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CLINICAL RESEARCH

Study to Test and Operationalize Preventive Approaches for CKD of Undetermined Etiology in Andhra Pradesh, India

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Introduction: High prevalence of chronic kidney disease (CKD) not associated with known risk factors has been reported from coastal districts of Andhra Pradesh. The Study to Test and Operationalize Preventive Approaches for Chronic Kidney Disease of Undetermined Etiology in Andhra Pradesh (STOP CKDu AP) aims to ascertain the burden (prevalence and incidence) of CKD, the risk factor profile, and the community perceptions about the disease in the Uddanam area of Andhra Pradesh.

Methods: Study participants will be sampled from the Uddanam area using multistage cluster random sampling. Information will be collected on the demographic profile, occupational history, and presence of conventional as well as nonconventional risk factors. Glomerular filtration rate (GFR) will be estimated using the Chronic Kidney Disease Epidemiology Collaboration equation, and proteinuria will be measured. All abnormal values will be confirmed by repeat testing after 3 months. Cases of CKD not associated with identified etiologies will be identified. Biospecimens will be stored to explore future hypotheses. The entire cohort will be followed up every 6 months to determine the incidence of CKD and to identify risk factors for decline in kidney function. Qualitative studies will be performed to understand the community perceptions and expectations with respect to the interventions.

Implications: CKD is an important public health challenge in low- and middle-income countries. This study will establish the prevalence and determine the incidence of CKD not associated with known risk factors in a reported high-burden region, and will provide insights to help design targeted health systems responses. The findings will contribute to the policy development to tackle CKD in the region and will permit international comparisons with other regions with similar high prevalence.

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Diabetes and hypertension are the leading causes of CKD worldwide.[1] Forms of progressive kidney injury not associated with any of the known causes or risk factors are being recognized, especially among the rural working-age populations in some low- and middle-income countries (LMICs), and have been dubbed "CKD of uncertain etiology" (CKDu). This

disease has emerged as an important problem in parts of El Salvador,[2] Nicaragua, Costa Rica, Mexico, Guatemala, Egypt,[3] Sri Lanka,[4] and India.[5] Adult men, primarily outdoor agricultural field workers in their third to fifth decade, are primarily affected.

CKDu typically remains asymptomatic in early stages. Features usually associated with progressive CKD, such as hypertension, edema, and oliguria are conspicuous by their absence. By the time patients report to the health system, the need for renal replacement therapy is often imminent. The kidney are usually small, making biopsy impossible. In the small number of cases in which it has been done, findings are dominated by bland interstitial fibrosis.[6] There is no definitive evidence for a specific etiological pathway,[7] and the proposed causes include heat stress, dehydration, pesticides, infections, and water contamination.[8]

In India, diabetes, chronic glomerulonephritis, and hypertension are the most common known etiological categories of CKD. In the report of the pan-India CKD Registry that included data on 52,273 adult patients with CKD,[9] "CKD—cause unknown" emerged as the second most frequent etiology (16%) after diabetes (30%). Patients with CKD of unknown origin were younger, poorer, and more likely to present in more advanced stages than were patients with CKD of known causes.

Geographic clusters with high burden of CKD have been reported from Andhra Pradesh, Odisha, Maharashtra, and Goa.[10] The best known of these hot-spots is the Uddanam region of Srikakulam District, Andhra Pradesh, a geographically distinct rural coastal area with rich cashew and coconut plantations. As in other world geographies where CKDu is endemic, young men have been reported to be most frequently involved.[11] An estimated 34,000 persons are reported to have kidney disease, with more than 4500 deaths in the last 10 years in this region. Despite extensive coverage in the lay press, there have been few studies of prevalence and natural history of the so called "Uddanam nephropathy." The few available surveys[5] have been nonsystematic and have used different methodologies, disease definitions, subject selection criteria, and nonvalidated creatinine and proteinuria assays. Unpublished cross-sectional data have indicated the existence of clusters with CKD prevalence ranging from 30% to 60%. A recent study estimated the prevalence of CKD at 18.3% in the area when proteinuria and/or decreased estimated glomerular filtration rate (eGFR) were taken as markers, and the cause could not be established in 13%.[12] This study, however, did not use the standard definition of CKD, which calls for confirmation after repeat testing.

Lay opinion puts the blame for the genesis of CKD on contaminated drinking water and pesticides. However, the few studies of chemical analyses of drinking water and cultivated rice from the region have failed to show any impurities, and there are few data on pesticides.[13,14] A cross-sectional study from another CKD-endemic village, noncontiguous to Uddanam, showed raised silica and strontium levels in drinking water.[15]

A recently published, standardized protocol (the Disadvantaged Populations eGFR Epidemiology Study [DEGREE]) provides a framework to identify and characterize communities where there is a high prevalence of reduced eGFR, and to undertake international comparisons by mandating a population-representative sample and standardized collection of information on sociodemographic factors, occupational and environmental exposures, body composition, and kidney function.[7]

We describe the protocol of a study designed to investigate the prevalence of various types of CKD in the Uddanam region including CKDu, and to determine the age-specific incidence and natural history of CKD in the region, with the goal of sharing expertise across disciplines and countries to accelerate knowledge dissemination and to guide research priorities toward establishing the causes.[16]

STUDY OBJECTIVES

The STOP CKDu AP aims to do the following: (i) conduct representative surveys to estimate the proportion of individuals with reduced eGFR including those without any known cause in the Uddanam region of Andhra Pradesh; (ii) measure the prevalence and describe the clinical presentation of CKDu in the region; (iii) establish a community-based cohort to determine the incidence of CKDu and identify risk factors for decline in kidney function over time; (iv) develop a methodological framework for the establishment of etiological factors behind the development of CKDu; and (v) understand the community perceptions around CKD, its burden, and community expectations with respect to interventions.

STUDY SETTING

The STOP CKDu AP will be undertaken in the Uddanam region of Srikakulam District, the extreme northeastern District of Andhra Pradesh. The District is skirted by mountains of the great Eastern Ghats. Vizianagaram district flanks it in the south and west, Orissa on the north,and the Bay of Bengal on the east. Srikakulam had a population of 2,703,114 as per the

2011 census,[17] and is divided into 38 administrative divisions (mandals).

DESIGN

The study will be implemented in 2 phases. In phase 1, the study will measure the prevalence and describe the pattern of CKD in the affected regions, in particular those with reduced eGFR but without any known cause. We aim to establish whether there is a clustering of disease. In case of clustering, we will evaluate its relationship to living space, lifestyle, and dietary habits. This phase will facilitate setting up a population cohort that will be followed up to determine incidence and risk factors for decline in kidney function. In addition, qualitative studies will be performed to understand stakeholder and community perspectives.

In phase 2, we will follow up this cohort at 6-month intervals with a focus on studying participants at risk for developing CKD and CKDu in particular, that is, participants who do not already have CKD or factors that would exclude a CKDu diagnosis. At the same time, the cohort with established CKD at baseline will be followed up to determine the rate of kidney function decline. Age-specific incidence will be determined over 3 years.

STUDY POPULATION AND SAMPLE SIZE CONSIDERATIONS

The study will be conducted in a geographically contiguous area comprising 118 villages among the 7 administrative regions (mandals) that constitute the Uddanam region.

A cross-sectional study will be undertaken using a cluster random sampling technique using probability proportionate to size (PPS) methodology.[18] A total of 2400 subjects will be sampled from 40 clusters (villages) selected in the defined study area. As the population prevalence of CKD in the area is unknown, the sample size was estimated assuming a prevalence of CKD of 10% in the low-prevalence clusters, a relative precision (acceptable error in the estimate) of 20% (2% absolute precision, that is ±2% on either side of 10%, i.e., 8%−12%), a design effect of 2 and inflated to account for an estimated 25% loss to follow-up in the prospective component of the study. The formula used was

$$n = 4 \times p \times (1 - p)/d^2,$$

where n is the sample size, p is the prevalence, and d is the precision.

If we assume that prevalence of CKDu is around 5%, then 2400 samples will allow us to estimate the true prevalence with 30% relative precision, that is, to within ±1.5%, with 95% confidence, accounting for a design effect of 2 and a 25% loss to follow-up.

In each of the selected clusters, households will be identified based on hand-drawn structural maps of the cluster. A total of 60 households will be selected within each cluster by a systematic random sampling technique. Within each household, the individual participant will be randomly selected among the members of the household based on the preassigned quota-based age-stratified groups and sex to ensure adequate representation from both sexes and age subgroups..

The disease CKDu has been reported typically to affect young people. However a recent study from the Uddhanam region showed that only a minority of individuals (<20%) were <40 years of age, and women are equally affected.[12] We anticipate, therefore, that changes in GFR occurring in all age groups will need to be carefully determined. To ensure inclusion of all participants old enough to experience an identifiable decline in kidney function, we will include all individuals >18 years of age with equal representation from men and women. Moreover, women with CKDu are of scientific interest in that their inclusion may suggest alternative risk factors or may help to rule out some that have been previously proposed. To ensure that we have adequate representation of each of the age groups, we will use preassigned quota with respect to the sex and age groups.

All the subjects in the cohort thus created will be followed up every 6 months for a period of 3 years.

The sample size calculations in the study have been based on estimating the prevalence of CKD and not CKDu. However, including a design effect of 2 will help to identify area-level clustering, presumably because of CKDu.

STUDY PROCEDURES

Community-level meetings will be conducted to inform the population about the study before initiating screening. The design includes a preparatory phase during which wide-ranging discussions and qualitative interviews will be conducted to understand the prevailing perceptions and practices around CKD in the study communities. Informed by the qualitative interviews, we will develop appropriate socio-cultural strategies for community acceptance and consent for study implementation.

After securing informed consent, the survey questionnaire will be administered, followed by clinical measurements and collection of blood and urine samples. In the case of refusal to participate in the study, the survey questionnaire will not be administered;

however, the listing of members of the household and their ages will be collected.

Focus group discussions and in-depth interviews will be conducted to understand the factors associated with CKD in the study area.

SURVEY QUESTIONNAIRE

The questionnaire (Supplementary Combined CKDu Subject Questionnaire) will elicit the basic demographic profile, socio-economic status, occupational history, medical history, and health-seeking behavior.

The questionnaire was developed by adapting the DEGREE Protocol,[7] the WHO STEPwise approach to noncommunicable disease risk factor surveillance (STEPS) survey[19]; the Comprehensive Kidney Disease Assessment for risk factors, epidemiology, Knowledge, and Attitudes (CKD AFRiKA) Study[20]; reducing the use of hazardous chemicals in developing countries: potential of implementing safer chemicals including nonchemical alternatives—tools for Georgia and the EECCA (Eastern Europe, Caucasus, and Central Asia) region[21]; the Water Balance Questionnaire[22]; the Measure of Medication Taking Behaviors (MMS-4)[23]; the Patient Health Questionnaire (PHQ)-12 (modified from the PHQ-9 by the Chennai Urban Rural Epidemiology Study [CURES], and validated in an Indian population)[24]; and the EuroQoL (EQ) 5D for quality of life assessment.[25]

The survey will include questions that will will seek to identify the type of habitation, the water supply for drinking, cooking and other household activities, water drinking patterns, type of cooking and ventilation in each of the households, household practices in terms of disposal of domestic waste, sourcing of food ingredients, use of any indigenous/local produce in the cooking, work habits, and consumption of herbs, indigenous medications, tobacco, or alcohol.

In addition to income, we will capture household living standard through questions on household's ownership of selected assets, such as televisions and bicycles; materials used for housing construction; and types of water access and sanitation facilities.

Furthermore, we will determine the number of hours that the study participants spend at home and at their place of work, in case of work that involves direct exposure to sun, and high temperatures (e.g., industrial ovens, brick kiln, large-scale cooking). The number of hours of such exposures and habits around hydration and rest in between these intense work periods will be determined. Intake of any medications for any symptoms developed due to these occupational exposures will be documented, and the duration of exposure will be recorded. Calorie and protein intake will be estimated by a standardized dietary diary validated for use in the Indian context.

CLINICAL MEASUREMENTS

Blood pressure would be measured after 5 minutes of rest in the sitting position using an automated clinically validated sphygmomanometer (OMRON model HEM 7121, Kyoto, Japan). An average of 3 readings will be recorded. Height and weight would be measured (without footwear) using a stadiometer (SECA model 213, Hamburg, Germany) and digital calibrated scales (OMRON Model HN 865).

BIOSAMPLES

A 20-ml sample of nonfasting venous blood will be collected in 2 Vacutainers (Becton Dickinson, Franklin Lakes, NJ), 1 vial containing ethylenediamine tetraacetic acid (EDTA) and the other plain. A 5-ml quantity of first morning void urine will be collected in sample collection cups distributed a day prior to the collection. Samples will be stored in the field in coolers with icebox (4 °C) for no more than 6 hours and shipped to the processing laboratory at the study coordinating center. Plasma, serum, and buffy coat will be separated and stored at −80 °C in barcoded cryovials.

Creatinine will be measured using the modified Jaffe assay (traceable to isotope dilution mass spectrometry [IDMS] reference standards). Urine protein will be measured using pyrogallol test and corrected for creatinine. Blood counts would be performed on a fully automated, 3-part differential hematology analyzer (Sysmex XP 100, Sysmex Asia Pacific, Singapore). and glycosylated hemoglobin would be determined on an automated analyser (Hb Vario, Erba Mannheim, London, United Kingdom) in compliance with the National Glycohemoglobin Standardization Programme (NGSP). All tests will be performed on the same day of collection. Glomerular filtration rate will be estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

FOLLOW-UP AND RETENTION

All subjects who are found to have an eGFR of $\leq$60 ml/min per 1.73 m^2 and/or urine protein-to-creatinine ratio of $\geq$0.15 in initial testing will undergo repeat testing after 3 months. Follow-up visits will be conducted in all subjects at 6-month intervals for 3 years. All new values of eGFR $<$60 ml/min per 1.73 m^2 and urine protein-to-creatinine ratio $>$0.15 will be confirmed on repeat testing 3 months apart.

We will carry out a series of activities to increase participant engagement and retention. These will include distribution of reading materials, text and

voice messages, and home visits by the study staff. Annual testing will be done to determine eGFR and protein-to-creatinine ratio in all subjects. We will also visit the households of those who refused participation and record whether any of the household members have had any major health events, hospitalizations, or have died. If there have been any major health outcomes, their relationship to kidney disease will be explored.

CKD will be diagnosed and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[26] CKDu will be defined according to the criteria proposed by Wijewickrama *et al.*,[27] with some modifications: eGFR of <60 ml/min per 1.73 m^2 and/or urine protein-to-creatinine ratio of >0.15 at 2 time points 3 months apart in individuals who do not have diabetes, long-standing hypertension (>5 years' duration), or urine protein-to-creatinine ratio of >3. Subjects with other known causes of CKD will be excluded.

QUALITATIVE STUDY

Focus group discussions and in-depth interviews will be conducted to understand the community perceptions around CKD, its burden, and community expectations with respect to the interventions. We will conduct 14 in-depth interviews and 12 focus group discussions.

The focus group discussion and in-depth interview participants will be community members, physicians, nephrologists, patients diagnosed with kidney disease, government officials, officials from the industry, and experts in environmental issues. A purposive sampling method will be used to recruit participants.

Written informed consent will be obtained from the participants. The project team will brief the participants on the purpose and aims of the discussion and interactions. The Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines[28] for reporting qualitative research for data collection and process will be followed. Each focus group discussion or interview will last for 45 to 90 minutes and will be conducted by a team of 2 individuals, a moderator and a note taker. The discussions will be audio-recorded and transcribed. Transcripts will be translated into English, and the quality will be checked by the study team members. Data will be analyzed based on the essential principles of qualitative research[29,30] to understand the perceived extent of the problem, referral patterns, and perceived barriers to kidney health, as well as opportunities for improvement. The focus group discussions and in-depth interviews will be analyzed using Nvivo 9 software (2008; QSR International Pvt Ltd, NVIVO Qualitative data analysis software, Melbourne, Australia).

Analysis will be based on the thematic framework approach to identify common emerging themes.[31] All data will be reviewed by 2 members of the research team to identify the recurrent themes to minimize the risk of subjectivity and established validity. Researchers will familiarize themselves with the data and will identiy broad thematic areas. A coding scheme will be formulated using an inductive approach, and the responses based on the codes will be grouped under each theme. Discrepancies in coding will be identified, and consensus will be obtained through discussion among study team members.

DATA MANAGEMENT

Questionnaires and samples will be labeled using unique participant identifiers and bar codes. A customized electronic data capture system using open source framework hosted on the secure servers with end-to-end data encryption will host the questionnaire database. Validation and data quality monitoring will be undertaken to eliminate transcription errors. Data management procedures will follow the standard operating practices and guidelines of the George Institute (Data Management SOP/DM –SOP-32 Version 3.0) and the Indian Council of Medical Research.[32]

DATA ANALYSIS

For the population prevalence component of the study, we will use descriptive statistics whereby categorical variables will be reported as proportions and continuous variables will be reported as means and standard deviations.

For the risk factor analysis, exposure variables under consideration are age, sex, level of education, occupation, presence of diabetes and hypertension, exposure to heat, agrochemicals, and tobacco, alcohol, painkillers, and indigenous medication use. The unadjusted relationships between the exposure variables and the outcomes of interest, that is, CKD and CKDu, will be examined in univariate analyses. Multiple logistic regression will be used to examine the simultaneous effects of various exposure variables while adjusting for potential confounders.

During follow-up, newly detected cases of CKD among individuals with eGFR of >60 ml/min per 1.73 m^2 and urine protein-to-creatinine ratio of <0.15 at baseline will be the incident cases. All newly identified abnormal values will be confirmed by repeat testing after 3 months. The risk factors from baseline and ongoing risk exposure variables collected during the follow-up phase will be analyzed to determine any

associations. Change in eGFR over time will be analyzed as a continuous variable, as well as as tertiles of renal function decline.[33]

ETHICS

The STOP CKDu AP has been approved by the Institutional Ethics Committee of The George Institute for Global Health, New Delhi, India and will be conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent will be obtained from all participants for use of the data and stored biosamples for future research. Findings will be disseminated widely by publication in peer-reviewed journals and presentations/representations to relevant local stakeholders. Interim findings of public health importance will be communicated through appropriate local administrative offices and with their approval through media channels to inform population at large. Any subject identified to have an abnormality will be referred to the appropriate public health facility. The study team will work in close partnership with local health providers/healthcare systems to handle participants needing referral for medical care.

GOVERNANCE

A Technical Advisory Group (TAG) comprising representatives from the Indian Council of Medical Research, Government of Andhra Pradesh (GoAP), and subject experts regularly review and provide guidance on the design, implementation, and progress of the study. An external Advisory Board will provide scientific oversight and will guide the study team in incorporating emerging evidence from the CKDu research globally. Detailed information about the progress of the study, field activities, and protocols are hosted on a dedicated study Web link hosted on the George Institute website (https://www.georgeinstitute.org/projects/stop-ckdu-study-to-test-operationalize-preventive-approaches-for-ckdu-in-ap).

DISCUSSION

The STOP CKDu AP study protocol has been developed in response of the public health need to define the epidemiology and to start investigations to establish cause(s) of CKD affecting the Uddanam area in Andhra Pradesh. The existing studies of CKDu in India have not yet defined the epidemiology of this condition—the first step needed to understand the disease burden, natural history, and risk factors. This protocol aims to provide a framework to address this, and is designed to capture the entire at-risk population by recruiting adult subjects from both sexes and all age groups.

Table 1. Anticipated operational challenges and strategies to overcome them

Envisaged challenges	Study design/mitigation strategies
Prior reports of high prevalence of CKD in certain geographic areas within the Uddhanam region of Srikakulam District, Andhra Pradesh	The study area was selected to ensure that both reported high- and low-prevalence villages are included in the geographic areas defined for the random selection of clusters using the PPS methodology. The sample size calculations include a design effect of 2 to account for the clustering.
Resistance by the communities and nonconsenting for study participation and collection of biological samples, as several research teams had collected biological samples in the Uddhanam region prior to this study and had not provided any reports or feedback to the communities.	The design includes a preparatory phase during which wide-ranging discussions and qualitative interviews will be conducted to understand the prevailing perceptions and practices around CKD in the study communities. Informed by the qualitative interviews, we will develop appropriate socio-cultural strategies for community acceptance and consenting for study implementation. The sample size calculation took into consideration a 33% loss to follow-up/ noncompliance with the biological sampling within the study defined time points.
The reduction in eGFR and/or proteinuria being transient	Only confirmed cases of CKD as per KDIGO guidelines based on 2 independent assessment 3 months apart for eGFR and proteinuria will be considered.
Risk factors/environmental exposure factors being missed due to seasonal variations	The environmental exposures/potential risk factors will be assessed at defined timepoints taking into consideration the seasonal variations, with special attention to summer and pre- and post-monsoon analysis.
Difficulties in ascertaining painkiller use due to over-the-counter purchase of medicines	Use of visual cue cards with the blister packs of common NSAIDs available in the study area and use of the same for the respondents to identify the medications and to record how long they have been used with or without prescriptions.
Subjects traveling away from study site for work	All subjects will be tracked and followed up when they return during festivals and holidays. They will be asked about specific work-related risk factors.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NSAIDs, nonsteroidal anti-inflammatory drugs; PPS, probability proportionate to size.

The protocol goes farther than administering only a 1-time cross-sectional survey: we will repeat the appropriate tests after 3 months to confirm the diagnosis, and will have a longitudinal component to understand the natural history of the disease by observing change in eGFR over time.

Following up all enrolled subjects will allow us to define disease incidence, to capture the earliest stages of disease, and to identify associations with possible exposures and potential risk factors. Our protocol uses a questionnaire that combines questions from a number of standard validated survey instruments aimed at capturing a variety of exposures, including sociodemographic data, occupational and environmental exposures, lifestyle factors, and health-seeking behavior in the population of interest.

The qualitative component of the study will help to understand the community perceptions about the burden of CKD and noncommunicable diseases in the

study area, prevailing belief systems around the causes of CKD, occupational patterns, dietary habits, and household practices, health-seeking patterns for chronic ailments including various stages of CKD, and popular expectations from the health delivery systems for tackling the disease.

Study of biosamples will allow future exploration of additional hypotheses through collaborative research. A bio-repository is embedded in the study, and specific consent for future analysis including genetic studies is being obtained. The samples will be stored in the India Chronic Kidney Disease Registry bio-repository,[34] which follows all mandatory requirements for a bio-repository. Tackling the problem of CKDu requires global cooperation. This and other such studies will allow identification of unique CKD risk factors to help the development of locally appropriate screening and prevention strategies. This study represents an example of cooperation among government and academic centers, and is of relevance to other state governments with similar hot-spots so that the menace of CKDu can be fought with greater political and administrative resolve and public health goals can be achieved.

During the development phase, we anticipated possible operational challenges and designed the protocol carefully to overcome those challenges (Table 1).

There are a few limitations, mainly related to the way that GFR is estimated in the study population. We are using Chronic Kidney Disease Epidemiology Collaboration formula, which can potentially overestimate GFR in Indian subjects. An independent study, however, is ongoing to develop a correction factor for the existing equation, and we will reanalyze the data. Also, our study is not designed to evaluate the impact of dietary factors, namely, protein intake, on GFR.

In conclusion, the STOP CKDu AP will aim to determine the incidence, prevalence, and rate of decline of kidney function in subjects with CKD in the Uddanam area of Andhra Pradesh, as well as to provide key insights that will help to establish the cause(s) of the disease.

DISCLOSURE

The funding agencies have no role in the design, implementation, analysis and reporting of the study. VJ reports consulting or paid advisory board fees from Baxter Healthcare, Zydus Cadilla, and NephroPlus and grant support from Baxter Healthcare, GlaxoSmithKline, Department of Biotechnology (India), Medical Research Council, United Kingdom, and Indian Council of Medical Research, New Delhi, India. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Combined CKDu Subject Questionnaire.

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