Screening of Elderly for Chronic Kidney Disease

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Key Words

Symptomless elderly · Kidney disease · Microalbuminuria

Abstract

Background and Aims: The frequency of chronic kidney disease (CKD) markers was assessed in two groups of patients over 60 years – one without and the other with hypertension.

Methods: The cross-sectional study involved 585 asymptomatic elderly patients (227 males), 93 without and 492 with hypertension. Data on patients were obtained by interview, analysis of medical records and physical examinations. Serum and urine creatinine, proteinuria, microalbuminuria (MAU, turbidimetry), and urinary sediment were analyzed.

Results: Among the 585 patients, there were 54.5% with a positive family history for hypertension and 14% for kidney diseases. MAU was significantly more frequent (30 vs. 11%) and the mean estimated glomerular filtration rate (eGFR) higher (71 ± 14 vs. 64 ± 14 ml/min/1.73 m²) in patients without hypertension than in those with hypertension. The majority of patients with stage 3 CKD had eGFR >45 ml/min/1.73 m² with normal urinary findings. Multivariate logistic regression analysis found age and treatment with angiotensin-converting enzyme inhibitors to be associated with reduced eGFR, MAU and proteinuria. In addition, smoking was associated with eGFR, but a family history for kidney disease and belonging to the group without hypertension were

associated with MAU. **Conclusion:** The high prevalence of markers for CKD in symptomless elderly without hypertension confirmed that the elderly, as a high-risk population, should be screened based on increased age alone.

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Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with an increasing incidence and prevalence, poor outcome and high treatment costs. Due to its asymptomatic nature, CKD is frequently detected at an advanced stage, resulting in the loss of opportunities to influence its course and outcome. Progression of CKD to renal failure or other adverse outcomes can be prevented or delayed through early detection and treatment [1, 2]. Currently, large efforts are being made for better detection of CKD. In 2002 the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) developed a practice guideline for CKD, recommending routine testing for detection of kidney disease during healthcare encounters for individuals at risk [3].

CKD disproportionately affects older persons. The incidence of end-stage renal disease increases with age and the majority of subjects who start renal replacement ther-

apy are over 60 years of age [4, 5]. Although there is a strong association between age and kidney function [6, 7], the clinical significance of reduced kidney function in older asymptomatic subjects remains disputable. In addition, it is unclear what portion of the decline in glomerular filtration rate (GFR) is due to higher prevalence of risk factors for kidney disease at older ages, such as hypertension, diabetes and vascular disease [8].

In the present study the frequency of markers for CKD was assessed in two groups of asymptomatic persons older than 60 years, one with hypertension and the other without hypertension. The aim of the study was to compare the frequency of markers for CKD in these two groups and find out whether older persons without hypertension had a sufficient prevalence of CKD markers to be screened, based on age alone.

Patients and Methods

Patient Selection and Study Design

This cross-sectional study involved 585 consecutive asymptomatic elderly patients (227 males; 68.97 ± 6.24 years, range 60–94) who presented for regular check-ups to their general practitioners in Belgrade Health Centers. Patients with previously known kidney and urinary tract diseases, diabetes, malignant disease, congestive heart disease, acute cardiovascular disturbances, systemic connective tissue disease, liver failure, acute infection or fever were not included in the study. The Ethics Committee of the Clinical Center of Serbia evaluated and approved this study, and patients gave their informed consents.

General practitioners carried out a survey of all patients that started with an interview in which the participants answered a detailed questionnaire on demographic issues, family and personal medical history with special attention to hypertension (duration, treatment) and data on smoking habits. From the medical records general practitioners also calculated mean systolic and diastolic blood pressure using all values of blood pressure registered in the previous year. After the interview all persons were examined physically including measurement of body weight, height and blood pressure. Arterial hypertension was defined as systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 80 mm Hg or if antihypertensive treatment was prescribed [9]. Smoking was defined as actual use of cigarettes (not ex-smokers).

Laboratory analyses involved serum and urine creatinine measurement by a kinetic Jaffé method, the urine dipstick test for proteinuria, determination of urine albumin using a turbidimetric method and urinary sediment analysis in the random spot urine specimen. Proteinuria was defined when the dipstick analysis quantified protein as 1+ or more. The urinary albumin/creatinine ratio was used for estimation of total daily albumin excretion [10]. A urinary albumin to urinary creatinine ratio ≥ 25 mg/g creatinine for women and ≥ 17 mg/g creatinine for men defined microalbuminuria (MAU) [11]. Urinary sediment was examined under a microscope and <5 red or white blood cells per high-

power field were considered normal. All analyses were done in the same laboratory (Institute for Laboratory Medicine Hexalab, Belgrade, Serbia).

Estimated GFR (eGFR) was estimated using the abbreviated MDRD study equation:

$$\text{eGFR (ml/min/1.73 m}^2\text{)} = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}).$$

Based on the presence of MAU and/or proteinuria and eGFR MDRD values, patients were classified into stages in accordance with the CKD classification of the NFK [3]: stage 1 (eGFR >90 ml/min/1.73 m²) and stage 2 (eGFR 60–89 ml/min/1.73 m²) were defined as renal damage characterized by the presence of MAU and/or proteinuria in addition to the equated eGFR values; stage 3 – eGFR 30–59 ml/min/1.73 m²; stage 4 – eGFR 15–30 ml/min/1.73 m², and stage 5 – eGFR <15 ml/min/1.73 m². In addition, stage 3 CKD was divided into two sub-stages: sub-stage 3a with a GFR of 45–59 ml/min/1.73 m² and sub-stage 3b with a GFR of 30–44 ml/min/1.73 m² [12, 13].

The results were expressed as mean values with standard deviations (mean $\pm$ SD). The significance of differences between mean values for groups was calculated using the Mann-Whitney U test and Student's t test. χ^2 or Fisher's test was used to compare frequency. The impact of covariates on the markers of CKD was tested by univariate/multivariate logistic regression analysis. Only those covariates found significant at the 0.1 level by univariate analysis were used in multivariate analysis. The analysis was used to assess the association of the dichotomous dependent variables proteinuria (1+ or more assessed by urine dipstick test), MAU (urinary albumin to creatinine ratio ≥ 25 mg/g creatinine for women and ≥ 17 mg/g creatinine for men) and eGFR (<60 ml/min/1.73 m²) with the following independent variables: age, gender, hypertension, BMI, smoking habit, positive family history for kidney disease and hypertension, actual systolic and diastolic blood pressure and angiotensin-converting enzyme inhibitor (ACEi) treatment. Analyses were adjusted for potential confounding factors. $p < 0.05$ was considered significant. All analyses were performed using the SPSS statistical software package (Version 10; SPSS).

Results

Data on the studied patients are presented in table 1. According to average systolic and diastolic blood pressure in the previous year the patients were divided into two groups: 492 patients with hypertension and 93 patients without hypertension. None of the patients without hypertension were treated with ACEi, while 69.7% of patients with hypertension were treated with ACEi. No significant differences in age and sex were found between normotensive and hypertensive patients. Although mean values for BMI indicated that overweight was common in both groups, normotensive patients had a significantly lower BMI, while 10.4% of normotensive but 18.5% of hypertensive patients were obese (BMI >30). According to

the proportion of patients undergoing regular urine and laboratory checks in the year preceding the study, it was obvious that most subjects were under medical control. 82 (14%) patients had a positive family history for kidney diseases and 319 (54.5%) for hypertension, mostly patients actually with hypertension.

The results of laboratory analyses are also presented in table 1. Mean serum creatinine levels were normal in males and females of both groups but the normotensive group had significantly lower values than the hypertensive group. In addition, 10 (10.8%) normotensive patients and 112 (22.8%) hypertensive patients exhibited serum creatinine concentrations above the upper normal limit ($\chi^2 = 4.211$, $p = 0.040$). Mean eGFR was >60 ml/min/ 1.73 m² in both groups but significantly higher in normotensive patients. The prevalence of patients in stage 2 tended to be higher in normotensive than in hypertensive patients but not significantly, while the prevalence of patients in stage 3 CKD was significantly higher in hypertensive than in normotensive patients ($\chi^2 = 4.183$, $p = 0.04$). MAU was found in 82 (14.0%) patients, significantly more frequently in the normotensive group ($\chi^2 = 14.923$, $p = 0.0001$). Proteinuria and erythrocyturia were similarly prevalent in both groups.

The frequency of all examined markers for kidney disease is presented separately for normotensive and hypertensive patients in figure 1a and b. eGFR >60 ml/min/ 1.73 m² with normal urinary findings occurred at a similar rate in patients from both groups (50 vs. 53%). Although fewer normotensive patients had eGFR <60 ml/min/ 1.73 m² with normal urinary findings than hypertensive subjects (16 vs. 31%), the difference was not significant. The remaining patients had a combination of abnormalities. In comparison to hypertensive patients, more normotensive patients had normal eGFR with proteinuria and/or MAU (24 vs. 5%), and the difference was significant ($\chi^2 = 31.561$, $p = 0.0001$). No significant difference was found in the frequency of other combinations of abnormalities between the two patient groups. Taken together, 307 of our patients (52.5%) had normal laboratory findings, while the remaining 47.5% had at least one marker for kidney disease.

Patients in stage 3 of CKD were subdivided into stage 3a with eGFR between 45 and 59.9 ml/min/ 1.73 m² and stage 3b with eGFR between 30 and 44.9 ml/min/ 1.73 m² (table 1). Urine analysis in these subgroups of patients showed that 11 out of 20 (55.0%) normotensive and 127 out of 185 (68.4%) hypertensive patients in subgroup 3a had normal urinary findings and the difference was not significant. Values were found to be similar for subgroup

Table 1. Data on patients obtained by questionnaire, medical record analysis, objective examination and laboratory analysis

	Patients without hypertension (n = 93)	Patients with hypertension (n = 492)
Mean age $\pm$ SD, years	69.6 $\pm$ 5.8	68.8 $\pm$ 6.3
Range	60 – 84	60 – 94
>70 years (>80 years), n	46 (3)	209 (25)
Males, n (%)	39 (41.9)	188 (38.2)
Mean BMI $\pm$ SD	25.43 $\pm$ 5.2 ^a	27.26 $\pm$ 5.4
BMI ≥ 30 kg/m ²	9 (10.4)	91 (18.5)
Mean blood pressure $\pm$ SD, mm Hg		
Systolic	125.28 $\pm$ 10.11 ^b	139.38 $\pm$ 17.8
Range	105 – 155	100 – 210
Diastolic	78.36 $\pm$ 6.32 ^b	84.36 $\pm$ 9.8
Range	70 – 100	60 – 125
Systolic in previous year	128.11 $\pm$ 10.53 ^b	143.77 $\pm$ 13.4
Diastolic in previous year	79.86 $\pm$ 5.98 ^b	85.0 $\pm$ 8.1
Hypertension duration, years	0	12.02 $\pm$ 7.6
ACEi therapy, n (%)	0	343 (69.7)
Positive family history for		
Kidney disease, n (%)	23 (24.7)	59 (12.1)
Hypertension, n (%)	17 (18.3)	302 (61.4)
Smoking habits, n (%)	17 (18.3)	54 (10.9)
Previous checking, n (%)		
Urine	65 (69.8)	366 (74.4)
Serum creatinine	57 (61.3)	324 (65.8)
Mean sCr $\pm$ SD, μ mol/l	85.33 $\pm$ 15.49 ^c	93.77 $\pm$ 22.74
Male	95.28 $\pm$ 15.2 ^d	106.44 $\pm$ 25.8
Female	78.18 $\pm$ 11.3 ^e	86.21 $\pm$ 16.6
Mean eGFR MDRD $\pm$ SD, ml/min/ 1.73 m ²	70.54 $\pm$ 14.40 ^b	63.73 $\pm$ 14.17
<60 ml/min/ 1.73 m ² , n (%)		
Male	6 (15.4)	74 (39.3)
Female	14 (25.9)	114 (37.5)
CKD stage, ml/min/ 1.73 m ² , n (%)		
1 eGFR ≥ 90	6 (6.4)	21 (4.7)
2 eGFR 60 – 89.9	67 (72.0)	283 (57.5)
3a eGFR 45 – 59.9	17 (18.3) ^f	143 (29.0)
3b eGFR 30 – 44.9	3 (3.2)	42 (8.5)
4 eGFR 15 – 29.9	0	3 (0.6)
Mean MAU $\pm$ SD, mg/g uCr	27.35 $\pm$ 36.1	23.53 $\pm$ 118.5
Patients, n (%) with	(3.85)	(5.79)
>17 mg/g uCr for males	10 ^b	24
>25 mg/g uCr for females	18 ^b	30
Proteinuria ($\geq +1$)	9 (9.6)	79 (16.0)
Erythrocyturia ($\geq +1$)	7 (7.5)	30 (6.1)

sCr = serum creatinine concentration; CKD = chronic kidney disease; MAU = microalbuminuria.

^a $p = 0.004$; ^b $p = 0.0001$; ^c $p = 0.012$; ^d $p = 0.05$, ^e $p = 0.017$; ^f both 3a + 3b CKD: $\chi^2 = 4.183$, $p = 0.04$.

Fig. 1. Frequency of all examined markers for kidney disease for normotensive (a) and hypertensive (b) patients.

Table 2. Variables associated with eGFR, MAU and proteinuria as dichotomous dependent variables determined by univariate/multivariate logistic regression analysis

Variable	B	p	95% CI
eGFR			
Age	0.091	0.000	1.095 (1.053; 1.139)
Smoking	-0.823	0.029	0.439 (0.210; 0.917)
ACEi	1.035	0.003	2.815 (1.431; 5.540)
Constant	-7.804	0.000	
MAU			
ACEi	0.934	0.021	2.283 (1.120; 4.832)
Family history for kidney disease			
Group	1.136	0.006	3.116 (1.378; 7.045)
Constant	-1.463	0.000	0.232 (0.113; 0.475)
Proteinuria			
Age	0.054	0.016	1.056 (1.010; 1.103)
ACEi	0.697	0.055	2.008 (0.984; 4.097)
Constant	-6.082	0.000	

3b: 2 (10%) normotensive and 26 (14.3%) hypertensive patients had normal urinary findings. A significant difference was only found in the frequency of proteinuria with erythrocyturia between patients without hypertension (3/20) and those with hypertension (1/185) in subgroup 3a (Fisher's test $p = 0.0044$), while the frequency in MAU and/or proteinuria as well as in isolated erythrocyturia differed insignificantly between the subgroups.

Variables associated with proteinuria, MAU and eGFR as dichotomous dependent variables were determined by univariate/multivariate logistic regression analysis (table 2). The results showed that eGFR <60 ml/min/1.73 m² was associated with older age (positive relationship), smoking (negative relationship), and ACEi treatment. MAU was associated with ACEi treatment (positive relationship) in addition to the family history for kidney disease (positive relationship) and belonging to the group without hypertension. Age and ACEi treatment were found as variables significantly associated with proteinuria.

Discussion

In the present study the prevalence of markers for CKD was determined in two groups of persons older than 60 years – one without hypertension and the other with hypertension. The patients were asymptomatic for kidney disease. Although fewer persons without hypertension had eGFR <60 ml/min/1.73 m² with normal urinary findings than those with hypertension, the difference was not significant. However, a significantly higher percent of normotensive patients had proteinuria and/or MAU in comparison with hypertensive ones. Taken together, 46 (50%) persons without hypertension and 231 (47%) with hypertension had at least one marker for kidney disease and the difference was not significant. This prevalence

was higher from the one found in the general population [5, 14] but similar to values reported in studies involving the elderly. Thus, in the PROSPER study that included 5,804 subjects between the ages of 70 and 82 years from Scotland, Ireland and the Netherlands, 53.3% had GFR <60 ml/min/1.73 m² [15]. The prevalence of CKD in persons ≥ 65 years was approximately 44% in both KEEP and NHANES participants [16].

A high prevalence of CKD in elderly persons is not only partly due to the well-known decline of GFR during normal aging [7], but also to multiple risk factors appearing in the elderly that contribute to its development. The selection criteria for the present study allowed inclusion of persons above 60 years without comorbidities that could influence kidney function, except hypertension. Nevertheless, analysis of the data obtained by the questionnaire showed that older age and hypertension were not the only risk factors for CKD in the examined group. A positive family history for kidney disease, smoking and obesity were present with similar frequency in persons without and with hypertension. Therefore, the difference in the prevalence of CKD markers in the two groups could not be explained by the difference in the prevalence of these risk factors. The main difference between the groups was the presence or absence of hypertension, a well-known risk factor for CKD. Comparison of prevalence of CKD markers in elderly persons without hypertension and those with hypertension enabled us to find out whether older age alone was associated with a significant prevalence of CKD markers. Normotensive patients had a significantly lower mean serum creatinine level and a significantly higher mean eGFR. In this group, eGFR <60 ml/min/1.73 m² was found in 20 (22%) persons, while in the group with hypertension it occurred in 188 (38%) persons ($\chi^2 = 4.183$, $p = 0.04$). However, when eGFR and urinary findings were considered together, prevalence of eGFR <60 ml/min/1.73 m² with normal urinary findings differed insignificantly between persons without and with hypertension.

Moreover, MAU was found significantly more frequently in normotensive (28–30%) than in hypertensive (54–11%) patients ($\chi^2 = 14.923$, $p = 0.0001$). A higher prevalence of MAU was found in normotensive patients with GFR >60 and <60 ml/min/1.73 m² when compared with hypertensive ones. Also, the prevalence of MAU and/or proteinuria was significantly higher in patients without hypertension than in those with hypertension [37 (40%) vs. 114 (23%); $\chi^2 = 5.535$, $p = 0.018$]. Although we cannot offer a complete explanation for these differences, one factor that contributes to the lower prevalence of protein-

uria in patients with hypertension might be the use of ACEi by 70% of the patients with hypertension, but none of the patients without hypertension. This is supported by the results of multivariate logistic regression that found the treatment with ACEi as a significant independent variable associated with MAU and proteinuria. In addition, hypertension was already known and treated before the screening study in all but 5 patients. It could be proposed that because hypertension was treated in almost all patients, blood pressure did not appear as a significant predictor either for eGFR or for MAU. Age was found to be significantly associated with reduced eGFR and proteinuria, but positive family history for kidney disease and belonging to the group without hypertension were associated with MAU. All these data obtained by logistic regression analysis as well as the high prevalence of MAU and proteinuria in persons over 60 years without hypertension showed that older age is significantly associated with kidney damage.

MAU and/or proteinuria are considered important markers for diagnosis, not only for stages 1 and 2 but also for stage 3 CKD. According to the classification of CKD in the NKF/DOQI clinical practice guidelines, stages 1 and 2 are defined by the presence of signs of kidney damage (albuminuria, erythrocyturia or abnormalities on renal ultrasound) but only impaired eGFR was necessary to classify someone with stage 3–5 CKD [11]. As eGFR declines with age, many elderly, especially women, have eGFR <60 ml/min/1.73 m². Therefore, if age and gender influences on eGFR are not taken into account, many persons with eGFR between 30 and 59 ml/min/1.73 m² will be falsely identified as patients with renal disease [12, 13]. Therefore, several authors proposed redefinition of stage 3 CKD to improve both the diagnostic and prognostic value of the classification [17, 18]. Recently, the clinical guidelines of the National Institute for Clinical Excellence (United Kingdom) suggested subdividing stage 3 CKD into no less than four subcategories, based on whether the eGFR is <45 or >45 ml/min/1.73 m² and the presence or absence of proteinuria [13]. Using this recommendation, we divided stage 3 CKD into two according to eGFR: stage 3a with eGFR between 45 and 59.9 ml/min/1.73 m² and stage 3b with eGFR between 30 and 44.9 ml/min/1.73 m², and analyzed the prevalence of proteinuria in these sub-stages. Most patients with eGFR <60 ml/min/1.73 m² belonged to stage 3a with normal urinary findings and that was found in both normotensive and hypertensive patients. Although some other authors also found that eGFR <45 ml/min/1.73 m² was much less common in older persons [19], the proposal for changes

of current KDIGO guidelines suggests splitting stage 3 into A and B and modification of stages by including different degrees of proteinuria [20]. Nevertheless, a reduction of eGFR <60 ml/min/1.73 m² was shown to be an independent risk factor for total and cardiovascular mortality [17, 19, 21, 22]. Therefore, older persons with eGFR <60 ml/min/1.73 m² should be treated and followed carefully regardless of the well-known decline of eGFR with age.

A diagnosis of CKD stage 3 or worse requires the presence of reduced kidney function to be documented over at least 3 months [23]. As our study was a cross-sectional one, we decided to present the prevalence of particular markers of CKD (eGFR, MAU, proteinuria, erythrocyturia) but not the prevalence of CKD, although many epidemiological studies use the term CKD for reduced eGFR with proteinuria detected at a single time point [19, 24, 25]. Although erythrocyturia is frequently the sign of urological disease, in the patients examined it most frequently appeared with MAU/proteinuria that indicated kidney damage. All patients with any detected urinary marker as well as those with eGFR <60 ml/min/1.73 m² were advised to continue examination by their family doctor. Clinical validation of eGFR to screen elderly for CKD is recommended whenever a serum creatinine is obtained. It would be of particular importance when prescribing a drug to this population which might cause progression due to drug-drug interactions or serious adverse effects. Although it is not a subject of the present study, the tendency of CKD stage 3 to progress to renal failure is less than estimated from studies of selected patient groups, and that high mortality forestalls the development of renal failure in many patients [26]. These facts entail cost-effectiveness, which can be alluded to as an area for future study.

Our study has some limitations. The subjects involved were selected from the population of patients vis-

iting their family doctors in Belgrade Health Centers. The results obtained for the studied group cannot be generalized to persons not using healthcare in Belgrade Health Centers or to individuals in other regions. The second limitation is the relatively small number of examined patients, especially those without hypertension due to the high prevalence of hypertension in the elderly. An additional limitation is the cross-sectional design and, as we have already underlined, such a study enabled us to find out only the prevalence of particular markers for CKD but not diagnosis and prevalence of CKD. Finally, kidney function was estimated by the creatinine-based four-variable MDRD formula, as we had no opportunity for calibration of the serum creatinine assay to be traceable to IDMS. The MDRD formula overestimates GFR in older persons [25, 27] and therefore careful interpretation of the results is necessary. Thus, we considered all persons with detected kidney function abnormalities as persons with suspected CKD who need further examination.

In conclusion, in the group of 585 elderly persons, that consisted of 93 persons without hypertension and 492 with hypertension, a high prevalence of CKD markers was found. At least one marker for kidney disease was found in 46 (50%) persons without hypertension and in 231 (47%) with hypertension. The high prevalence of markers for CKD in symptomless elderly without hypertension indicated that the elderly, as a high-risk population, should be screened based on increased age alone. Further study in more diverse populations is needed before precise recommendations can be made.

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