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CLINICAL STUDY

High Prevalence of Risk Factors for Chronic Kidney Disease in Balkan Endemic Nephropathy Foci

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Abstract

Background/Aims: The aim of this study was to find out the prevalence of the most frequent risk factors for chronic kidney disease (CKD) and the prevalence of urinary abnormalities in adult inhabitants of three Balkan endemic nephropathy (BEN) villages near Bijeljina, Bosnia and Herzegovina. *Methods*: The survey consisted of an interview, blood pressure measurement, and urine dipstick test for proteinuria, hematuria, and glycosuria. *Results*: The study involved 1625 (739 males, aged 51 ± 16 years) subjects: 319 (19.6%) with positive family history for BEN, 585 (36%) with hypertension, 604 (37.2%) above 60 years, 146 (9%) with diabetes, and 566 (34.8%) with none of these risk factors. Proteinuria was present in 6.2–7.1% of the subjects with risk factors for CKD but in 3.4% of those without risk factors. Systolic blood pressure and BEN in brother/sister were found to be significant variables associated with proteinuria, but female gender and history of kidney disease with hematuria. *Conclusion*: In addition to a family burden for BEN, other risk factors for CKD were highly prevalent in BEN villages of the Bijeljina municipality. The frequency of proteinuria was higher in the at-risk group than in the group without risk factors and increased with the number of risk factors.

Keywords: risk factors for CKD, Balkan endemic nephropathy foci

INTRODUCTION

The first cases of Balkan endemic nephropathy (BEN) in Bosnia and Herzegovina (BH) were discovered in 1957, and studies on the disease, started in 1958 lasted continuously until 1990.[1,2] In 1977, extensive epidemiological surveys were carried out in all known BEN municipalities of northeastern BH including the epidemiological, geographical, and demographical characteristics of BEN.[3,4] However, no data on other kidney diseases were reported in these studies. In the meantime, the prevalence of chronic kidney disease (CKD) has increased dramatically all over the world, while diabetes and hypertension have become the leading causes of end-stage renal disease (ESRD) in the developed countries.[5–7] In the less-developed countries, such as BH, glomerular diseases continue to be the leading cause of ESRD, although the prevalence of diabetes and hypertension has increased in the last decade.[8,9]

In the spring of 2008, the Foča Medical Faculty started screening surveys in endemic villages of the municipality of Bijeljina, BH and already the first results indicated that, in addition to a family burden for BEN, several other risk factors for CKD were highly prevalent. Therefore, this study was undertaken with the aim to find out the prevalence of the four most frequent risk factors for CKD in adult inhabitants of three endemic villages, and the frequency of urinary abnormalities was detected in the populations with different risk factors.

METHODS

The screening study in the endemic villages—Donje Crnjelovo, Gornje Crnjelovo, and Brodac, Republic of

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Srpska, BH—was carried out by physicians and students from the Foča Medical Faculty and physicians from the Bijeljina Health Center. According to available data, these three villages had 4457 adult inhabitants (>18 years), and all were invited to the screening. A total of 1625 (36.5%) individuals responded and gave their informed consent. The Ethics Committee of the Foča Medical Faculty, University of East Sarajevo, approved the study.

The survey started with an interview in which the participants answered a detailed questionnaire on demographic issues, personal medical and family history with special attention to family history for BEN. Thereafter, the blood pressure of each subject was measured after they were made to sit upright in a chair with both feet flat on the floor for a minimum of 5 min. Two blood pressure measurements were made for each person with a 2 min rest period between them, and if the values were ≥140 mmHg and/or diastolic pressure was ≥90 mmHg or if antihypertensive treatment was previously prescribed, the person was considered as having arterial hypertension. Patients with known and treated diabetes were considered diabetics.

All participants were instructed to bring their first morning urine samples in containers distributed with the invitation letters. Using the urine dipstick test, proteinuria, hematuria, and glycosuria were assessed semiquantitatively.

Descriptive statistics are presented as mean values ± standard deviation for continuous variables, or as frequencies for categorical variables. Analysis of variance accompanied by Bonferroni multiple comparison tests and chi-square analysis was used for between-group comparisons of continuous and categorical variables.

The impact of covariates on proteinuria and hematuria was tested by univariate/multivariate logistic regression analysis. In univariate analysis, the following were used as independent variables: sex, age, personal history of kidney disease, hypertension, diabetes and analgesics abuse, family history of BEN, histories of BEN in mother's or father's or both parents' families, brother/sister with BEN, family history of hypertension, diabetes, systolic and diastolic blood pressure, and presence of urinary abnormalities (proteinuria or hematuria and glycosuria). Only those covariates found to be statistically significant using univariate analysis were used in the multivariate analysis. Logistic regression coefficients were employed to estimate the odds ratios for each of the independent variables in the model.

All analyses were performed using the SPSS statistical software package (Version 15 for Windows; SPSS, Inc., Chicago, IL, USA).

RESULTS

The screening study involved 1625 inhabitants from three endemic villages situated in the municipality of Bijeljina, BH. There were 739 males and 886 females, aged between 18 and 89 (51 ± 16) years. Data on risk factors for CKD (positive family history for BEN, hypertension, diabetes mellitus and age above 60 years) present in the examined subjects showed that a positive family history for BEN (319 subjects, 19.6%) was not the most frequent risk factor, but hypertension (585 subjects, 36%) and older age (604 subjects, 37.2%) were more frequent and diabetes was found in 146 subjects (9%). According to the presence of risk factors, the examined subjects were placed in one of the five groups shown in Table 1. Significant differences were found for age, sex, and blood pressure among the groups.

The frequency of urinary abnormalities in the five groups is shown in Table 2. All the four groups with risk factors for CKD had higher frequencies of proteinuria than the group without risk factors, and only the difference between the smallest group with diabetes and the group without risk factors was not significant. No significant differences among the groups were found in the frequency of hematuria but the highest percent of patients with diabetes had glycosuria.

As expected, some subjects had more than one risk factor for CKD. Thus, among subjects with a positive family history for BEN, 21.3% had hypertension, 8.6% had hypertension and were above 60 years, 8.6% were above 60 years but did not have hypertension, 3.4% had both hypertension and diabetes and were more than 60 years, and 3.9% had diabetes with (2.5%) or without hypertension (1.4%). The frequency of urinary abnormalities depended on the number of risk factors (Figure 1). The frequency of proteinuria was about

Table 1. Data for the five groups formed according to the presence of risk factors for chronic kidney disease.

			Sex		Blood pressure	
Persons with	Number	Age (years)	Male	Female	Systolic	Diastolic
BEN family history	319	48.9 ± 15.7[a]	176[a]	143[a]	139 ± 24[a]	83 ± 11[b]
Hypertension	585	62.6 ± 12.4	202	383	148 ± 23	85 ± 11
Diabetes mellitus	146	63.1 ± 12.0	62	84	132 ± 21[a]	81 ± 11[a]
>60 years	604	70.3 ± 6.0[a]	255	349	149 ± 23	85 ± 11
None of these risk factors	566	39.6 ± 12.2[a]	340[a]	222[a]	126 ± 16[a]	79 ± 9[a]

Notes: Data presented as mean ± SD or number.
[a] $p < 0.05$ compared with all other groups.
[b] $p < 0.05$ compared with groups 2, 4, and 5.

Table 2. Frequency of urinary abnormalities detected by urine dipstick test in persons with different risk factors for chronic kidney disease.

Persons with	Proteinuria	Hematuria	Glycosuria
BEN family history	21 (6.6%)	21 (6.6%)	12 (3.8%)
Hypertension	36 (6.2%)	43 (7.4%)	26 (4.4%)
Diabetes mellitus	9 (6.2%)	5 (3.4%)	36 (23.3%)[b]
>60 years	43 (7.1%)	45 (7.5%)	31 (5.1%)
None of these risk factors	19 (3.4%)[a]	26 (4.6%)	4 (0.7%)

[a]$p < 0.05$ compared with groups 1, 2, and 4.
[b]$p < 0.05$ compared with all other groups.

Table 3. Factors associated with proteinuria and hematuria obtained using multivariate logistic regression analysis for all examined subjects.

	B	Sig.	Exp(B)	95.0% CI for Exp(B)
Proteinuria				
BEN in brother/sister	1.27	0.053	3.57	0.98–12.9
Systolic blood pressure (mmHg)	0.013	0.041	1.01	1.01–1.03
Constant	−4.98	0.000	0.007	
Hematuria				
Sex	1.29	0.000	3.61	2.13–6.14
History of kidney disease	0.60	0.033	1.82	1.05–3.2
Constant	−4.92	0.000	0.007	

three times higher in subjects with three or more risk factors than in those without risk factors.

Univariate logistic regression analysis indicated that female sex, age, systolic blood pressure, BEN in brother/sister, and family history for hypertension were associated with proteinuria, but female gender and a personal history of kidney disease with hematuria. When these variables entered multivariate logistic regression analysis, systolic blood pressure and BEN in brother/sister were found to be independent variables associated with proteinuria, and female gender and a history of kidney disease were found to be independent variables associated with hematuria (Table 3).

DISCUSSION

The screening survey of adult inhabitants from three BEN villages in the municipality of Bijeljina was undertaken to find out the frequency of risk factors for CKD in this population and the frequency of urinary abnormalities depending on the presence of risk factors. Among the examined subjects 19.6% had a positive family history for BEN, but hypertension (36%) and age above 60 years (37.2%) were almost twice as frequent, and 9% of the subjects had diabetes. Proteinuria was present in 6.2–7.1% of the subjects with risk factors for CKD but in 3.4% of those without risk factors. The frequency of urinary abnormalities increased with the number of risk factors.

The continuous increase of CKD prevalence requires more attention to be paid to early detection, so numerous screening programs have been conducted all over the world.[10–12] However, in BEN regions, screening studies had started 50 years ago, at the very beginning of the disease investigation. During the 1990s, studies of BEN almost ceased and some authors indicated that BEN was disappearing.[13,14] However, systematic surveys in endemic villages in the Kolubara region (Serbia) and analysis of the Registry for Endemic Nephropathy in the municipality of Lazarevac disclaimed this proposal.[15,16] That directed us to undertake a systematic survey in the municipality of Bijeljina, the most affected BEN region in R. Srpska, BH. Although recent studies have shown that universal screening of unselected populations was not cost effective,[17] the whole adult population of the endemic villages was invited for the screening. Namely, our first intention was to determine the prevalence of BEN and to answer the question whether BEN is disappearing. The first screening results

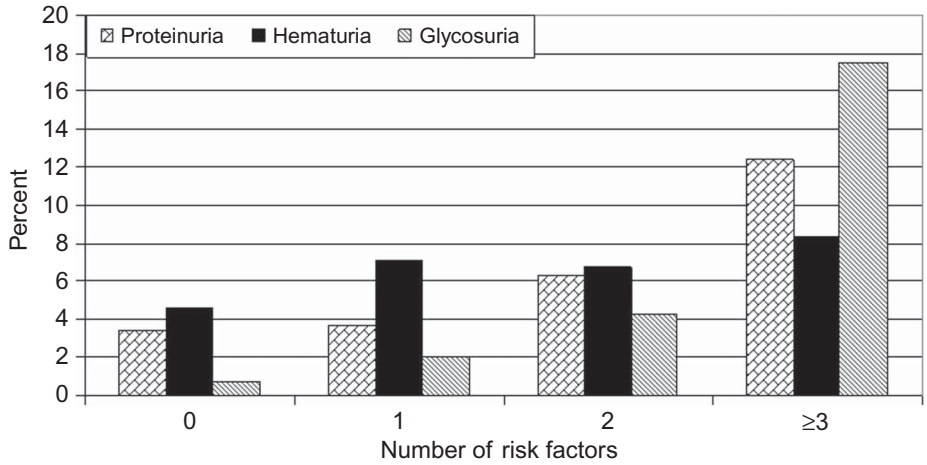

Figure 1. Frequency of urinary abnormalities increases with increasing number of risk factors for chronic kidney disease.

indicated that, in addition to a family burden for BEN, several other risk factors for CKD were highly prevalent in the endemic villages. Therefore, examination of the prevalence of risk factors for CKD in the three BEN villages was considered the main objective of this study. The results showed that hypertension and old age were more frequent risk factors than a family burden with BEN. Only one-third of the examined inhabitants (566 subjects, 34.8%) had none of the four analyzed risk factors for CKD. Such a high prevalence of risk factors for CKD justifies screening the whole population of the endemic villages.

Previous epidemiological studies in BEN foci were directed to BEN detection only, so data on other kidney diseases are scarce. In 1977, Vukušić et al.[18] found hypertension in 22% of the inhabitants of BEN villages near the South Morava River, but recently more than 50% of hypertensive patients were found in the endemic foci in northeastern Bosnia and Croatia.[19,20] In our study, hypertension was detected in 36% of the subjects, which is a higher rate than in the whole population of R. Srpska where hypertension was found in 19.7%.[21] Also, the prevalence of diabetes detected here in 9% of our subjects is twice as high as that reported for R. Srpska (4.8%).[21] The prevalence of hypertension and diabetes has increased substantially during the last two decades, first in developed countries and thereafter all over the world.[22,23] In addition, prolonged human life has led to an increased proportion of the elderly. According to the Report of the Institute for Public Health, F. BH, in 1971 only 4.5% of the inhabitants were older than 65 years, but in 2007 this had increased to 15.4%.[24] A much higher proportion of inhabitants above 60 years were found in the three endemic villages. However, that is characteristic of the rural population, and a demographic analysis of inhabitants in R. Srpska showed that 60.8% of individuals above 65 years lived in villages.[21] The older age of the endemic village populations can at least partly explain the higher prevalence of hypertension and diabetes than in the whole of R. Srpska. In addition, more than one-third of the subjects with a positive family history for BEN had hypertension, which additionally increased the prevalence of hypertension in these villages. It should be underlined that hypertension in all diabetics was already known and treated, while in 126 nondiabetics, hypertension was detected during the screening, and the majority of them were above 60 years (data not presented). This explained the significantly lower mean blood pressure in the group with diabetes compared with patients with hypertension and those older than 60 years. In addition, in many of the treated hypertensive patients, target blood pressure was not achieved. These data indicated that more education about hypertension, its early detection and management for physicians as well as general population, is necessary.

The results of urine analysis showed that the frequency of proteinuria, detected by the dipstick test, was similar in all four at-risk groups. In other reports of studies, carried out in the first decades of BEN investigations, only data on proteinuria in BEN family members were presented.[3,4,25,26] Recently, Dimitrov et al. found that protein and albumin excretion tended to be higher in the BEN offspring than in the control non-BEN offspring, but not significantly.[27] Stefanović et al.[28] detected proteinuria in children from endemic and non-endemic families, although significantly lower in the latter. In a recent screening study in an endemic village in northeastern BH, Mešić et al.[19] found proteinuria in 28.86% of inhabitants with a family burden for BEN, but in 20.52% of those without this burden. Although these proportions are much higher than those found here, they confirm our finding about the high prevalence of proteinuria in subjects without a family burden for BEN.

The increasing prevalence of hypertension and diabetes in endemic foci is also an important diagnostic problem. In subjects with detected proteinuria, a careful differential diagnostic procedure should be carried out to differentiate BEN from other kidney diseases, especially from hypertensive and diabetic nephropathy. There are almost no written data on this diagnostic problem and only Hrisoho et al.[29] described a group of 79 registered BEN patients, where detailed clinical investigations revealed that 24 patients had other kidney diseases and 6 had nephroangiosclerosis. This problem has recently been emphasized in studies dealing with diagnostic criteria for BEN,[30,31] but evaluation of the diagnostic value of particular biomarkers for differentiation of BEN from other kidney diseases, especially hypertensive and diabetic nephropathy, remains an important task in BEN investigations.

Multivariate logistic regression analysis found systolic blood pressure and BEN in brother/sister as significant independent variables associated with proteinuria. Many other screening studies have reported hypertension as an independent predictor of albuminuria.[11,32] Dimitrov et al.[27] found that proteinuria was significantly higher among offspring of mothers with BEN in comparison with offspring with no affected parents, but this was not true for those whose fathers had BEN. Our analysis found BEN diagnosed in brother/sister as a variable associated significantly with proteinuria, but not histories of BEN in mother's or father's or both parents' families. On the other hand, hematuria was significantly associated with female gender and a history of kidney diseases other than BEN. It is well known that hematuria is not a characteristic of BEN and its appearance in BEN patients arouses suspicion of urothelial tumor.[26]

The main limitation of our study was that it comprised only 36.5% of the population from the three endemic villages. The subjects who responded to the invitation and came to the screening may not have been a representative sample of the whole population. Nevertheless, the results of this screening study in endemic foci of the Bijeljina municipality showed a high prevalence of risk factors for CKD and significant prevalence

of urinary abnormalities in all at-risk populations indicating that further studies are warranted.

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