Prevalence of Chronic Kidney Disease and its Association with Risk Factors in Eastern Uttar Pradesh, India

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Abstract

**Background:** Chronic kidney disease (CKD) is a global health problem with high mortality and morbidity rates. CKD is found associated with a number of life threatening diseases such as diabetes, anemia, liver and cardiovascular diseases. CKD is highly prevalent in India but its etiology varies in different part of the country.

**Methods:** Here, we analyzed the prevalence of CKD (~4%) among population (n=1808) living at eastern part of Uttar Pradesh in India during September 2018 to October 2019 based on GFR and urine albumin levels, and tried to explore the risk factors associated with this disease.

**Results:** CKD with stage 3 and 4 was comparatively found more prevalent among patients with significantly higher levels of serum creatinine, blood urea nitrogen (BUN) and uric acid than normal patients. Anemia was diagnosed in 86% of the CKD patients, out of which 79% were found, affected with normocytic hypochromic anemia. More interestingly, diabetes was also equally prevalent (82%) among CKD patients mostly in stage 4. This study was also aligned with a study reporting an endemicity of fluoride toxicity in drinking water in this region particularly in Dalmau and Amawa blocks. We found that chronic exposure to fluoride (more than 1.5 ppm) in drinking water appeared as a key risk factor for causing diabetic nephropathy leading to CKD in affected individuals.

**Conclusion:** Fluoride appeared as a major environmental factor that contributed in prevalence of CKD in eastern Uttar Pradesh particularly in Raebareli district.

**Keywords:** Chronic kidney disease; Glomerular filtration rate; Kidney

Introduction

India constitute 17% of world population living at <3% of land mass. Poor sanitation, contaminated water, pollutants, nephrotoxins etc. result in kidney diseases. Reduced kidney function defined as glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² and damage to kidneys (indicated by albuminuria or proteinuria) for a period of 3 months or more lead to chronic kidney disease (CKD) [1,2]. But, large number of population below or around poverty line and lack of proper medication make CKD highly prevalent in India because more than half of the patients with advanced CKD are diagnosed first time with GFR <15 mL/min/1.73 m² which is the last stage of CKD [3]. Therefore, CKD patients are at the high risk of end stage renal disease (ESRD) that requires costly treatment such as dialysis and renal replacement therapy (RRT), because they are quite limited and expensive for most of the patients therefore aid in high morbidity and mortality rate [4]. The most common social impact of CKD is to impose financial burden on the patients for the treatment. Etiology of CKD is highly variable across India as some states e.g. Andhra Pradesh, Goa and Odisha have high prevalence of unknown etiology comprising interstitial nephropathy etc [5].

GFR is a well establish index to estimate kidney function and classify CKD into five stages [6]. But its progression may be majorly determined by high urine albumin levels [7]. A number of studies have been conducted on impaired kidney function based on combination of GFR and albuminuria [2]. Blood urea nitrogen (BUN), creatinine and uric acid are the parameters used for kidney function test (KFT) but serum creatinine level is a benchmark for calculating GFR. Lower estimated GFR (eGFR) is recognized as major and independent risk factor for developing cardiovascular disease and anemia [8-11]. Kidney is a main site for production of erythropoietin which is responsible for production of erythrocytes in response to low oxygen levels in blood. Erythropoietin deficiency has been considered as a predominant cause for developing anemia in CKD patients [12].
Erythropoiesis stimulating agents (ESAs) have been demonstrated to cure anemia in patients with ESRD [13,14].

Type-2 diabetes (T2D) is characterized by persistent hyperglycemia resulting predominantly due to insulin resistance. Kidney plays a key role in glycemic control through tubular reabsorption of glucose and renal gluconeogenesis [15]. Diabetes induced kidney disease or diabetic nephropathy is a most frequent and lethal complication of T2D affecting 20%-40% of diabetic patients [16]. Therefore, screening of diabetic patients for nephropathy is required from the starting with initial diagnosis of hyperglycemia. Increased urine albumin levels is an initial stage of developing CKD in diabetic patients leading to gradual decline in GFR, therefore it is important to conduct both blood and urine screening tests on such patients. The urine albumin measurement and reporting is important for early diagnosis and subsequent treatment of diabetic nephropathy. Chronic exposure to fluoride has been demonstrated to confer insulin resistance and kidney damage from drinking water [17,18]. A number of animal studies reported that fluoride is linked to hyperglycemia through increased glycogenolysis and reduced insulin secretion [19]. In addition, fluoride is also associated with impaired renal function and damage particularly in tubular epithelium and glomerulus [20]. Elevated fluoride concentration in drinking water has been found to be associated with prevalence of CKD in various fluoride endemic zones across the world [21,22].

A number of studies on CKD prevalence have been conducted in eastern Uttar Pradesh excluding Raebareli and adjacent regions based on age and other factors [23,24]. Here, we have conducted a hospital based cross sectional study on prevalence of CKD among individuals living in eastern Uttar Pradesh particularly in Raebareli and adjacent districts. Our study demonstrates that fluoride induced prolonged and untreated T2D is linked to incidence of CKD or ESRD in the patients of fluoride endemic regions [25].

Methodology

Study design

This is a hospital based retrospective study conducted on the patients (n=1808) with age group of 57 ± 15 years during the month of September 2018 to October 2019 at Outpatient department (OPD), All India Institute of Medical Sciences (AIIMS), Raebareli. The blood samples were collected in sodium fluoride in K2-EDTA vaccutainers. Urine albumin levels were detected using urine dip-stick test and clinical examinations. All diagnostic tests including urine examinations were conducted at laboratory, AIIMS, Raebareli.

Study variables and definitions

GFR was calculated using IDMS-traceable MDRD study equation: 
\[
GFR=175 \times (S_C)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if Black}),
\]
where \(S_C\) is serum creatinine in mg/dL and age is expressed in years. CKD is defined by structural or functional abnormality of kidney or impaired creatinine clearance or reduced GFR<1.73 mL/min/1.73 m² for a period of 3 months or more [26]. CKD was classified into 5 stages based on calculated GFR and evidence of kidney damage (Albuminuria), as per recommendations by National Kidney Foundation (Table 1).

Inclusions and exclusions

This study includes patients with prevalent CKD and diagnosed at OPD AIIMS, Raebareli during the period of one year (September 2018 to October 2019). Here, we excluded patients with cancer except skin cancer, hematological disorders, inflammatory, infectious (e.g. malaria, dengue), bleeding and transplant history.

Statistical analysis

We have used Student’s t-Test and one-way ANOVA for determining significance for our analysis. A p value of less than 0.01 was considered significant and less than 0.05 was considered as partially significant for our study.

Results

This study was conducted on the individuals (n=1808, age=17-95 years) living at eastern Uttar Pradesh during the period of one year and were diagnosed for CKD based on elevated serum creatinine levels, urine dipstick tests and clinical symptoms (weight loss, high blood pressure, joint pain etc.) at OPD, AIIMS, Raebareli. Thereafter, we categorized these CKD patients into various stages (1-5) based on GFR rates (Table 1).

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD 1</td>
<td>&gt;89</td>
<td>Slight kidney damage with normal GFR</td>
</tr>
<tr>
<td>CKD 2</td>
<td>60-89</td>
<td>Kidney damage with mildly decreased GFR</td>
</tr>
<tr>
<td>CKD 3</td>
<td>30-59</td>
<td>Kidney damage with moderately decreased GFR</td>
</tr>
<tr>
<td>CKD 4</td>
<td>15-29</td>
<td>Severe decrease in kidney function</td>
</tr>
<tr>
<td>CKD 5</td>
<td>&lt;15</td>
<td>End-stage kidney failure</td>
</tr>
</tbody>
</table>

The patients from various blocks of Raebareli district including Amethi and Unnao district of Uttar Pradesh were included in this study. The prevalence of CKD was quite high in Dalmau (15.07%), Rahi (13.7%), Lalganj (10.96%) and Amawa (9.59%) blocks (Figure 1a) including Raebareli city (28.77%) of Raebareli district.
In our study, 4.03% of population was found prone to CKD out of which patients with stage 3 (36.99%) and 4 (38.36%) were more prevalent than the other stages (Figure 1b and Figure 1c). Around 17.80% of CKD patients were found at the risk of last stage (stage 5) or ESRD (Figure 1c).

**Table 2**: Prevalence (%) of CKD patients in different blocks of Raebareli, Amethi and Unnao district of Uttar Pradesh.

<table>
<thead>
<tr>
<th>Location</th>
<th>% Prevalence of CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raebareli district</td>
<td></td>
</tr>
<tr>
<td>Lalganj</td>
<td>10.96</td>
</tr>
<tr>
<td>Amawan</td>
<td>9.59</td>
</tr>
<tr>
<td>Dalmau</td>
<td>15.07</td>
</tr>
<tr>
<td>Salon</td>
<td>4.11</td>
</tr>
<tr>
<td>Rahi</td>
<td>13.7</td>
</tr>
<tr>
<td>Sataon</td>
<td>4.11</td>
</tr>
<tr>
<td>Shivgarh</td>
<td>1.37</td>
</tr>
<tr>
<td>Deen shah gaura</td>
<td>1.37</td>
</tr>
<tr>
<td>Maharajganj</td>
<td>2.73</td>
</tr>
<tr>
<td>Deeh</td>
<td>1.37</td>
</tr>
<tr>
<td>Sareni</td>
<td>1.37</td>
</tr>
<tr>
<td>Bachhrawan</td>
<td>1.37</td>
</tr>
<tr>
<td>Raebareli city</td>
<td>28.77</td>
</tr>
<tr>
<td>Amethi district</td>
<td></td>
</tr>
<tr>
<td>Amethi city</td>
<td>2.74</td>
</tr>
</tbody>
</table>

Kidney functions were severely compromised in CKD patients

Various parameters of kidney function test on patient’s serum were compared to normal healthy patients. Serum creatinine levels were significantly elevated in CKD patients (2.86 ± 2.14 mg/dL) with p value<0.001 (n=20-73) compared to normal healthy individuals (1.0 ± 0.14 mg/dL) (Figure 2a). Blood urea nitrogen (BUN) was also significantly increased in CKD patients (43.3 ± 27.6 mg/dL) than normal individuals (10.33 ± 2.8 mg/dL) with p value<0.00001 (n=20-73) (Figure 2b). Interestingly, uric acid (UA) level was found slightly elevated in CKD patients (6.42 ± 1.8 mg/dL) compared to normal individuals (4.7 ± 1.8 mg/dL) and this increase was found significant with p value<0.001 (Figure 2c). In addition, we also found that more than 86% of CKD patients were diagnosed for albuminuria (Figure 2d). Urine albumin levels in CKD patients (200 ± 109 mg/dL) were significantly elevated with p value<0.01 (n=6-15) as compared to normal healthy individuals (11.25 ± 4.3 mg/dL) (Figure 2e).

**Figure 1**: Prevalence of chronic kidney disease (CKD) in eastern Uttar Pradesh. (a) A map modified from, depicts various blocks of Raebareli district and associated districts of eastern U. P. (b) Prevalence of CKD patients (4.02%, orange color) among individuals after diagnosis. (c) Distribution of various CKD stages based on glomerular filtration rates (Table 1); CKD 1 (black), CKD 2 (red), CKD 3 (green), CKD 4 (yellow) and CKD 5 (blue).

**Figure 2**: Comparison of various parameters denoting kidney function and its damage in the population. (a) Mean ± SD (standard deviation) values of serum creatinine level (mg/dL) in normal and CKD patients (black and red dots respectively, n=20-73). (b) Mean ± SD values of blood urea nitrogen (BUN, in mg/dL) in normal and CKD patients (black and red dots respectively, n=20-73). Mean ± SD values of uric acid level (mg/dL) in normal and CKD patients (black and red dots respectively, n=20-65). The levels of serum creatinine, BUN, uric acid were significantly elevated in CKD patients. (d) Pie chart depicting % of CKD patients with albuminuria (red color). Levels of urine albumin (in mg/dL) in normal individuals (grey bar) and CKD patients (red bar) respectively (n=6-15). *represent p value<0.01, **represent p value<0.00001).
Normocytic hypochromic anemia was highly prevalent in CKD patients

Our study demonstrates that CKD patients are highly susceptible to anemia as 86% of CKD patients were diagnosed for low Hb levels (Figure 3a). Hb levels in CKD patients (10 ± 2 g/dl) were significantly lower as compared to normal individuals (13.5 ± 1.5 g/dl) with p value<0.01 (n=18-49). Interestingly, normocytic hyperchromic anemia (~ 79%) was found significantly more prevalent in CKD patients with anemia (p value<0.00001, n=2-42) than other forms e.g. microcytic and macrocytic anemia (Figure 3b). We further looked for distribution of anemia in various CKD stages and found CKD patients with stage 4 (~ 41.9%) were more prone to anemia than the other stages (1-3, 5) (Figure 3c).

CKD patients were found highly susceptible to T2D mostly in stage 4

Our results revealed 82% of CKD patients were diabetic based on blood glucose levels (Figure 4a), out of which maximum number of patients with stage 4 (~ 41%) were found suffered from T2D (Figure 4b). Furthermore, we found that CKD patients with diabetes (86.4%) were more prone to anemia than CKD patients without diabetes (66.7%) but the difference was insignificant (p value 5>0.01) (Figure 4c).

Chronic exposure to fluoride appeared as a risk factor for causing diabetes induced nephropathy leading to CKD

Fluoride levels in drinking water from Dalmau (2.4 ± 0.77 ppm) and Amawa blocks (1.9 ± 0.87 ppm) were significantly higher as compared to Sadar block (0.92 ± 0.30 ppm) with p value less than 0.001 and 0.01 respectively (Figure 5a) [25]. Therefore, patients from high fluoride endemic areas of Raebareli district e.g. Dalmau and Awama were used as test (chronic exposure to fluoride, more than 1.5 ppm), whereas from Sadar block were used as control having fluoride concentration within permissible limit (less than 1.0 ppm) [25]. Fasting glucose levels of patients from Dalmau and Amawa blocks were significantly higher than Sadar block with p value<0.05 (Figure 5b). In addition we also looked for susceptibility of CKD patients for albuminuria by detecting urine albumin levels. We found that urine albumin levels of patients from Dalmau and Amawa block were significantly higher than Sadar block with p value<0.05 (Figure 5c). On the basis of clinical diagnosis, our results demonstrate coincidence of diabetes and kidney dysfunction (diabetic nephropathy, DN) in CKD patients belong to Dalmau and Amawa block was 15-25 times more prevalent than patients from Sadar block (Figure 5d). These results indicate that fluoride appeared as a risk factor causing diabetes induced nephropathy (DN) that leads to CKD in affected individuals from high fluoride endemic areas (Figure 6).
Discussion

CKD is a global health problem which is highly prevalent in both developing as well as developed countries [3,11,28-30]. Highest reported prevalence of CKD ~ 6.3% as reported by a study conducted on rural area of Karnataka state in India [31]. CKD is associated with a number of life-threatening diseases e.g. cardiovascular diseases [32,33]. A number of lifestyle (smoking and alcohol consumption) and environmental (toxic metals) factors contribute in incidence of CKD among world-wide population. But, diabetes and hypertension were considered as key risk factors for developing CKD in South Asian countries including India where they account for 40%-60% cases of CKD [30,34].

This study was conducted on 1808 patients of eastern part of Uttar Pradesh, India over a period of one year and we found that 4.03% of total patients were susceptible to CKD. Most of CKD patients were diagnosed with moderate (stage 3) and severe (stage 4) kidney damage based on GFR (Figure 1 and Table 1). A number of factors such as poverty, social unawareness, lack of symptoms, and improper diagnosis and medication lead to high prevalence of patients with later stages (3 and 4) of CKD leading to ESRD. The patients were diagnosed for CKD based on kidney function test (KFT) and urine albumin levels [1,2]. Serum creatinine and BUN levels were significantly higher (above normal range) in CKD patients than normal individuals for a longer period of time (>3 months), are suggestive of impaired kidney function (Figure 2). Additionally, we have also found a modest but significant elevation in uric acid levels of CKD patients revealing complete deterioration of renal function conferring gout like symptoms in the patients (Figure 2).

Albuminuria is a well-established risk factor for progression of CKD to ESRD [7]. Therefore, we examined patients with kidney dysfunction by measuring urine albumin levels and albuminuria was diagnosed in 86.7% of total CKD patients (Figure 2d). Urine albumin levels were significantly elevated in case of CKD patients that support our results (Figure 1c) depicting majority of CKD patients at the risk of moderate and severe kidney damage and may progress towards ESRD (stage 5) based on the function of combination of GFR and urine albumin [35-37].

Kidney is the main site for production of erythropoietin (EPO) hormone that induces synthesis of erythrocytes by bone marrow [38]. Therefore, we looked for prevalence of anemia in CKD patients which was quite higher ~ 86% (Figure 3a) and most were diagnosed for normocytic hypochromic anemia (Figure 3b). Mostly, patients at the risk of severe kidney damage (stage 4, ~ 42%) were prone to anemia (Figure 3c), suggest that kidney dysfunction leads to anemia primarily due to EPO deficiency (Figure 6) [12,39]. However, other factors e.g. uremic-induced inhibitors, short erythrocyte life, disordered iron homeostasis and most recent hepcidin (by impairing iron absorption and mobilization) are also found to be linked with anemia in CKD patients [40,41]. Diabetes is a key risk factor for renal dysfunction therefore, we looked for glycemic index of CKD patients and found ~ 82% patients were prone to T2D mostly in stage 4 of CKD (Figures 4a-4b). This result indicates that hyperglycemia increases the risk of kidney dysfunction which
increases the rate of progression of renal failure/damage. Regular blood glucose monitoring and elevated HbA1c levels suggest that these patients were prolonged diabetic and developed severe complications related to kidney those may lead to CKD if left untreated. Anemia was equally prevalent (with no significant difference) in CKD patients with and without diabetes suggesting an independent factor may cause anemia irrespective of impaired erythropoietin secretion during kidney failure.

We aligned our study with a report showing fluoride endemic areas in Raebareli district and adjacent regions [25]. The results demonstrated that fluoride levels in drinking water were significantly elevated above recommended range (>1.5 ppm) in Dalmau and Amawa blocks according to World Health Organization (WHO) and Indian Council of Medical Research (ICMR) water quality guidelines (Figure 5a) [25,42]. Our results show that blood sugar levels were significantly higher in the patients from fluoride endemic regions (Dalmau and Amawa) compared to Sadar block with normal fluoride concentration in drinking water (<1.5 ppm) (Figure 5b). This result supports that fluoride induced insulin resistance may be responsible for conferring T2D in the patients during fluoride overexposure. Interestingly, urine albumin levels were also found elevated but insignificantly indicating kidney damage in case of patients from fluoride endemic zones compared to Sadar block (Figure 5c). This insignificant change suggests that independent fluoride induced kidney damage is not prevalent in this region unlike reports supporting fluoride associated ultrastructural deterioration of architecture of tubular epithelia, endothelial and mesangial cells of renal glomerulus [20,43]. Therefore, we propose that fluoride induced kidney dysfunction is basically resulted from diabetic nephropathy due to progression of fluoride induced prolonged and untreated T2D in patients from fluoride endemic regions [44]. This is also reflected in our results where diabetic nephropathy was more prevalent in fluoride endemic zones compared to Sadar block (Figure 5d). Here, we deduce that fluoride appeared as a major environmental factor that contributed in prevalence of CKD in eastern Uttar Pradesh particularly in Raebareli district [22,25,45]. We report that fluoride overexposure to the patients result in insulin resistance leading to T2D resulted from pathogenesis of endemic fluorosis [46,47]. Due to lack of diagnosis and proper medication these patients develop diabetes induced nephropathy and anemia (Figure 6).

**Conclusion**

Patients with diabetic nephropathy require glycemic control and regular screening to diagnose albuminuria and reduction in GFR. A multifactorial approach needs to be applied by involving broad expertise e.g. diabetologist, nephrologist, pathologist and toxicologist for prevention and treatment of diabetic nephropathy.

**Data Availability**

The data for this paper will always be available whenever needed.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Ethical approval**

This study has been performed in accordance with ethical guidelines of institutional ethics committee (IEC), however being a retrospective study it does not need any ethical clearance.

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**Author’s contribution**

AG, AR, BK collected and analyzed the data. AG, AR and RG wrote while PK contributed through his key inputs to improve the manuscript.

**References**


