The Indian Chronic Kidney Disease (ICKD) Study: Design and Methods

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ABSTRACT

Background: The rate and factors that influence progression of chronic kidney disease (CKD) in developing countries like India are unknown. A pan-country prospective, observational cohort study is needed to address these knowledge gaps.

Methods: The Indian Chronic Kidney Disease (ICKD) study will be a cohort study of approximately 5000 patients with mild to moderate CKD presenting to centers that represent different geographical regions in India. Time to 50% decline in baseline estimated glomerular filtration rate, need of renal replacement therapy or any new cardiovascular disease (CVD) event or death from CVD are the primary end points.

Value of Study: This study will provide the opportunity to determine risk factors for CKD progression and development of CVD in Indian subjects and perform international comparisons to determine ethnic and geographical differences. A bio-repository will provide a chance to discover biomarkers and explore genetic risk factors.

KEYWORDS

Chronic kidney disease, renal replacement therapy, cardiovascular diseases, cohort studies, epidemiology, biobanking

BACKGROUND

Chronic kidney disease (CKD) is an important emerging public health problem. The age adjusted death rates and absolute number of deaths attributable to CKD rose by 36.9% and 134.6%, respectively between 1990 and 2013.[1] CKD deaths are under-reported because of overlap with those due to diabetes mellitus and hypertension.[1] Re-analysis of cause of death data from the United States and Australia have shown that coded mortality due to renal involvement in diabetes mellitus was 4-9 times less.[2]

Worldwide, the prevalence of CKD has been estimated at 8-16%.[3] A recent population-based screening study from India pegged the CKD prevalence at 7.5%.[4] Projected epidemiologic transitions like aging, urbanization and increase in prevalence of diabetes and hypertension are likely to worsen the CKD burden.[3, 5, 6] While diabetes is the most frequent cause of CKD, the cause cannot be established in a significant proportion of cases, calling into question the appropriateness of applying western risk-factor based models in India.[7] A population-based study determined the crude annual end stage renal disease (ESRD) incidence at 151 per million population.[8] As providing treatment to all patients is beyond the limits of the current healthcare spending, it is important to develop and implement strategies to identify and treat subjects at risk of adverse outcomes.[7]

Studies are needed to identify risk factors for CKD development and progression, prediction of cardiovascular disease (CVD) events, and other important complications .[3] Prospective, observational cohort studies permit identification of population-specific factors that impact on CKD progression and complications, and generate research questions in order to provide answers to these challenges.

The Indian Chronic Kidney Disease (ICKD) study is an investigator initiated, government-funded initiative that aims to identify risk factors for progression of CKD, and development of ESRD and CVD in CKD patients. The study protocol and procedures have been harmonized with current disease definitions and ongoing CKD cohort studies elsewhere in the world so that the results are comparable with

other populations. In addition to recording clinical data, the study will create a bio-repository where serial biological samples of all participants will be stored.

METHODS

Study objectives

The ICKD study will conduct a prospective cohort study on 5000 patients with mild to moderate renal dysfunction. The participants will receive care at their respective centers according to the prevailing standards of care and treating physicians' judgment. The specific study objectives are as follows:

Primary objective

1. To elucidate risk factors for progression of CKD, development of ESRD and CVD

Secondary objectives

1. To evaluate gender-related differences in progression and development of ESRD and CVD in CKD
2. To assess quality of life of CKD patients and economic costs of CKD care
3. To assess and validate biomarkers for CKD progression, development of ESRD and CVD in CKD

Study organization and sites

The George Institute for Global Health (GIGH), New Delhi, India will be the coordinating center, with responsibility for overall operational, financial and quality control aspects of the study. There are nine participating centers spread across India (Figure 1). A central bio-repository will be set up at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India where blood and urine samples of all participants will be stored.

A Steering Committee consisting of representatives from all participating centers will oversee the design, conduct, progress, data collection, data analysis and publication of study results. A Scientific Advisory Committee will be constituted in consultation with the Chronic Disease Biology Task Force of the Department of Biotechnology, Government of India, and will periodically review the progress of

this study. The study has received funding for 5 years from the Department of Biotechnology, Government of India.

Study design

The study has a prospective cohort design coupled with a serial bio-bank. All participants will be followed and clinically relevant events recorded throughout the study period.

Ethical considerations

The study protocol and procedures are concordant with the principles of Declaration of Helsinki and have been approved by Institute Ethics Committees/Institute Review Boards at the coordinating and participating centers. A study trial was run at PGIMER, Chandigarh to test and validate the study protocol and procedures after approval by Institute Ethics Committee.

Study enrolment

Stable CKD patients visiting outpatient clinics at participating center will be screened (Figure 2, Table 1). The participants will be invited to the centers in fasting state for blood draws. A second morning urine sample will also be collected. Details of history, socio-demography, physical examination, quality of life and other clinically relevant factors will be collected (Table 2). Kidney Disease Quality of Life 36 (KDQOL-36) survey and 7-point subjective global assessment (SGA) form will be used to assess participant's quality of life (QOL). We plan to enroll 550-600 patients at each center over next 1.5-2 years.

Follow up

To improve retention, participants will be contacted every 6 months by telephone. A follow up visit will be scheduled every 12 months. Blood and urine samples will be collected at each visit. Follow-up questionnaire targeted at recording clinical events and reviewing the physical status, medication use and quality of life will be administered.

Bio-repository

At all scheduled visits, 8 ml each of fasting plasma and serum, and 10 ml second morning urine sample will be collected, processed and stored in multiple aliquots in a freezer at -80°C. At baseline visit, there will also be a one-time blood draw of 6 ml for genetic analyses. All samples will be bar-coded, pseudonymized and stored securely with restricted access.

Data management

An electronic case record form (CRF) that includes baseline and annual follow up questionnaires, and record of events and reasons of study termination has been prepared after discussions in Steering Committee and pilot run (Table 2). The user interface will be connected to a database hosted on a dedicated secure server at the coordinating center. Only pseudonymized data will be used for analysis. The study protocol and database conform to the latest recommendations of Government of India with respect to electronic medical records for clinical care and research purposes.[9]

Study endpoints

Primary endpoints

1. Time to ESRD state, defined as irreversible requirement of dialysis or need of kidney transplantation
2. Time to 50% decline in eGFR
3. Time to any new cardiovascular event (coronary artery disease, cerebrovascular accident or stroke, peripheral vascular disease, heart failure or arrhythmia) or death from cardiovascular disease

Secondary endpoints

1. Time to death from any cause
2. Time to hospitalization from any cause

Statistical considerations

Descriptive statistics will be used to describe baseline and follow up characteristics of study population. Groups would be compared using parametric

and non-parametric tests as appropriate. Association of various characteristics with study endpoints would be assessed by multivariate regression analysis. Time to event analysis using Kaplan-Meier curves, log-rank tests and Cox proportional hazards model will be used to examine association of baseline parameters with study endpoints. For repeated measures analysis, generalized estimation equation or mixed effect model will be used.

Approximately 3700 patients are expected to remain in the study for planned duration of 5 years if we presume an annual dropout rate of 5%. Assuming event rates of 0.04 and 0.08 per year, this sample size would be able to detect minimum detectable hazard ratios of 1.3 and 1.2, respectively, for two equal sized groups in time to event analysis (80% power, two sided $\alpha = 0.05$). For groups with other sizes, the corresponding minimum detectable hazard ratios are going to be higher with this sample size (e.g. hazard ratios of 1.4 and 1.3, and 1.9 and 1.6 would be detectable for event rates of 0.04 and 0.08 per year for subgroups distributed in ratio of 2:1 and 9:1, respectively).

DISCUSSION

The epidemiology of chronic non-communicable diseases is different between developing and developed countries. In case of chronic diseases, epidemiology and risk factor characterization are best done through prospective cohort studies.[10] Several cohort studies in CKD population are currently ongoing.[11-17] The best-known example is the Chronic Renal Insufficiency Cohort (CRIC) study in the United States (US that started in 2001 and is still continuing. It has generated hypotheses, provided clinical and biological database to test various other hypotheses and become an important knowledge base for nephrology community across the world.[18] Most studies have excluded patients with eGFR >60 ml/min/1.73m^2 so that patients at high risk of adverse renal and CVD outcomes are included. However, the recent German Chronic Kidney Disease (GCKD) cohort has in addition enrolled patients with persistent overt albuminuria or proteinuria and eGFR >60 ml/min/1.73m^2 as this category is also now perceived to be at high risk.[13]

Continuous review and analysis of the data will allow exploration of different populations that appear relevant to future collection of data. The CRIC study design has evolved over years, based on the knowledge about CKD trends gained from previous clinical trials, secondary analyses of other cohort studies without renal endpoints as primary outcomes, and national surveys.[11, 18] For example, a deliberate over-representation of black population and patients with diabetes mellitus was sought to ensure adequate representation of patients already known to be at increased risk in phase I. The eligibility criteria were further modified in the phase III to address morbidity and mortality in mild to moderate disease and disease consequences in older population.[18] We plan periodic data reviews with experts to explore ideas for sub-studies or independent research studies. We also plan to collaborate, compare and share information with other large CKD cohorts, through the International Network of CKD (iNET-CKD) under the umbrella of the International Society of Nephrology.

To the best of our knowledge, this is the first CKD cohort in a developing country. ICKD study will examine several issues that are of particular relevance to the developing world and tropical context, such as the potential factors associated with CKD development and progression at an early age and association with dietary habits, and role of environmental exposure to pesticides, heavy metals or other compounds, alternative drugs or herbal medicines use, dietary factors, complications of pregnancy or effects of tropical infections.[3, 7] The results will form basis for large, appropriately-designed community based studies exploring any new hypothesis. Accurate and complete phenotyping combined with follow up and creation of bio-repository would give opportunities in future to look at changes in serum or urinary biomarkers, and use of genomic, proteomic and metabolomics approaches for more complete understanding of disease mechanisms.[19, 20]

Regular assessment of QOL, as in this study through tools like KDQOL-36 survey and 7-point SGA form, gives opportunities to collect patient reported outcomes, and validation of these tools for local conditions in developing countries.[21] The study will also explore overall direct and indirect costs of CKD care. This will help

develop cost effective strategies to provide CKD care and make them part of national health programs.

The study protocol conforms to latest disease definitions and is concordant with methods and type of data collection, consistent with other CKD cohort studies. These are important methodological strengths that would add reliability and comparability to study results. Participant retention strategies through email, messaging and phone support would be implemented to ensure follow up.

Tackling CKD worldwide requires global cooperation. The rapid rise in at-risk population is likely to stress otherwise improving healthcare infrastructure in the poor developing regions. Such studies will allow tailoring of needs and solutions in developing countries like India, and be of relevance to other developed world countries. We hope that cooperation between professional bodies and academic centers across the world would culminate in a greater political and administrative resolve to fight the menace of CKD so that goals of public health could be achieved.

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CONFLICT OF INTEREST STATEMENT

None declared

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Figure Legend

Figure 1: Map of India showing location of study centers and geographical distribution

Figure 2: ICKD study screening, enrolment and follow up

Table 1: The ICKD study inclusion and exclusion criteria*

Inclusion Criteria

1. Age between 18-70 years
2. CKD (KDIGO definition)
3. eGFR (CKD-EPI) 30-60 ml/min/1.73m^2

   OR

   eGFR (CKD-EPI) >60 ml/min/1.73m^2 AND proteinuria/albuminuria (proteinuria: ≥500 mg/g of creatinine or ≥500 mg/day; albuminuria: ≥300 mg/g of creatinine or ≥300 mg/day)
4. Clinically stable course for the last 3 months

Exclusion Criteria

1. Any solid organ or bone marrow transplant recipient
2. Active malignancy in last 2 years
3. Palpitation or dyspnea at rest or asymptomatic only when resting
4. Ethnicity: Non-Indian
5. Pregnancy (in case of females)
6. Current immunosuppressive drug therapy
7. Expected life expectancy <1 year

*All inclusion criteria must be present and all exclusion criteria must be absent for study eligibility. CKD: Chronic Kidney Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, eGFR: estimated glomerular filtration rate, ICKD: Indian Chronic Kidney Disease; KDIGO: Kidney Disease: Improving Global Outcomes.

Table 2: The ICKD study data collection

BASELINE/ENROLMENT	
Sociodemographic, occupational, income and cost of medical care	
History	
1.	Family history
2.	Renal disease history
3.	Hypertension, diabetes mellitus, renal stone disease, UTI and voiding problems history
4.	Pregnancy history (in case of females)
5.	CVD history
6.	Alternative or desi medicine intake history
7.	Past or co-morbid conditions history
8.	Vaccination, addiction history
9.	Birth details
10.	AKI, renal biopsy and dialysis history
Physical examination	
Laboratory investigations	
1.	Blood: Hemoglobin, fasting blood glucose, blood urea, serum creatinine, serum calcium, serum inorganic phosphorus, serum protein, serum albumin, serum alkaline phosphatase, serum uric acid, serum total cholesterol, serum triglycerides, glycosylated hemoglobin
2.	Urine: protein, albumin, creatinine
Diagnosis	
Medications details (name, dose)	
Quality of life questionnaire (KDQOL 36, 7 point SGA)	
FOLLOW UP	
Event record (unscheduled): event type (outpatient/inpatient), outcome, AKI present or not	
Scheduled annual follow up	
1.	Check events details record
2.	Symptoms
3.	Physical examination
4.	Investigations
5.	Medications details (name, dose)
6.	Quality of life questionnaire (KDQOL 36, 7 point SGA)
TERMINATION	
Study termination details: Reason for termination	

AKI: Acute kidney injury, ICKD: Indian Chronic Kidney Disease, KDQOL 36: Kidney Disease Quality of Life 36, SGA: Subjective global assessment