were recruited. The recruitment rate was 5-7subjects/day. Subject recruitment and questionnaire was administered between 1st February 2019 to 22nd April 2019.

The mean age (minimum-maximum) of cases was 38.2 years (20-80years) and controls were 36.08 years (21-66) (Table 4). The mean BMI of cases was 25.14±5.07 and controls were 26.46±4.34, respectively (Table 4). The history of kidney stone disease in cases was mostly first time stone former 65% and recurrent stone formers were 35% (Table 5). In occupation, most of the cases were labors, house workers, and not working groups were engaged in the risk of kidney stone disease. The middle socio economic status were high in the cases of 51%, whereas the upper and lower was only 18% and 12% (Table 5). Both cases of 59% and 90.7% of controls were from urban location when compared with rural, because Sri Ramachandra and MIOT hospital located in the nearest urban area (Table 4). Over 92% and 8% of study subjects were recruited from SRMC and MIOT, urology OP clinic (Table 4).

From the marital status we observed that 80% of cases and 54% of controls were distributed in married. In type of family, 80% of cases were from nuclear family and 20% were joint family, whereas in controls 94% nuclear family and 6% joint family (Table 5). In living alone group, there were no cases and controls. Residence proximity to highway road showed 50% cases were residing near the highways (Table 5). In geographic variability, 72% of the cases covered with low green space when compared with controls (Table 5). Sources of drinking water were equally distributed in cases and controls except mixed water type. In cases, 35% were drinking mixed water than controls (Table 5).

Table4. General description of the study population (n=250)

Characteristics	Cases (n=100)	Controls (n=150)
Personal (%)		
Age (Mean±SD)	38.2±16.2	36.08±14.7
Body mass index (Mean±SD)	25.14±5.07	26.46±4.34
Normal	38 (38)	65 (43.3)
Over weight	35 (35)	51 (34)
Obese	14 (14)	34 (22.6)
Under weight	10 (10)	0
Hospital Recruitment (%)		
SRIHER	92	0
MIOT	8	0
Population (%)		
Adult	93	148 (98.6)
Pediatric	7	2 (1.3)
Household Characteristics		
Location (%)		
Urban	59	136 (90.7)
Rural	41	14 (9.3)
House type (%)		
Pucca	86	98
Semi Pucca	11	2
Kutcha	3	0
Diet pattern (%)		
Vegetarian	9	95.3
Non-vegetarian	91	4.6

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Table 5. Distribution of cases and controls across background characteristics

Characteristics	Cases(n=100)	Control(n=150)
Age in years		
<15	7 (7)	2 (1.3)
20-40	43 (43)	105 (70)
41-60	35 (35)	33 (22)
61-80	15 (15)	10 (6.6)
Sex		
Male	65 (65)	84 (56)
Female	35 (35)	66 (44)
Occupation		
Housework	27 (27)	22 (14.6)
Agricultural work	8 (8)	2 (1.3)
Labour	28 (28)	31 (20.6)
Professionals	14 (14)	63 (42)
Not working	23 (23)	32 (21.3)
Years of education		
Illiterate	9 (9)	11 (7.3)
Primary	26 (26)	13 (8.6)
Higher secondary	27 (27)	9 (6)
Degree	38 (38)	117 (78)
Religion		
Hindu	79 (79)	84 (56)
Muslim	6 (6)	8 (5.3)
Christian	15 (15)	58 (38.6)
Marital status		
Married	80 (80)	81 (54)
Unmarried	20 (20)	69 (46)
Type of family		
Joint family	20 (20)	9 (6)
Nuclear family	80 (80)	141 (94)
Living alone	0 (0)	0 (0)
Socio-Economic status		
Upper	18 (18)	53 (35.3)
Middle	51 (51)	85 (56.6)
Low	31 (31)	12 (8)
Comorbidities		
With comorbidities	18 (18)	5 (3.3)
Without comorbidities	82 (82)	145 (96.6)
Environmental risk factor		
Distance of the House from main road		
Less than 500m	50 (50)	25 (16.6)
More than 500m	50 (50)	125 (83.3)
Source of Drinking water		
Bore-well	15 (15)	28 (18.6)
Municipal	13 (13)	40 (26.6)
Well water	2 (2)	2 (1.3)
Packaged water	12 (12)	10 (6.6)
R.O water	22 (22)	60 (40)
Lake water	3 (3)	0
Mixed water	35 (35)	10 (6.6)

5.2 Bivariate analysis of risk factors for KSD

In a questionnaire the information's collected were identified as a significant risk factor associated with KSD in Bivariate analysis. Some of the significant risk factors with highest OR include distance from main road, water consumption, religion, BMI, boiling drinking water. In this study, it was found that age of 20-40 was a significant risk factor for KSD. In male subjects the odds ratio of 1.46 times (CI; 0.87-2.46) (Table 6) increases the risk of KSD when compared to female subjects. In the occupation, labors, house workers (i.e., house wife's and house keepings) odds ratio was 0.25% (CI; 0.1-0.57), 0.18 (CI; 0.07-0.44) and 0.31 (CI; 0.13-0.73) (Table 6). The agriculture workers were only 8% with odds ratio of 0.6 (CI; 0.01-0.33). In the religion, the odds ratio for Christian was 3.62 times (CI; 3.59-7.45) higher risk of KSD when compared with Muslim (Table 6). The odds ratio of municipal water was 2 (CI; 0.73-5.65) and R.O water was 1.51(CI; 0.63-3.6) times increased than bore water, packaged water and mixed water (Table 6). Consumption of water less than 3 liter per day has showed the high odds ratio of 8.7times (CI; 4.62-17) increases the risk of KSD when compared to subject who drink more than 3 liters per day (Table 6). The moderate rate of vehicles near the residence showed the odds ratio of 1.84 times (CI; 0.78-4.29) risk of KSD when compared to high and low rate of vehicles (Table 6). Subject who do not drink the boiling water has showed the odds ratio of 4.16 (CI; 2.07-8.36) when compared to who drinks the boiling water (Table 6). Subjects whose residence proximity to highways (< 500m) were 5 times (CI; 2.8-8.94) increase the risk of KSD when compared to residence away from highways (Table 6). Subjects whose residence covers low green space the odds ratio was 4.38 times (CI; 2.34-8.2) increase in the risk of KSD when compared to high green space (Table 6). Subjects who drink Tea/Coffee/Milk the odds ratio was 3.37 times (CI; 1.49-7.63) increases the risk of developing KSD when compared to the subject who don't drink in the given table 3. In exposure to heat, 71% of the cases and 90% of the controls were exposed with the OR of 0.29 (CI; 0.14-0.57) (Table 6).

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Table6. Bivariate analysis for the risk factors for KSD

Variables	Cases (n=100)	Controls (n=150)	OR, 95%CI	P value
Age				
<15	7 (7)	2 (1.3)	1	
20-40	43 (43)	105 (70)	8.42(1.52-86.37)	
41-60	35 (35)	33 (22)	3.25(0.56-34.31)	0
61-80	15 (15)	10 (6.6)	2.28(0.33-26.921)	
Occupation				
Housework	27 (27)	22 (14.6)	0.18(0.07-0.44)	
Agriculture	8 (8)	2 (1.3)	0.06(0.01-0.33)	
Labour	28 (28)	31 (20.6)	0.25(0.1-0.57)	0
Professionals	14 (14)	63 (42)	1	
Not working	23 (23)	32 (21.3)	0.31(0.13-0.73)	
Socio-Economic status				
Upper	18 (18)	53 (35.3)	1	
Middle	51 (51)	85 (56.6)	0.57(0.28-1.11)	0
Low	31 (31)	12 (8)	0.13(0.05-0.33)	
Alcoholic				
Yes	14 (14)	42 (28)		
No	86 (86)	108 (72)	0.42(0.21-0.82)	0.00
Source of Drinking water				
Bore-well	15 (15)	28 (18.6)	1	
Municipal	13 (13)	40 (26.6)	2(0.73-5.65)	
Well water	2 (2)	2 (1.3)	0.56(0.04-8.5)	
Packaged	12 (12)	10 (6.63)	0.51(0.16-1.62)	0
R.O water	22 (22)	60 (40)	1.51(0.63-3.6)	
Lake water	3 (3)	0	0	
Mixed water	35 (35)	10 (6.6)	0.16(0.05-0.45)	
Amount of water intake per day				
<3 liters	80 (80)	44 (29.3)	8.7(4.62-17)	
≥3 liters	20 (20)	106 (70.6)	1	0
Rate of vehicles				
High	15 (15)	19 (12.6)	1	
Moderate	38 (38)	89 (59.3)	1.84(0.78-4.29)	0.00
Low	47 (47)	42 (28)	0.71(0.29-1.68)	
Boiling drinking water				
Yes	30 (30)	14 (9.3)		
No	70 (70)	136 (90.6)	4.16(2.07-8.36)	0
Distance of the House from main road				
<500m	50 (50)	25 (16.6)		
>500m	50 (50)	125 (83.3)	5(2.8-8.94)	0
Exposure to Heat				
≥4 hours	71 (71)	135 (90)		
<4 hours	28 (28)	15 (10)	0.29(0.14-0.57)	0
Green space				
Low	72 (72)	25 (16.6)	4.38 (2.34-8.2)	0
High	28 (28)	83 (55.3)		
Physical activity				
Sedentary	39 (39)	39 (26)	1	
Moderate	47 (47)	92 (61.3)	1.44(0.61-3.34)	0.00
Heavy	14 (14)	19 (12.6)	0.9(0.36-2.23)	
Tea /Coffee /Milk				
Yes	92(92)	116(77.3)	3.37(1.49-7.63)	0.00
No	8(8)	34(22.6)		

5.3 Multivariate analysis of risk factors for KSD

Final multivariate regression model after adjusting for confounders, eight variable i.e. religion, green space, boiling drinking water, distance from main road, amount of water intake per day and drinking tea/coffee/milk were observed to be significant. In multivariate analysis the adjusted confounder's are age, gender, occupation and location. The risk of developing KSD in the study participants who drink less than 3 Liters of water per day 10.58 times (CI; 5.29-21.18) higher when compared to all other risk (Table 7). Another significant risk of developing KSD in terms of calculated OR was Distance from highway roads (<500m). The residence proximity to highways increased the risk of KSD by 4.66 times (CI; 4.46-8.85) when compared to residence away (Table 7). Next important factor was drinking boiling water. The risk was 3.22 (CI; 1.51-6.88) times higher among those who don't consume boiling water. In addition the other significant risk factor is religion. The risk was 3.56 times (CI; 1.74-7.28) higher among Christian religion (Table 7). Drinking Tea/ Coffee/ Milk increased the risk of KSD disease by 2.72 times (CI; 1.12-6.61) higher when compared to controls (Table 7).

Table7. Multinomial logistic regression analysis; Final model of Environmental risk factors for KSD.

Variables	cases (n=100)	controls (n=150)	adjusted or, 95% CI
Religion			
Hindu	79 (79)	84 (56)	1
Muslim	6 (6)	8 (5.3)	3.04 (0.82-11.29)
Christian	15 (15)	58 (38.6)	3.56 (1.74-7.28)
Sources of drinking water			
Bore water	15 (15)	28 (18.6)	1
Municipal	13 (13)	40 (26.6)	1.40 (0.90-2.19)
Well water	2 (2)	2 (1.3)	3.57 (2.30-5.54)
Packaged	12 (12)	10 (6.63)	0.56 (0.18-0.67)
R.O water	22 (22)	60 (40)	0.37 (0.40-0.52)
Mixed	35 (38)	10 (6.6)	0.36 (0.12-1.14)
Distance from main road to house			
<500m	50 (50)	25 (16.6)	4.66 (4.46-8.85)
>500m	50 (50)	125 (83.3)	
Green space			
Low	72 (72)	25 (16.6)	0.30 (0.17-0.52)
High	28 (28)	83 (55.3)	
Boiling drinking water			
Yes	30 (30)	14 (9.3)	3.22 (1.51-6.88)
No	70 (70)	136 (90.6)	
Rate of vehicles			
High	15 (15)	19 (12.6)	1
Moderate	38 (38)	89 (59.3)	1.00 (0.42-2.40)
Low	47 (47)	42 (28)	0.47 (0.25-0.88)
Amount of water intake per day			
<3 lit	80 (80)	44 (29.3)	10.58 (5.29-21.18)
>3 lit	20 (20)	106 (70.6)	
Tea/Coffee/Milk			
Yes	92 (92)	116 (77.3)	2.72 (1.12-6.61)
No	8 (8)	34 (22.6)	

5.4 Assessment of water quantity, quality and green space as risk factors for KSD among selected cases:

To assess the drinking water quality, water samples were collected from selected 30 cases. The collected water samples were borewell, municipal, packaged, well, lake water and mixed source of water. From the collected samples most were bore well, municipal and mixed source of water. We observed that there was an association between drinking water geochemistry and KSD. Similar to this study, there was an association between water geochemistry and KSD was observed (Kale et al 2013). Relationship for water parameter from different sources of drinking water was made to understand the effect of geo environmental condition on KSD. In subjects who consume R.O water has high pH average of 8.21±0 when compared with other sources of drinking water (Table 8). The mean and standard deviation for electrical conductivity was observed in limited range in all sources of water (Table 8). The average for turbidity was observed in limited range in all sources of drinking water (Table 8). TDS was high in subjects who consume R.O water with the average of 419.33±0 when compared to other sources of water (Table 8). Calcium was high in subjects who consume borewell (61.83±61.59) and municipal (61.83±61.59) water (Table 8). The normal limited range for water hardness was 60-120 (McGowan et al, 2000). In current study, water hardness was observed high in all sources of water were exceeding above limited range. High water hardness was observed in subjects who consume mixed sources of water 333.2±202.87 (Table 8). In present study, there was a significantly correlation between calcium and water hardness (p=0.00) (B) (Figure 2). There is no statistically significant between Mg, alkalinity, TDS, turbidity with KSD. Mg was positively correlated with calcium (Figure 3). Subjects who consumed bore water and municipal water were associated with KSD because of high calcium content in the water 61.83 (Table 8). In figure 1, we observed that TDS and water hardness was high among fresh stone formers than recurrent stone formers. Fresh stone formers were high (n=24) when compared to recurrent stone formers (n=6) (Figure 2). Water consumed by Fresh stone formers has high TDS than recurrent stone formers (Figure 2). Recurrent stone formers were more aware about the water quality and quantity on KSD than the fresh stone formers. In the relationship between water parameter and drinking boiled water, we observed that, TDS, water hardness and alkalinity was high in the subject who consumes boiled drinking water. Drinking boiled water were statistically significant with odds ratio of 3.22 (CI; 1.51-6.88) among cases and controls (Table 7).

The geographic variability indicates the residence proximity to highways and green space cover. In current study, we observe that 72% of the cases were from low green space (Table 10). Low green space was observed statistically significant with 3.19 times CI; 1.85-5.48) in the risk of KSD among cases (Table 10). The residence proximity to highways was significant with 4.66 times (CI; 4.46-8.85) risk of KSD. In location, urban/rural area plays a major role in the low green space and KSD. Since 59% (Table 4) of the cases were from urban area, they were lack from high green space and there residences were near to highways.

Table8. Summary statistics of water parameter and source of drinking water

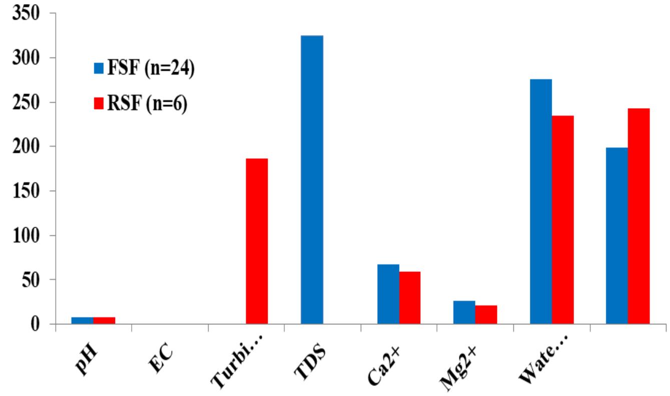
WATER PARAMETERS	BORE Mean±SD	MUNICIPAL Mean±SD	PACKAGED Mean±SD	R.O Mean±SD	MIXED Mean±SD
pH	7.59±0.33	7.66±0.34	7.6±0.34	8.21±0	7.58±0.36
EC	0.71±0.72	0.76±0.71	0.59±0.66	0.88±0	0.52±0.6
Turbidity	0.09±0.11	0.09±0.11	0.09±0.09	0.06±0	0.1±0.1
TDS	335.42±343.4	363.49±340.56	278.78±313.06	419.33±0	245.11±284.15
Calcium	61.83±61.59	61.83±61.59	61.43±57.03	59±0	82.2±55.02
Magnesium	22.83±17.83	22.83±17.83	22.57±16.52	21±0	31.2±17.24
Water hardness	248±224.95	248±224.95	246.14±208.31	235±0	333.2±202.87
Alkalinity	180.5±162.23	180.5±162.23	189.43±151.78	243±0	232.6±117.43

Table9. Summary statistics of the water samples from urban and rural location, Chennai

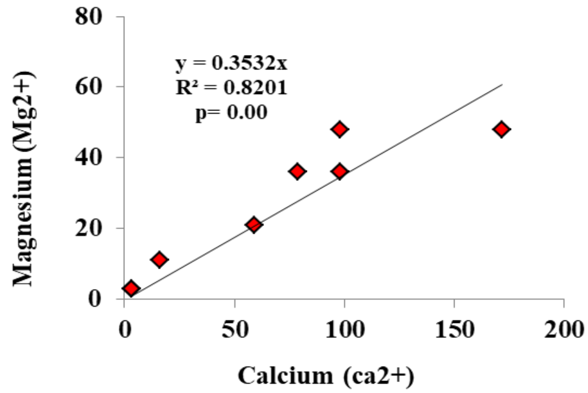
WATERPARAMETER	URBAN Mean±SD	RURAL Mean±SD
Ph	7.55±0.34	7.62±0.36
EC	0.45±0.55	0.63±0.66
Turbidity	0.1±0.16	0.09±0.09
TDS	213.41±262.77	297.29±314.86
Calcium	55.33±59.45	66±54.7
Magnesium	20.33±16.83	25.75±17.59
Water hardness	221.83±215.61	270.5±202.24
Alkalinity	153.17±132.93	204.5±147.47

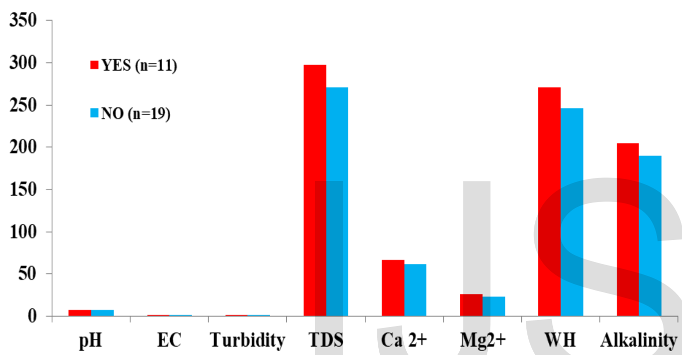
Table10. Geographic variability

TYPE OF SUBJECTS (n=250)	GREEN SPACE (%)		OR,CI	P VALUE
	LOW	HIGH		
Cases (n=100)	72	18.6	3.19 (1.85-5.48)	0
Controls (n=150)	67	55.3		

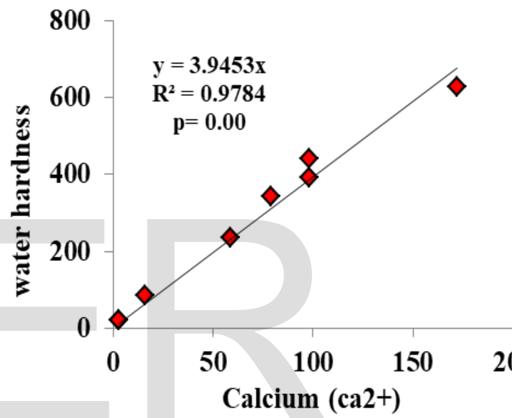


Relationship of water parameters and type of stone former





Relationship of water parameter and drinking boiled water by cases subjects



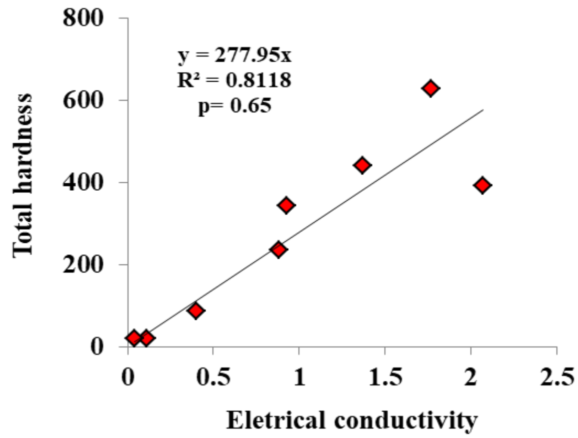


Figure4. Major ions relationships for drinking water in Chennai region

5.5 GENERAL DISCUSSION

As the incidence of KSD increases day by day, it becomes a major health issue around worldwide. Due to contribution of kidney stone disease in terms of mortalities and morbidities, India was ranked 9th place in the worldwide burden of disease (www.ihme.org). about 10-15% human population was targeted all over world and reported as "kidney stone belt" (Coe et al, 2005). The etiology of kidney stones was multi-factorial with traditional factors that include age, gender, race, genetic, and diet. The environmental factors such as water quality and quantity, geographic variability, hot environment and occupation have been found to be associated with KSDs. In addition, co-morbidities include obesity, diabetes mellitus, and hypertension were associated risk factors for kidney stone formation (Jiang et al, 2017). With rapid urbanization, shortage of water resources both in terms of quantity and quality and behavioral modifications, KSDs was raised across India. Based on the studies from few countries, they have observed that age, environmental factors such as water quality and quantity was associated with kidney stone disease. The water consumed less than 3liters per day, associated with KSD (Mitra et al, 2013), the another study found that there was an association between KSD and drinking water geochemistry as evident with high calcium and water hardness content in water used by the subjects (Abeywickarama et al, 2015). Another study observed that EC, Na and F are correlated in the formation of KSD (Kale et al, 2013). Geographical variability such as residence proximity to highways was associated with KSD (Soucie et al 1994, Wang et al, Lue SH et al, 2013). Among environmental factors, water quality and quantity plays a significant role in the stone formation. The risk of kidney stone formation aggravates when the low consumption of fluid, especially water (Borgi et al, 1999). The chemical compositions in the drinking water were performed to have an impact on the human health. The water pretreatment were also linked with the occurrence of kidney stone because of dissolution, precipitation of solution, mixing of different types of water, evaporation, selective removal of ions and resident time of water are major natural factor. There is also an association with geographic variability and KSD. The geographic variability includes residence, green space cover, living status which indicates the built environment.

In the current study, I have focused on whether there was an association between environmental risk factors particularly water quality, quantity and geo-graphic variability with the KSD. The cases and controls were recruited from Sri Ramachandra and MIOT hospital, Chennai, between February 1st to march 28th, 2019. The environmental risk factors for KSD was assessed for cases (n=100) and controls (n=150) by using questionnaire. In addition of, water samples were collected from the selected 30 cases to assess the water chemistry. Geographic variability was assessed by locating the participant's addresses to identify the green space cover.

In order to assess the environmental risk factor association with KSD, case-control study design was chosen. Though the rate of kidney stone patient's visiting the urology op clinics were high in both hospital, the recruitment of cases (n=100) and controls (n=150) was easy. In the current study 65% were fresh stone formers. The most important age group in the study was 20-40. The study observed a statistical significant of age group between 20-40 with 8.42 (OR, CI: 1.52-86.37) among cases and controls. Similar to this study, the age group of 30-40 has showed the highest kidney stone incidence in men (Cupisti et al, 2007) and for women 35-55 years (Madhusudan et al 2015). Mathiyalagen et al 2017 these studies observed a strong correlation between high BMI. The present study has significantly no correlation BMI. The other important significant risk factor was boiling drinking water with 4.16 (OR,CI: 2.07-8.36) among cases and controls. Arumugam et al study found that there was no statistical significant for boiling drinking water (Arumugam et al, 2018). In the current study, the residence proximity to highways was found a statistical significant of 5 (OR, CI: 2.8-8.94) than the residence away from highways. Ideally, this study found that the residence proximity to major highways associated with impact on kidney disease (Lue et al, 2013). In present study, low green space cover has found a statistical significant of 4.38 (OR, CI: 2.34-8.2). Keeping in the mind the occupation status, environmental activities, and built environment in Chennai city, we set a water intake of 3lit per day as recommended by the clinical practitioners. Correspondingly we have found that 80% of the cases were drinking less than 3 liters of water per day. The tendency for low consumption of water was significantly higher (p=0) in cases than in controls. This observation was similar to the study which was done in India. They found that 53.6% (p=0.0002) of the cases consume less than 3 liters water day (Mitra et al, 2017).

There was only few studies were examined the relationship between water quality, quantity, geographic variability and kidney stone disease, to my knowledge. Correspondingly we collected drinking water samples from selected 30 cases and analyzed for different parameter in the water. From the analyzed water parameter we have found that there is significant correlation between drinking water geochemistry and KSD by the calcium and water hardness (p=0.00) content in the water. The similar observation was found that, there was an association between stone formation and drinking water geochemistry by the calcium and water hardness content in spring water (Abeywickarama et al, 2015). Bore well and municipal water was used as main source of water in Chennai city, as it comparatively inexpensive and mostly safe except in few areas. In the current study the geographic variability was statistically significant 3.19 (OR, CI: 1.85-5.48) with low green space cover in the cases among controls. The similar observation was found that geographic variability is the significant risk factor for KSD (Soucie et al, 1994).

The environmental risk factors particularly water quality, quantity and geographic variability identified in this study strongly corroborates the findings of several case-control studies form both India and elsewhere. Further, Water quality, quantity, location and geographic variability were found to significant risk factors for KSD among cases.

6 LIMITATION OF THE STUDY

Since it was a double-institutional study, the sample size was less. If it is multi-institution design, the sample size would be high. Water Analysis cost was expensive, so it was performed with limited cases. Another limitation to the study was less time period for subject's recruitment. Limited studies were available they have examined the relationship between water quantity, quality and geographic variability.

7 RECOMMENDATION

A total of 290 study participants were screened out of which 250 (100 cases, 150 controls) were voluntarily consented to participate in the study. The environmental risk factors particularly water quality; quantity and geographic variability were observed to be associated with incidence of KSD. Increased consumption of water intake, avoidance of drinking tea/coffee/milk could prevent from kidney stone disease. Excessive intake of mineralized salts in drinking water should be avoided. Bore well or municipal water should be treated properly to reduce the dissolved ionic salts. First time stone formers should take extra precaution of keeping themselves in hot environment.

Future research should focus on examining the following aspects:

- Multi-institutional case-control study to obtain true incidence and prevalence rates
- Physico-chemical evaluation of kidney stones and its relation to geographic location, metabolism and dietary habits
- A statewide time-series analysis of climatic factors and incidence rate of kidney stones to inform health policies at State and National levels
- Risk of kidney stones among patients with hypertension, diabetes and obesity
- Economics of kidney stone disease management India and quality of life

8 CONCLUSION

The primary aim of the study was to assess the environmental risk factor particularly water quality, quantity and geographic variability in the incidence of the kidney stone disease. Significant risk factors identified for kidney stone disease include age, drinking boiling water, distance form highways, green space cover, amount of water intake per day, consumption of Tea/Coffee/Milk. Boiling water and type of drinking water (i.e., borewell and municipal) was observed to be a common risk factor among first stone formers when compared to recurrent cases. Residence proximity to highways and low green space were found to significant risk factor for KSD. Water hardness and calcium levels in drinking water of first time stone formers was significantly high compared recurrent stone formers. Identified risk factors in this study were in agreement with findings from studies from Tamil Nadu, other parts of India and developed countries.

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