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CLINICAL STUDY

High prevalence of kidney disease in two rural communities in Kosovo and Metohia

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ABSTRACT

A systematic survey was carried out in an enclave in Kosovo and Metohia, with the aim of assessing the prevalence of kidney diseases. The survey involved 423 (180 males) adult inhabitants from two small settlements, Velika Hoča and Orahovac, and included an interview, medical documentation, physical, ultrasound, and laboratory examinations. Persons with any detected disorder indicating kidney disease were invited for additional examination of kidney function. Using urine dipstick test, proteinuria was detected in 19.1% and hemoglobinuria in 4.5% of the examined subjects. Glomerular filtration rate (Modification of Diet in Renal Disease (MDRD) formula) below 60 mL/min/1.73 m^2 was found in 5.2% of subjects. Kidney ultrasound examination detected reduced length of right and left kidneys in 38 and 24 persons, respectively. Cysts were also a frequent finding, but polycystic kidney, hydronephrosis, and kidney stones were found in about 2% each. The analysis of data obtained by the present examination and available medical documentation revealed kidney and urinary tract diseases in 98 persons: 52 patients with already known disease and 46 patients detected in the survey. Out of them in 22 patients diagnosis of kidney disease could not be established during the survey but laboratory analyses indicated that they might suffer from tubulointerstitial disease: 14 had tubular dysfunctions, 8 of them low-grade proteinuria, and 12 had a positive family history for kidney disease. In the enclave of Velika Hoča and Orahovac the prevalence of kidney disease was 7.0% indicating that these communities might be placed among those with a high prevalence of kidney disease in Serbia.

Keywords: kidney disease prevalence; rural settlements; Kosovo and Metohia

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INTRODUCTION

The number of patients who require renal replacement therapy is increasing all around the world.[1] In addition, chronic kidney disease (CKD) is associated with an increased risk for cardiovascular disease morbidity and mortality.[2] Therefore, although CKD is not among the first 10 conditions in terms of disability and mortality, it is becoming a global public health problem. That moved the attention of nephrologists from treating advanced stages of CKD toward prevention and early detection of CKD, and screening studies have been carried out in both developed and developing countries.[3–5]

In 2003, a screening survey was carried out in Vitina, the only Balkan endemic nephropathy (BEN) focus in Kosovo and Metohia. Despite the dramatic demographic changes of the population during the period 1999–2000 high prevalence of kidney failure was found.[6] In addition, primary care physicians from Velika Hoča and Orahovac, two rural communities in a Serbian enclave situated in southwestern Kosovo and Metohia, have reported an increasing prevalence of patients with CKD.[7,8] To check these data a systematic survey was undertaken in Velika Hoča and Orahovac with the aim to assess the prevalence of kidney disease in this population.

PATIENTS AND METHODS

Our team, three doctors (two nephrologists, one cardiologist), two nurses, one laboratory technician, and one driver, spent 2 months (July and August 2006) working

in the health dispensary in Velika Hoča. The cross-sectional survey involved all inhabitants above 18 years of age from Velika Hoča and Orahovac. According to available data 545 people remained in Orahovac after 1999 (around 440 adults) and 700 (around 550 adults) in Velika Hoča.[7,8] Five hundred inhabitants responded to the invitation but 423 completely examined were analyzed. There were 180 males and 243 females aged 51 ± 16 years. Informed consent was obtained from all patients and the Ethics Committee of the Medical Faculty, University of Belgrade, approved the study.

The survey started with an interview in which the participants answered a detailed questionnaire on demographic issues, and personal medical and family history including data on risk factors for chronic diseases and previously diagnosed diseases. Smoking status was categorized into never smoker and smoker who had smoked at least 100 cigarettes in his life. Alcohol intake was dichotomized on the basis of intake frequency, at least weekly (drinker) against rarely or never (nondrinker).

After the interview all persons were subjected to detailed physical examinations including measurement of body weight, height, and blood pressure in addition to kidney ultrasound. Prior to blood pressure measurement persons had to be sitting upright in a chair with their feet flat on the floor for a minimum of 5 minutes. Two repeated blood pressure measurements of each person were done with 2-minute rest period, and if blood pressure was ≥140 mmHg and/or diastolic pressure was ≥90 mmHg or if antihypertensive treatment was previously prescribed, the person was considered as having arterial hypertension.

At the time of the systematic survey the hematocrit was measured (Microhematocrit Electro Mag.) and proteinuria and hemoglobinuria were estimated using visually read dipsticks (Chemstrip; Roche, Basel, Switzerland). Fasting venous blood samples were collected from all participants for biochemical analysis of sera that was carried out by routine methods at the laboratory of the Laplje Selo Regional Hospital.

The glomerular filtration rate was estimated using the original Modification of Diet in Renal Disease (MDRD) Study formula (eGFR).[9]

Kidney ultrasound imaging was performed by one dedicated doctor (GŠG) for all individuals using a Sonoline Adara (Siemens) ultrasound machine with sector probe of 3.5 MHz.

Presence of proteinuria and/or hemoglobinuria (detected by urine dipstick test) and/or eGFR below 60 mL/min/1.73 m^2 and/or structural abnormality found by ultrasound was designated as kidney damage. Persons with any detected marker of kidney damage were invited to bring fresh morning urine samples that were centrifuged, urinary sediments were examined, and supernatants were immediately frozen and stored at −25°C. In these urine samples protein (biuret method), creatinine (kinetic rate Jaffe method), alpha1-microglobulin (immunoturbidimetric assay, Turbitex alpha1-microglobulin; Roche/Hitachi 902; normal value <1.3 mg/mmol creatinine), *N*-acetyl-β-D-glucosaminidase (NAG; colorimetric assay with 3-cresol-sulfonephthalein, Roche; normal value <3.0 U/L), alkaline phosphatase (colorimetric method; normal value < 0.37 U/mmol creatinine) were determined at the Institute of Medical Biochemistry, Clinical Center Serbia, Belgrade. The diagnosis of kidney diseases was done based on data obtained from the questionnaire, physical, laboratory, and ultrasound examinations as well as the analysis of medical documentation of patients with previously known kidney disease. When the presence of diagnostic criteria for BEN was examined in patients with detected tubular disorders, a modified version of Danilović's criteria defined elsewhere was used.[10] Epidemiological criteria were not taken into consideration because the examined settlements were not registered as BEN foci. Therefore, in this analysis the following criteria were used: (1) familial history positive for kidney disease, (2) mild proteinuria, (3) alpha1-microglobulinuria, (4) eGFR<60 mL/min/1.73 m^2, (5) anemia, (6) low specific gravity of the urine, and (7) reduced kidney length.

Descriptive statistics were presented as mean values ± standard deviation (SD) for the numeric variables or as frequencies for categorical variables. Predictors for CKD were analyzed by univariate analysis, supplemented with multivariate linear regression analyses using all demographic, clinical, laboratory, and ultrasound variables determined in all 423 examined persons as independent variables.

RESULTS

In systematic survey carried out in Velika Hoča and Orahovac 423 adult inhabitants were completely examined. The results of laboratory analyses for all examined persons, including the frequency of pathological findings, are presented in Table 1. The most frequently detected disorder was hyperlipidemia followed by hyperglycemia and proteinuria.

Analysis of data obtained from the questionnaire and physical and laboratory examinations showed that hyperlipidemia was the most common risk factor detected in 70% of examined persons. Hypertension, obesity, smoking, and alcohol consumption appeared with similar frequencies of about 40%. A positive family history for kidney disease was noted for 27% of the subjects and previously known diabetes was reported for 13%. The above data indicated that these communities are at high risk for both chronic kidney and cardiovascular disease.

TABLE 1. Results of laboratory analyses for 423 adult inhabitants from Velika Hoča and Orahovac.

Parameter	Reference values	Mean ± SD	Pts with pathological finding	
			No.	%
Hematocrit	M: 40–54%	43.4 ± 4.6	25	5.9
	F: 37–47%	39.7 ± 3.5	40	9.5
Glucose	3.9–6.1 mmol/L	5.5 ± 2.4	89	21
Albumin	34–55 g/L	45.7 ± 4.4	1	0.2
Total cholesterol	<5.2 mmol/L	6.4 ± 1.7	315	74.5
Triglycerides	<1.7 mmol/L	2.0 ± 0.9	214	50.6
Urea	2.5–7.5 mmol/L	5.2 ± 2.3	34	8.0
Creatinine	M: 74–124 μmol/L	81 ± 61	7	1.7
	F: 53–106 μmol/L	64 ± 52	4	0.9
eGFR (MDRD)	>60 mL/min/1.73 m^2	103 ± 33	22	5.2
Proteinuria ± hemoglobinuria	1+ to 3+		81	19.1
Hemoglobinuria	1+ to 2+		19	4.5

TABLE 2. Frequency of kidney abnormalities found by ultrasound in 423 adults from the communities of Velika Hoča and Orahovac.

	Kidney	
	Right	Left
Length < 10.0 cm	38 (9.0%)[a]	24 (5.7%)
Cysts	21 (5.0%)	27 (6.4%)
Polycystic kidney	4 (0.9%)	4 (0.9%)
Hydronephrosis	3 (0.7%)	5 (1.2%)
Chronic pyelonephritis	2 (0.5%)	6 (1.4%)
Kidney stone	9 (2.1%)	3 (0.7%)
Ren duplex	2 (0.5%)	

Note: [a]Number of patients (%).

The results of kidney ultrasound examination of all 423 persons are presented in Table 2. Reduced length of right and left kidneys was observed in 38 and 24 persons, respectively. Cysts were also a frequent finding, but polycystic kidney, hydronephrosis, kidney stones, and characteristics of chronic pyelonephritis were found in about 2% of examined persons each.

Clinical, laboratory, and sonography examinations carried out in this survey showed that 123 (28.8%) subjects had at least one pathological finding indicating kidney injury. Previous kidney or urinary tract disease was known in 41 out of these 123 persons and they had medical documentation on previous diagnostic procedures and treatment (Table 3). In addition, 11 persons reported a history of kidney or urinary tract disease but no pathological finding was found in them during this survey. The remaining 82 patients with markers for kidney disease found here were not aware of their kidney disease and they were invited to a control checkup. Seventy-two persons responded to the invitation and kidney disease was not confirmed in 26 persons. In the remaining 46 persons laboratory and ultrasound examination showed different abnormalities, which enabled the diagnosis of particular kidney or urinary tract diseases to be established in 24 patients presented in Table 3. In the remaining 22 persons diagnosis of kidney disease remained unclear and 12 (55%) of them reported positive family

TABLE 3. Number of patients with kidney and urinary tract disease found in examined populations by the use of questionnaire, physical, laboratory, and ultrasound examination, and available medical documentation.

Diagnosis	Known before survey	Detected at survey
Polycystic kidney disease	2	2
Diabetic nephropathy	2	4
Pyelonephritis	6	2
Tuberculosis	2	0
Nephrolithiasis	9	3
Chronic renal failure[a]	10	2
ESRD (hemodialysis)[a]	4	0
Nephrectomy[b]	2	0
Urinary tract infection	4	5
Urinary bladder tumor	3	0
Prostate hyperplasia	8	6

Notes: ESRD, end-stage renal disease.
[a]Chronic renal failure or ESRD of unknown etiology.
[b]Nephrectomy because of kidney stone according to anamnesis, medical documentation not available.

TABLE 4. Demographic data and laboratory results obtained in 22 patients with kidney disease detected in the present survey which require further clinical examination to establish diagnosis of kidney disease.

	Sex (M/F)	Age (years)	eGFR<60 mL/min/1.73 m^2	u-Protein (g/g Cr)	Alpha1MG (mg/mmol Cr)	NAG (U/L)	AP (U/mmol Cr)	Kidney length (cm)
Mean ± SD		48 ± 27	83 ± 32	0.113 ± 0.144	1.8 ± 1.9	1.7 ± 1.5	1.3 ± 1.2	10.3 ± 0.3
No. of patients[a]	9/8		8	12	11	5	7	3

Notes: eGFR calculated by MDRD; alpha1MG-urine, alpha1-microglobulin, NAG, *N*-acetyl-β-D-glucosaminidase; AP, urine alkaline phosphatase.
[a]Number of patients with pathological finding.

history for kidney disease and 14 had at least one tubular dysfunction (Table 4). As BEN is the most frequent familial tubulointerstitial kidney disease in Serbia, the presence of the criteria for the diagnosis of BEN in 22 patients with unclear diagnosis was examined. Figure 1 shows that all 12 patients with positive family history for kidney disease had proteinuria and/or alpha1-microglobulinuria, two of them also had eGFR below 60 mL/min/1.73 m^2 but another two had impaired eGFR, anemia, and reduced kidney length in addition to proteinuria and/or alpha1-microglobulinuria. Among 10 patients with negative family history for kidney disease two had neither one criterion for BEN, six had one or two disorders (most frequently proteinuria or low-molecular proteinuria and impaired eGFR), and one had reduced kidney length in addition to proteinuria and alpha1-microglobulinuria. Patient number 12 had proteinuria, alpha1-microglobulinuria, impaired GFR, and anemia. Although this patient reported negative family history for kidney disease, the data check showed that patient number 14 was his relative. All these 22 persons were advised to continue investigations in one of the university clinical centers in Serbia.

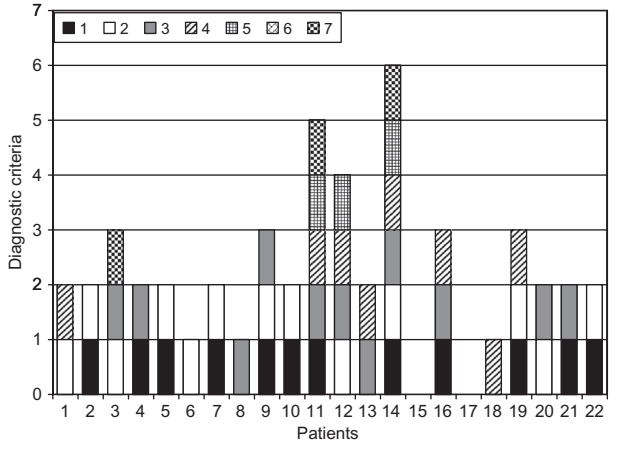

FIGURE 1. Presence of diagnostic criteria for Balkan endemic nephropathy (BEN) in 22 patients with detected kidney disease and unclear diagnosis. Criteria: (1) familial history positive for BEN, (2) mild proteinuria, (3) alpha1-microglobulinuria, (4) eGFR<60 mL/min/1.73 m^2, (5) anemia, (6) low specific gravity of the urine, and (7) reduced kidney length.

To reveal significant predictor of kidney disease detected in 70 out of 423 examined persons univariate/multivariate regression analysis was used. The analysis revealed diastolic blood pressure (β = 1.032; 95% CI 1.007–1.058; p = 0.013) and proteinuria (β = 1.031; 95% CI 1.007–1.044; $p < 0.001$) as significant independent predictors for kidney disease.

DISCUSSION

The main objective of the present study was to find out the prevalence of kidney and urinary tract disease in Serbian enclave Velika Hoča and Orahovac in Kosovo and Metohia. This survey was stimulated by the data on increased prevalence of CKD in these communities.[7,8] Kidney and urinary tract disease were detected in 98 persons: 52 with disease diagnosed prior to the present study and 46 with disease detected in this survey. Out of them 70 patients had kidney diseases (35 previously known and 35 detected in the present survey) and 28 had urinary tract diseases. The prevalence of kidney and urinary tract disease in the population of Velika Hoča and Orahovac was 9.9%, whereas the prevalence of kidney disease was 7.0%. There are no exact data on the prevalence of kidney disease in Serbia. According to medical records for outpatients and inpatients for 1983–1992, kidney and urinary tract diseases represented 3.0–4.2% of all diseases.[11] Screening studies carried out in villages affected by BEN in Serbia found prevalence rate of BEN between 1.7% and 8.9%.[12,13] Although data on kidney and urinary tract disease prevalence in the examined enclave could not be compared with these data, they indicated that these two communities might be placed among those with a high prevalence of kidney disease. In support of this is a positive family history for kidney disease as reported by 27% of all the

examined persons. Furthermore, out of 98 patients with kidney disease 40% had a positive family history for kidney disease. These percentages are higher than those detected in a recent screening study undertaken in Belgrade. The study involved two at-risk populations for CKD: patients with hypertension and persons above 60 years of age. Positive family history for kidney disease was reported by 17% of the subjects.[14]

The population examined was characterized by high prevalence of risk factors for CKD. The most frequent risk factor was hyperlipidemia present in about 70% of examined persons followed by three other modifiable risk factors hypertension, obesity (body mass index >30 kg/m^2), and smoking reported with frequency of 32% to 42%. In addition, 27% of examined persons were above 60 years old and diabetes was reported by 54 (13%) of the examined persons. However, hyperglycemia was detected in 89 persons that indicated possible higher prevalence of diabetes. As CKD was detected in 7.0% of the examined persons, question arouses as to which factors were associated with CKD development in the examined rural communities, because different risk factors were reported from different geographic regions.[15–17] Therefore, all demographic, clinical, laboratory, and ultrasound variables determined in all 423 examined persons were combined as independent variables in a univariate/multivariate regression analysis to reveal significant predictor of CKD detected in 70 patients. The analysis revealed diastolic blood pressure and proteinuria as significant independent predictors for CKD.

In 22 patients, markers for kidney disease detected in the present study were insufficient to define diagnosis. Twelve of these patients had positive family history for CKD but of unknown diagnosis, although 10 of these relatives were treated with regular hemodialysis. The majority of patients had different markers for tubular dysfunction which suggested that these patients might suffer from tubulointerstitial disease. Six of 12 persons with positive family history had at least one tubular disorder, three had reduced kidney length and most of them were of older age and asymptomatic. All the above characteristics are considered to be the characteristics of BEN, but these places are not known as BEN foci. Nevertheless, the presence of criteria for diagnosis of BEN was examined in these 22 patients. As diagnostic criteria we used those proposed by Danilović[10] supplemented with alpha1-microglobulinuria according to the results of our previous study and the proposal by an international panel.[18,19] All 12 patients with positive family history for kidney disease had proteinuria and/or alpha1-microglobulinuria. In addition to these findings one patient had impaired eGFR and two had impaired GFR, anemia, and reduced kidney length, i.e., almost all criteria for BEN diagnosis. Findings were similar for the patient (patient no. 12, Figure 1) who reported negative family history but it was later revealed that this person was a relative of patient no. 14, the one with the highest number of BEN diagnostic criteria. This analysis indicated that four patients (nos. 11, 12, 14, and 16, Figure 1) fulfilled clinical and laboratory criteria for BEN and three patients (nos. 4, 9, and 21) had the main clinical and laboratory features of BEN. Velika Hoča and Orahovac were not registered as BEN foci and without epidemiological criteria of BEN, the diagnosis of BEN could be established by kidney biopsy only.[19] Therefore, all these subjects with detected kidney function and/or structure abnormalities and unclear diagnosis were advised to undergo further investigations in one of the university clinical centers in Serbia. Only further diagnostic procedures including kidney biopsy could explain high prevalence of kidney diseases in these communities.

The most important strength of our study is that it was not simply a screening for CKD but a systematic survey in which, in addition to the screening methods for CKD, more detailed laboratory and ultrasound examination as well as the analysis of medical documentation were done. This enabled us to establish diagnosis of CKD in the majority of patients and to recommend local general practitioners how to treat these patients and how to continue the examination of those with unclear diagnosis. Such systematic survey was of special importance for the inhabitants of this enclave. However, our study had some limitations. As it was a cross-sectional study, some disorders were detected and registered although final diagnosis could be done only by repeated examinations. This was the case with hypertension that for the majority of the examined persons was measured only at the first visit and all those with blood pressure above 140/90 mmHg as well as those who had already used antihypertensive treatment were considered as having arterial hypertension. Therefore, the frequency of hypertension in the examined population could be overestimated. Another limitation is the unsolved question on CKD diagnosis in 17 patients, especially in 7 patients with clinical, laboratory, and ultrasound features of BEN. As the diagnosis of BEN outside endemic villages can be done only by kidney biopsy, patients with unclear diagnosis and with suspected tubulointerstitial disease were advised to undergo investigations in some clinical center of Serbia. However, until now no information on their further examination could be obtained and that remains an unsolved question.

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