Community-Based Screening for Chronic Kidney Disease, Hypertension and Diabetes in Dharan

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ABSTRACT

Introduction: Nepal cannot afford renal replacement therapy for End Stage Renal Disease due to lack of resources. Early diagnosis of Chronic Kidney Disease and its risk factors may reduce the need of renal replacement therapy.

Methods: A community-based screening on, 3218 people ≥20 years were assessed by door-to-door survey in Dharan, Nepal. Health status, lifestyle habit, physical examination and blood pressure were evaluated. Spot urine was examined for proteins and glucose by dipstick. Fasting blood glucose and serum creatinine were measured in a subset of 1000 people and the prevalence of Chronic Kidney Disease was evaluated.

Results: Overweight, obesity, hypertension, diabetes and proteinuria were found in 20%, 5.0%, 38.6%, 7.5%, and 5.1% respectively. In the subset group, Chronic Kidney Disease was detected in 10.6%. Multivariate analysis indicated age (P <0.0001) and diabetes (P = 0.027) as statistically significant predictors for Chronic Kidney Disease. Total of 848 patients entered the management program of lifestyle modification and pharmacologic intervention. Glycemic and blood pressure control was achieved in 60% and 72%, respectively. Regression or stabilization of proteinuria was reported in 52% of patients.

Conclusions: Burden of Chronic Kidney Disease and cardiovascular risk factors are high in Dharan. Reasonable control of blood sugar, hypertension and proteinuria was achieved in this program. Findings indicate that activation a large prevention and intervention program to tackle Chronic Kidney Disease and Cardiovascular Disease in Nepal is needed.

Keywords: *chronic kidney disease; community-screening; diabetes; hypertension; intervention; Nepal.*

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. Nepal, one of the poorest countries in the world - at 138th position of human development index,[1] has grossly limited treatment options for CKD. The cost per month treatment per patient for dialysis makes the RRT a rare choice for most of the ESRD patients.

Till now kidney transplant is limited to two centers in the Capital city of Nepal. Thus, because of the cost and complexity of the treatment less than 5% of ESRD population receives any form of renal replacement therapy in the country, which undermines the need to establish programs to prevent renal disease progression. Before advocate for action, however, it would be useful to know the prevalence of CKD and its risk factors.

In this scenario, a community-based screening in people ≥20 years old was conducted in Dharan – a large town in eastern Nepal - with the aims to assess the prevalence of risk factors for chronic kidney disease (hypertension, diabetes and obesity), to define the prevalence of CKD, and to characterize the overall cardiovascular disease risk in this population. This finding summaries result of the screening that was carried out sequentially in the initial four administrative wards of Dharan in overall 3218 people.

METHODS

A survey is being conducted in the Dharan municipality. As a part of sequential survey this study was conducted in 4 VDS out of 19 VDCs in Dharan municipality, Dharan, Nepal from 2003 to 2005. Ethical approval wask taken from IRC-BPKIHS.

A series of meetings were held in Dharan initially with local leaders, local Non-governmental organizations - to explain the initiative, procedures and possible benefits of screening and intervention program to the community in the long run. In the meantime, a series of articles were published in the local language national daily newspaper to create awareness among people. Furthermore, leaflets on prevention and treatment of kidney diseases were distributed and exhibited in public places. All these activities were also accompanied by meetings and interaction programs with the general population, including awareness parade in the city.

BP Koirala Institute of Health Sciences (BPKIHS) has planned and coordinated the program. The local NGOs were responsible for mobilisation of local volunteers, coordination with local leaders and the community participation.

Survey teams have been organized and consist of a local leader, resident doctors, medical students and nurses. The local leader was the head of the ward, a member of the NGO's. The entire team was trained on the methodology and the procedures prior to survey by coordinators of the project at BPKIHS and re-enforced from time to time. The medical students were chosen from the highest rank to lowest rank in a team (i.e. post graduate of medicine, third, fourth and final year of medical school). This strategic organisation has been established in order to sensitise medical students on preventive aspects of CKD and cardiovascular diseases. Each team had a team leader, which visited door-to-door each household of the given area planned to be screened.

The records of household numbers in the administrative ward one to four of Dharan were retrieved from the local administrative office. The four wards had 1927 households with a population of 8585. The population ≥20 years were 3312. A total of 94 persons were excluded from screening due to either acute illness or fever, pregnancy, not available in the household or not willing for screening. All the screening procedures were carried out within each household of individuals.

All subjects aged 20 years or older were considered eligible for the evaluation. On the day of screening a brief questionnaire that included demographic data, and information on smoking habit, and physical activity as well as personal and family history of diabetes, hypertension, cerebrovascular accident, heart attack or angina, and kidney disease was introduced to a given person in a family and filled by the team personnel. Thereafter height, weight and blood pressure were measured according to standard guidelines.

Participants were then instructed to void a clean, mid-stream spot urine specimen in a vessel which was examined for protein and glucose. Random blood glucose measurement was also performed. In a subset of 1000 people, fasting blood sugar and serum creatinine were also measured, at later stage when new resources became available. One thousand subjects were selected by means of a proportionate stratification, according to age and gender at the time of the screening. This sample was representative of the 3200 screened subjects because each category was adequately represented selecting a sample from each stratum separately and considering sample size proportional to the relative size of the strata. The screening visit was also used for the health education of the members of the family on kidney and cardiovascular diseases.

Blood pressure recording and hypertension was defined according to the guideline The JNC 7 Report.[2]

Body weight and height was assessed with all subjects standing without shoes and heavy outer garments to the nearest 0.1 kg and 1 cm, respectively, and body mass index estimated according to standard normograms. WHO criteria 1999 was used to define overweight and obesity.[3] Proteinuria and glycosuria were measured by dipstick (Multistix, 10SG, Bayer Diagnostics Bridgend, UK). Subjects with positive proteinuria dipstick had a second confirmatory urinary dipstick evaluation 10 to 15 days after the initial screening. Subjects who at screening had urinary tract infection, fever or menstruation (for women) were excluded from the evaluation to avoid the bias of transiently elevated proteinuria.

Plasma glucose concentration was determined by glucose oxidase-peroxidase method (Vitalab Selectra-2, Merck, Germany). The diagnosis of diabetes was defined as per ADA criteria.[4] Individuals with self-reported prior physician-diagnosis of diabetes were classified as having previously diagnosed diabetes.

In the subset of 1000 subjects who underwent estimation of serum creatinine, Glomerular Filtration Rate (GFR) was also calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation with four variables.[5] CKD was defined according to the National Kidney Foundation Practice Guidelines,[6] Five stages of CKD were classified.[7]

In addition, the risk for cardiovascular disease was assessed in the same subset of 1000 subjects by modification of previously published score system.[8] To this purpose, for each subject, a cardiovascular risk score, 0 to 6, was estimated by allocating the value of one to each of the following six features when present at screening: a) overweight (BMI >25 Kg/m^2), b) hypertension (SBP ≥ 140 or DBP ≥ 90 mmHg), c) fasting plasma glucose level >97.2 mg/dl) d) proteinuria (dipstick positive), e) smoking, f) serum creatinine (>1.5 mg/dl). Since renal dysfunction is an independent risk factor for cardiovascular events (9) serum creatinine was also added in the proposed scoring system.

Chi-square test was used to compare prevalence of CKD and its risk factors by age classes (20-39 years, 40-59 years, ≥ 60 years). A multiple logistic regression was implemented with the PROC LOGISTIC in SAS in order to identify putative risk factors associated with prevalence of CKD.

To identify a minimal set of independent predictors all the covariates measured at screening were univariately evaluated in logistic regression models. All factors found significantly ($P<0.05$) associated with the dependent variable were included in the final model. Age, BMI, SBP, DBP were considered as continuous variables in the primary analysis and categorized in a secondary explorative analysis.

The Hosmer-Lemeshow goodness-of-fit statistic was used to evaluate model fit. The data were entered with the use of Microsoft Excel and were exported and analyzed with the use of SAS software (version 9.1, SAS Institute, Inc., Cary, NC). The data were presented as number (percentage). Statistical significance was assessed at the 5% level of significance. All p values were two-sided.

RESULTS

A total of 3218 subjects were screened in the program, with slight female preponderance (52%) (Table 1). The mean age of the participants was 42.9 ± 14.9 years. Housewife and shop-owner constituted the majority of the screened population. There were 19.7% farmers. The majority of screened subjects were either illiterate or educated up to secondary school (64.2%).

Table 1. Characteristics of the screened population.

Particulars		Number (%)
Gender	Male	1542 (47.9)
	Female	1676 (52.1)
Occupation		
	Housewife	1132 (35.2)
	Shop-owner	863 (26.8)
	Farmers	634 (19.7)
	Daily wage-earner	134 (4.2)
	Other	455 (14.1)
Education		
	Illiterate	496 (15.4)
	Secondary School	1569 (48.8)
	High School	1153 (35.8)
Smoker		758 (23.7)
Sedentary habit		1705 (53)
Body Mass Index	<18	630 (19.6)
	18-25	1773 (55.1)
	25.29	643 (20)
	≥ 30	172 (5.3)
Hypertension		1243 (38.6)
Diabetes		242 (7.5)
Proteinuria		163 (5.1)

Most of the subjects (55%) had a normal BMI, while overweight accounted for 20% of the screened population. Obesity was found in 5% of the people (Table 1). Interestingly, underweight was documented in 20%. Overweight and obese were mostly women (33%).

Table 2. Prevalence of CKD and its risk factors by age.

Particulars	Age (years) in percentage			
	20-39	40-59	≥60	P value
CKD	3.4	11.4	30.5	<0.001
Proteinuria	2.2	6.1	11.1	<0.001
Hypertension	23.2	47.3	64.2	<0.001
Diabetes	2.5	9.3	18.9	<0.001
Obesity	3.8	7.3	5.4	<0.003

Table 3. Multiple logistic regression model to predict CKD.

Risk Factors	Odds ratio	95% CI*	P value
Age	1.05	1.03, 1.06	<0.0001
Sex	1.5	0.95, 2.43	0.08
Education	0.98	0.94, 1.01	0.183
Smoking	0.83	0.49, 1.39	0.47
BMI	0.97	0.92, 1.02	0.226
SBP	1.01	0.99, 1.03	0.18
DBP	0.99	0.96, 1.01	0.36
Diabetes	2.44	1.11, 5.32	0.027

*two values are upper and lower limit of confidence interval

Hypertension was found in 38.6% (n = 1243) of subjects (Table 1). The mean age of hypertensive was 49.2 ± 14.3 years. The proportion of the subjects with hypertension increased with age (Table 2). Hypertension was more common in obese (53.5%) than in non-obese (37.8%). 47% of the hypertensive were newly detected during the screening. 51% of the known hypertensive were on treatment with blood pressure lowering medications and only 14% of them (n = 135) had adequate blood pressure control according to JNC7 criteria.

Diabetes was found in 7.5% (n = 242) of subjects. The mean age of all diabetics was 55.5 ± 14.4 years, and 44.2 ± 11.2 years for the newly diagnosed subjects. The prevalence of diabetes increased with age (Table 2). More diabetes was documented in overweight or obese than in underweight subjects. Less than half (n = 114) of the previously diagnosed diabetic patients were on treatment and among them only 25% (n = 28) had adequate control of their blood sugar level.

Hypertension and diabetes in combination were found in 4.67% (n = 150) of screened population.

Proteinuria measured by dipstick of random voided urine sample was found in 5.1% (n = 163) of the screened population. The distribution of proteinuria is depicted in Figure 1. Majority of them had 1^+ proteinuria. Dipstick positive protein $\geq 3^+$ was recorded in 0.6% of the screened asymptomatic population. There is a trend for higher prevalence of proteinuria in underweight (6.0%) than in the overweight (5%) and obese (4%) subjects. Proteinuria was found in 7.9% of hypertensive population but only 3.3% in normotensive subjects. 14.5% diabetics were proteinuric as compared to 4.2% of non-diabetics. There was linear relationship between age and proteinuria with prevalence of proteinuria 5 times higher in subjects ≥60 years than in young people (≥20 - 39 years). Together proteinuria and diabetes were observed in 1.1% (n = 35) of the screened population, whereas 0.8% (n = 27) of subjects had combination of proteinuria, hypertension and diabetes.

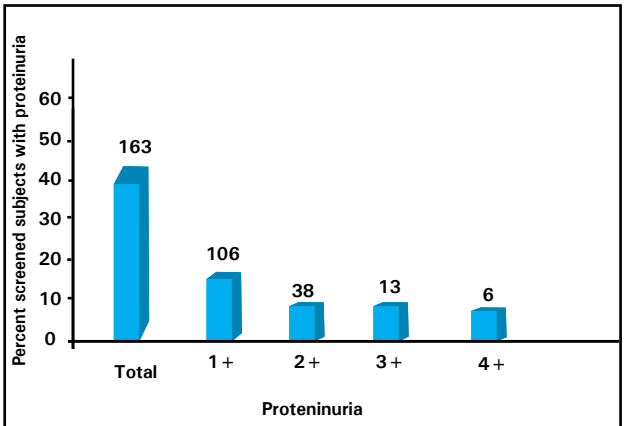

Figure 1. Distribution of dipstick positive proteinuria in the screened population (n = 3218 subjects).

In the subpopulation of 1000 subjects screened in the second phase of the program, serum creatinine ≥1.4 mg/dL (normal: 0.6 – 1.3 mg/dL) was recorded in 1.4 % (n = 14). In CKD stage 0 eGFR (by MDRD formula) 92.4 ± 23.0 ml/min/1.73 m^2. In stage 1, 2, and 3 eGFR was 104.1 ± 11.8, 78.4 ± 9.1 and 52.0 ± 7.0 ml/min/1.73 m^2, respectively. In stage 4 eGFR was 21.3 ± 5.1 ml/min/1.73 m^2 and in stage 5 was 12.0 ± 1.5 ml/min/1.73 m^2. Overall CKD was present in 10.6% (n = 106) and proteinuria in 5.2% (n = 52). The distribution of proteinuria was 2.4% (n = 24) in CKD stage 1, 2.0 (n = 20) in CKD stage 2, 0.4% (n = 4) in CKD stage 3 and 0.4% (n = 4) in CKD stage 4.

According to MDRD equation, GFR ≤60 ml/min/1.73m^2 (stage 3-5) was found in 6.3% (n = 63) of the subjects. 85% of the CKD cases were detected during the screening. The mean age of CKD patients was 52.1 ± 14.2 years with prevalence of CKD increasing with age. In subjects with BMI below 18 eGFR was 91.1 ± 25.0 ml/min/1.73 m^2.

Multivariate logistic regression analysis of screened risk factors showed that age [OR 1.05 (1.03 to 1.06), p <0.0001] and presence of diabetes [OR 2.44 (1.11 to 5.32, p=0.027)] were the only statistically significant predictors for CKD (Table 3).

The frequency distribution of Cardiovascular Disease (CVD) risk score in the subgroup of screened subjects showed that 78% of the screened population had at least one risk factor for CVD. CVD risk score ≥ 2 or more was present in 47.3% (n=472) of subjects.

Eight hundred and forty eight subjects screened positive for hypertension, diabetes, proteinuria and CKD entered the intervention phase of the program. The patients were followed up in 'Renal Disease Prevention Clinic' at B P Koirala Institute of Health Sciences. They were counseled for healthy lifestyles, which include moderation of alcohol consumption, cessation of smoking, increase in physical activity, reduction of dietary sodium/salt, weight reduction in those individuals who are overweight or obese, and prescribed cheap available medicine for their ailment. 15% drop out during follow-up within one year. After 1 year of management, blood pressure reduction to <140/90 mmHg in hypertensive patients was achieved in 72% (i.e. from 141.8±21.3 mmHg to 129.9±18.6 mmHg, P<0.0001 for systolic blood pressure; and from 91.7±11.9 mmHg to 83.6±10.6 mmHg, P<0.0001 for diastolic blood pressure).

Similarly, glycemic control (fasting glucose <120 mg/dL and/or HbA1c ≤7%) was reached in 60% of diabetic patients. Blood glucose lowered from 127.7±60.5 mg/dl to 113.2±62.4 mg/dl (P<0.0001).

Regression or stabilization of proteinuria was reported in 52% of patients. In the 74 subjects with Dipstix positive (i.e. ≥1^{+}) the proteinuria lowered from 0.94 g/24h (0.68 to 1.70 g/24h) to 0.30 g/24h (0.14 to 1.30 g/24h) (P=0.19). Before intervention 1.4% (n=1) of subjects was in CKD stage 0, 48.7% (n=36) in CKD stage 1, 39.2% (n=29) in CKD stage 2, 5.4% (n=4) in stage 3, and 5.4% (n=4) in stage 4. At the end of the follow-up on treatment, 41.9% (n=31) of subjects was in CKD stage 0, 29.7% (n=22) in CKD stage 1, 16.2% (n=12) in CKD stage 2, 8.1% (n=6) in stage 3, and 2.7% (n=2) in stage 4, and 1.4% (n=1) in stage 5. Five patients died including 2 patients on RRT.

DISCUSSION

This is the first community-based screening and intervention study in Nepal with the aim to detect and manage risk factors for chronic kidney disease and cardiovascular disease, which ultimately would prevent renal disease progression and Cardiovascular deaths.

According to this screening, one fourth of the subjects were ≥20 years were either overweight or obese. Interestingly, underweight was also documented in a significant percentage of the screened subjects (20%). Typically, there were more female in the overweight and obese group than male counterpart, as documented elsewhere.[10] Recent rapid urbanization of Dharan, making energy dense food available in the city for relatively rich people may be associated with weight gain. On the other hand, those who migrated from rural areas to city and remained relatively poor might have to depend on low quality of food, therefore, at risk to become underweight. However, to closely define this relationship, family income and food habit should have been evaluated.

Hypertension was present in one third of the screened subjects, of which only 50% were previously known to have high blood pressure. This high prevalence of hypertension is in line with early findings in selective Nepalese population such as Sherpa[11] and Tibetans.[11,12] Results from studies in Nepalese population suggest that not only age (as we found), the body fat and salt intake, but also intake of potassium, magnesium and calcium contribute to the genesis of hypertension in Nepalese inhabitants.[6]

Similarly, a high prevalence of diabetes (7.5%) was observed in the present screening program, although markedly lower than previously reported (14.6%) in Nepal.[13] These numbers, however, contrast sharply with the projected estimate by WHO of 4% of diabetes in Nepal for 2030.[14] The high prevalence of diabetes in Nepal might just reflect better screening strategies than those adopted in the past. To this, however, it should be certainly added the influence of lifestyle changes associated with socioeconomic development and urbanization.[15] Indeed, together the influence of crucial events in the past three to five decades might have resulted in the current high prevalence of hypertension and diabetes. Migration of population from hilly to plain areas leading to gross reduction in physical activities,[11] consumption of locally made high salt containing junk foods, rapid urbanization, increased in body fat due to consumption of westernized diet of poor quality,[15] maternal malnutrition leading to low birth weight,[10] lack of awareness on prevention of diseases might be some of the contributors.

Screening for CKD has relied on the detection of albuminuria or proteinuria in urine samples.[7] Dipstick protein on spot urine samples analysis has imperfect accuracy in the diagnosis of persistent proteinuria, but it is an inexpensive and simple test that can be performed in mass screening of apparently healthy subjects,[16] particularly in low-resource environment. It has also been reported to predict progression of CKD to ESRD.[17]

Using the dipstick test, here we found that in the Dharan community screening the prevalence of proteinuria was 5%, comparable to values (4.4%) reported in a close region in an Indian survey in Delhi,[18] but higher than the more westernized worksite screening in Singapore (1.1%),[19] the general population screening in Hong Kong (3.2%),[20] or the Ausdiab screening in Australia (2.4%).[21] It was similar to that of Okinawa general population survey (5.3%) in Japan in more than 100,000 people.[17] The difference in the prevalence of proteinuria may be due to different ethnicity of screened populations, age or selection of the screened cohort. When resources became available, serum creatinine was also measured in a subset of 1000 subjects among the full cohort screened previously for proteinuria. Based on the NKF definition of CKD[7]- where albuminuria was substituted by dipstick proteinuria (score $\geq 1+$) - the prevalence of CKD in the Nepalese population was 10.6%, similar to that reported in the $\geq$ 40 years people of Beijing China (11.3%),[22] and in the developed countries, namely USA (NHANES III: 11%),[23] and Australia (AusDiab: 14%)[21] that also used proteinuria as screening test. Since albuminuria is an earlier, more sensitive index of CKD than proteinuria,[24] it could be reasonably expected that the prevalence of CKD documented in the Dharan population was actually underestimated. So far, however there has been no attempt to relate risk factors to the development of CKD in Nepal. Age, hypertension, diabetes, dyslipidemia, smoking, and non-Caucasian ethnicity have been recognized as risk factors for CKD worldwide.[16,17,19,25-27] By multiple logistic regression analysis, we found that, beside age, only diabetes was statistically significant predictor of CKD. These findings further underline the need to screen people at least for diabetes in the Nepalese community in order to prevent as much as possible the renal and CV complications. Indeed, evidence is available that primary prevention of diabetic nephropathies in hypertensive,[28,29] and normotensive patients,[30] with diabetes is feasible with cheap angiotensin converting enzyme inhibitors.

There is no particular benefit from the screening if subjects, positive at the survey for the major parameters could not enter an intervention phase of the program. After one year follow-up - based on low cost antihypertensive, antiproteinuric (mainly ACE inhibitors) or oral antidiabetic drugs - 60 to 70% patients entered the intervention phase had good blood pressure or glycemic control, while stabilization or regression of proteinuria was achieved in 50% of the cases. Moreover, even patients already known to be hypertensive or diabetic, but with poor compliance to therapy or not on treatment before screening, did benefit from participating to the management phase of this program. Evidence is available that complications related to hypertension and/or diabetes can be largely preventable. In diabetic patients, 10 mmHg reduction of blood pressure values lowers micro-vascular complications up to 37%,[31] as well as one percent lowering of glycosylated hemoglobin results in 16% reduction in myocardial infarction.[32] The initial findings of the Nepal intervention program showing better blood pressure and glycemic control than in the past provides hope for long-term significant benefit on renal and cardiovascular outcomes. Moreover these results indicate that pharmacological interventions, recently shown to slow the burden of ESRD in developed countries,[33,34] could be effective in providing reno- and cardiovascular protection also in the low-resource setting of the emerging world, proving that a proper organization is set up. There are certain shortcomings in the Dharan screening. Hematuria and leukocyturia, that might have affected proteinuria results, was not routinely evaluated. However, all subjects with fever or symptomatic urinary tract infection were excluded from the proteinuria screening. Moreover, the prevalence of CKD was estimated using MDRD prediction equation of GFR, not validated in the Nepalese population.

Large-scale screening and management program in resource poor setting should be mandatory. In a developing country, like Nepal, people do not seek regularly medical advice due to lack of awareness of disease, belief of 'apparently healthy' in the absence of symptoms of chronic diseases, and, not last, lost of day-wage. This would result in too late referral, if any, to the medical unit or, more commonly, death without known reasons. The involvement of local community people and leaders along with large and sustained educational programs for people and healthcare workers and development of an organizational network of doctors, medical students, nurses and volunteers under an academic coordinating center, as we did in Nepal, is a requirement to assure smooth and reliable screenings and, far more important, to use at best the limited resources and interventions for effective care of patients and management of amenable risk factors for CKD and CVD. This more concerted and multi-sectorial approach is essential to help reverse the negative trend in the incidence of these chronic diseases in emerging countries and overcome the cost and complexity of renal replacement therapy out of reach for these low-income environments.

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