Original article

Classification of patients at risk for chronic kidney disease by use of eGFR and albuminuria

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Summary

Introduction. Screening for chronic kidney disease (CKD) has been advised in high-risk populations. However, data on the prevalence of early asymptomatic stages vary and depend on the definition of CKD. In the present study, subjects at risk for CKD (patients with diabetes mellitus type 2-DM2, with hypertension and older than 60 years without diabetes and hypertension) were classified in categories defined by eGFR and albuminuria staging system.

Methods. After regular check-up in primary health center, 285 consecutive patients at risk for CKD were selected: 75 patients with well-controlled DM2 without hypertension, 130 with hypertension and 80 subjects older than 60 years without diabetes or hypertension. Screening included a questionnaire, blood pressure measurement, single albuminuria determined by immunonephelometry, and eGFR estimation using MDRD.

Results. Six DM2 patients, 15 with hypertension and 12 elderly had eGFR<60 (assessed in ml/min/1.73m²) with optimal albuminuria. High albuminuria was observed in one DM2 and four hypertensive patients, and 28 elderly. When eGFR and albuminuria staging system for predicting risk for major CKD outcomes was used, 41.2% of the elderly were classified in the moderate and 8.8% in the high risk group, for DM2 patients these percentages were 9.3% and 0%, and for hypertensive patients 16.9% and 4.7%, respectively.

Conclusion. The majority of examined patients did not have CKD, and in all three groups most individuals with reduced eGFR did not have albuminuria >30mg/g. Using the classification of CKD based on eGFR and albuminuria, it was found that elderly patients had the highest risk for a CKD outcome.

Keywords: patients at risk for CKD, eGFR, albuminuria, CKD categories

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]. Data on the prevalence of early asymptomatic stages vary and depend on the definition of CKD. In 2002 the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) developed a practice guideline for diagnosis and classification of CKD into five stages using glomerular filtration rate (GFR) as the main criterion [2]. Recent studies have emphasized the role of albuminuria, as a marker of kidney damage, in predicting outcomes. Therefore, CKD classification including both albuminuria and eGFR was derived from a Controversies Conference and a Prognosis Consortium study group in 2009 [3], and recently recommended in the KDIGO 2012 Clinical Practice guideline for the evaluation and management of CKD [4].

Albuminuria is the simplest and most sensitive prognostic factor to evaluate the risk of overt nephropathy in diabetes, representing the first stage of progressive diabetic renal disease [5]. Also, it is an early sign of kidney disease in people with hypertension. However, about 10-25% of patients with DM2 follow a ‘normoalbuminuric pathway’ in which GFR progressively declines without worsening proteinuria [6,7]. Our recent study was in agreement with these findings and demonstrated that impaired kidney function was frequently found in asymptomatic, normotensive, non-albuminuric patients with well controlled type 2 diabetes mellitus (DM2) but also that 14.5% of these patients had diastolic dysfunction and silent myocardial ischemia [8]. The question arises whether such normoalbuminuric progression of CKD is just a characteristic of DM2, or it occurs in hypertensive and/or elderly subjects who, in addition to DM, are now the most numerous populations at risk for CKD.

In addition to CKD classification, the KDIGO guideline proposed the use of GFR and albuminuria categories for prediction of CKD prognosis. The guideline used the results of a meta-analysis initiated by KDIGO that defined the relative risk across eGFR and albuminuria categories for five important outcomes, including all-cause mortality, cardiovascular disease, and kidney failure [4]. The relative risk for each eGFR and albuminuria combination represents the point estimate from this meta-analysis. The analysis provides joint associations of these two CKD markers with risk. Risk increases in both directions - down the GFR categories and across the albuminuria categories [3,4].

Objective of this study was to assess the prevalence of CKD and the risk for CKD outcomes in three patient groups at risk for CKD (DM2, hypertension and age over 60 years without diabetes and hypertension).

Methods

This cross-sectional study included 285 patients (61.3 ± 10.7 years, males 132) consisting of 75 patients with DM2 (group 1), 80 persons older than 60 years without hypertension and diabetes (group 2) and 130 patients with hypertension (group 3), who came for regular check-ups to their general practitioners in a Belgrade health center. Inclusion criteria for patients from group 1 were DM2 for more than 3 years, glycemic control measured by HbA1c< 8.0%, and blood pressure <135/85 mmHg without antihypertensive medication. Patients with diabetes diagnosed before the age of 26, a history of type 1 diabetes or diabetic keto-acidosis, with insulin therapy and/or diabetic microvascular complications (retinopathy, neuropathy, overt nephropathy) were excluded from the study. Inclusion criteria for patients with hypertension was duration of raised blood pressure (BP) for more than 5 years, regular treatment and control with maintenance of BP below 140/90 mmHg. Furthermore, patients with previously known kidney disorders, malignant diseases, congestive heart failure, any acute illness, persons younger than 18 years and pregnant women were not included in the study. The general practitioners selected 285 (10.4%) consecutive patients that met the above criteria from the whole population of 2740 subjects who addressed them during the study month. The Ethics Committee of the Clinical Center of Serbia evaluated and approved the study, and patients gave their informed consent.

All selected patients answered a detailed questionnaire on demographic issues, family and personal medical history with special attention to hypertension and diabetes (duration, treatment). After the interview, each person
was subjected to a physical examination including measurement of body weight, height and BP. Blood pressure was measured in the seated position, after the participant had rested for at least 5 min, using a standard mercury sphygmomanometer. Two readings were taken and the mean value calculated.

**Laboratory analyses.** Random spot urine specimen and fasting venous blood sample were taken from all participants who gave informed consent. Serum creatinine (Cr) was determined by the Jaffe method. Albuminuria was measured by immunonephelometry (Behring Nephelometer II analyzer). The urinary albumin/creatinine ratio on the random spot urine specimen was used for estimation of total daily albumin excretion [9]. None of the studied patients had massive haematuria that could influence the albuminuria values. Glomerular filtration rate was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation for non-standardized creatinine [10]. As we had no opportunity to calibrate the serum creatinine assay to be traceable to Isotope Dilution Mass Spectrometry (IDMS), the original four-variable MDRD Study equation was used [11]:

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eGFR \text{ (mL/min/1.73 m}^2) = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})
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Subjects were divided into five stages by eGFR MDRD category (G1-5) and three albuminuria categories (A1-3) according to the KDI-GO 2012 [4]: stage 1 - eGFR ≥90 ml/min/1.73m², stage 2 - eGFR 60-89 ml/min/1.73m², stage 3a - eGFR 45-59 ml/min/1.73m², stage 3b - sGFR 30-44 ml/min/1.73m², stage 4 - eGFR 15-29 ml/min/1.73m², stage 5 eGFR<15 ml/min/1.73m².

Also, albuminuria was classified as follows: optimal (<10 mg/g uCr) and high-optimal (10 - 29 mg/g uCr) both = A1, high (30 - 299 mg/g uCr) = A2 and very high (> 300 mg/g uCr) = A3 [4].

**Statistical analysis.** The results were expressed as mean values with standard deviations (mean ± SD) for the numeric variables, or as frequencies for categorical variables. Comparison among the groups was based on one-way analysis of variance (ANOVA) accompanied by Bonferroni multiple comparison tests for continuous data and with the Chi-square test for categorical data. P values of <0.05 were considered to indicate statistical significance. All analyses were performed using the SPSS statistical software package (version 10).

**Results**

Data on the studied participants are presented in Table 1. Diabetics were significantly younger, while elderly people, as expected, were significantly older than members of the other two groups. As anticipated, mean BP was the highest in the hypertensive group. Mean duration of hypertension was almost 10 years (range 5-20 years), and mean duration of diabetes was almost 4 years (range 3-15 years). Three-quarters of the hypertensive and none of diabetic patients were treated with ACEi, and the remaining patients received calcium channel blockers in combination with diuretics. Medical treatment of diabetes consisted of diet and/or oral antihyperglycemic agents (sulfonylurea and/or metformin). Mean eGFR was significantly higher, but albuminuria significantly lower in the diabetic group than in the other two groups.

Classification of patients based on eGFR and albuminuria is presented in Tables 2-4. The majority of patients in all three groups had eGFR above 60 ml/min/1.73m²: 69 (92%) with DM2, 63 (78.7%) of those older than 60 years and 102 (78.5%) with hypertension. Most patients had optimal albuminuria, but some differences between the groups were observed.

Only one DM2 patient with eGFR above 60 ml/min/1.73m², and none with a lower eGFR had albuminuria above 30 mg/g (Table 2). Among patients older than 60 years (Table 3), high albuminuria was mostly found in individuals with eGFR above 60 ml/min/1.73m², while out of 17 patients in stage 3 (both 3a and 3b) only five had high albuminuria. Elevated albuminuria was rare in hypertensive patients (Table 4): two had high and another two very high albuminuria.

Using the eGFR and albuminuria staging system for predicting risk for outcome of CKD, as proposed by the KDIGO guideline [4], all examined subjects were classified into five risk groups (Figure 1). The number of subjects decreased with increasing severity of risk in all three examined health groups. The majority
of DM2 and hypertensive patients, and half of the participants older than 60 years had eGFR above 60 ml/min/1.73m² and albuminuria below 30 mg/g uCr and they fall in the group with low risk for major CKD outcomes (all cause and cardiovascular mortality, end-stage renal disease, acute kidney injury and CKD progression). Seventeen DM2 patients, 33 subjects in the elderly group, and 22 patients with hypertension had a moderate risk. There were seven subjects in the elderly group, and 6 patients with hypertension at high risk for
the major outcomes. Finally, two patients with hypertension were at very high risk for the major CKD outcomes. In comparison to older subjects and patients with hypertension, significantly more DM2 patients were at low risk for a CKD outcome (p = 0.0098). There were no differences in the frequency of risk in the other groups examined.

Discussion

This cross-sectional survey involved three groups of individuals at risk for CKD i.e. patients with DM2 without hypertension, subjects older than 60 without DM2 and hypertension, and those with hypertension, in order to assess
the prevalence and severity of CKD as measured by eGFR and albuminuria. Most of the studied participants had eGFR above 60 ml/min/1.73 m² and optimal albuminuria, but significant differences were observed between the groups in the relative number of subjects with eGFR lower than 60 ml/min/1.73 m² and albuminuria above 30 mg/g, the threshold commonly accepted for the A2 category of albuminuria.

Reduced eGFR and albuminuria were proposed as two basic markers for CKD classification by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation [3] and these markers have been employed for detection of CKD in numerous screening studies. In several mass screenings carried out in the general population the prevalence of eGFR below 60 ml/min/1.73 m² was between 3.2% and 11.2% [12-15] and ≥A2 category of albuminuria between 2.4% and 15.6% [12-17]. In screening studies that included subjects at risk for CKD even higher prevalence was reported. The initial data of the The Kidney Early Evaluation Program (KEEP) program that targeted persons with diabetes, hypertension, or a family history of diabetes or hypertension or CKD showed that among 6,071 participants 29% had ≥A2 category of albuminuria and 16% had eGFR below 60 mL/min/1.73 m² [18]. In the present study 15.1% of all patients had high albuminuria and 17.9% had eGFR below 60 ml/min/1.73 m². Our previous study included 1617 patients with hypertension, diabetes and age over 60 years, who were unaware of earlier kidney disease. Almost half of them had at least one of the markers of CKD: 25% had only albuminuria (≥A2 category) and/or proteinuria but not reduced eGFR, while 21% had eGFR below 60 ml/min/1.73m² - 14% without albuminuria and proteinuria and 7% with ≥A2 category of albuminuria and/or proteinuria but not reduced eGFR, while 21% had eGFR below 60 ml/min/1.73m². A similar prevalence was obtained in KEEP Mexico [21] as well as in Japan [22]. In two other investigations involving adult patients with diabetes, pathological albuminuria was found in 20.4% to 48.6% and reduced eGFR in 27.5% and 38% [23, 24]. However, several studies showed that 10-25% patients with DM1 and DM2 had a non-albuminuric pathway to renal impairment [6,25,26]. Other authors indicated that estimating or measuring GFR could be a more reliable index in the early diabetic nephropathy phase than elevated albuminuria. While high albuminuria showed great intraindividual variability, low specificity and spontaneous regression [5,27,28], changes in GFR are usually progressive, with low variability, high specificity and infrequent regression [29,30]. These results are in concert with our recent study that demonstrated impaired kidney function in 9% of asymptomatic, normotensive, non-albuminuric patients with well-controlled type 2 diabetes mellitus, indicating that albuminuria is not a surrogate marker for declining kidney function in DM2 patients [7]. These results prompted us to analyze the distribution of elderly and hypertensive patients in categories defined by eGFR and albuminuria according to a two-dimensional grid derived recently from the KDIGO 2012 guideline [4]. The results presented here confirm that both in patients with hypertension and in the elderly many subjects with reduced eGFR had no albuminuria. Therefore, although classification of CKD based on both eGFR and albuminuria is generally accepted, it seems that the absence of ≥A2 category of albuminuria in stages 2-3 of CKD does not exclude progressive CKD.

On the other hand, as recently shown, a combination of eGFR and albuminuria enabled prediction of patient prognosis. Namely, the recent Controversies Conference was organized with the aim of establishing a reliable basis for classification of CKD that would not only improve early detection of CKD but also predict patient prognosis [3]. On the basis of analyses in 45 cohorts that included 1,555,332 participants from general, high-risk and kidney disease populations a modified classification of CKD was proposed by adding albuminuria stage and subdivision of stage 3 CKD. This meta-analysis enabled the detection of the relative risks of varying levels of eGFR and albuminuria for five major outcomes: all-cause mortality, cardiovascular mortality, ESRD, acute kidney injury and progression of kidney disease. From this, patients with eGFR<60 ml/min/1.73m² and albuminuria >30 mg/g uCr were considered as subjects with CKD and they could be classified into groups at moderate, high or very high risk [3,4]. One of the objectives of our study was to place the subjects from the
three examined groups in these categories for prediction of CKD outcome. Using this classification elderly patients were found to be at the highest risk for a CKD outcome. Namely, 41.2% and 8.8% of the elderly fell in the groups with a moderate and high risk, respectively, while these proportions for DM2 patients were 9.3% and 0%, and for patients with hypertension 16.9% and 4.6%, respectively. These results indicate that old age alone is a greater risk for adverse CKD outcome than well controlled diabetes or hypertension.

The relatively small number of examined patients is one limitation of our study, in addition to the cross-sectional design. Since the study was cross sectional, the single estimation of serum creatinine and albuminuria limits the value of our findings. Also, it was not clear whether subjects with optimal albuminuria and stage 2 and stage 3a represent the extremes of a normal distribution, who will have stable (but low) renal function, or does the low eGFR indicate a risk for progressive GFR loss despite the lack of proteinuria. Only follow up of the patients involved in our and other studies can give an answer to this question and validate the proposed classification of patients according to eGFR and albuminuria. The age difference among groups could be considered as another limitation of the study. However, the aim of the study was to assess the prevalence of CKD and the risk for CKD outcome in three groups at risk. Although diabetes and hypertension are the most frequent causes of end-stage renal disease all over the world, a continuous increase in the prevalence of elderly patients with end-stage renal disease is also being registered.

Conclusion

The present study showed that old age is a higher risk factor not only for CKD (the highest proportion of subjects over 60 years had two main markers of CKD) but also for poor prognosis of CKD in comparison to patients with well-controlled diabetes and hypertension. Small number of participants, cross-sectional design, sampling method, and different age structure of the three compared groups limit the value of our study.

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References


Klasifikacija bolesnika sa rizikom za nastanak hronične bubrežne bolesti prema jačini glomerulske filtracije i albuminuriji

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Uvod. Redovan skrining hronične bolesti bubrega (HBB) preporučuje se kod rizične populacije. Međutim, podaci o prevalenciji ranih asimptomatskih stadijuma variraju i zavise od definicije HBB. U ovo radu bolesnici tri grupe sa rizikom za nastanak HBB (bolesnici sa dijabetes melitusom tip 2 (DM2), sa hipertenzijom i osobe starije od 60 godina bez dijabetesa i hipertenzije) su grupisani u kategorije HBB prema jačini glomerulske filtracije (JGF) i albuminuriji kao klasifikacionim kriterijumima.

Mетод. Tokom pregleda u ustanovi primarne zdravstvene zaštite, 285 ispitanika sa rizikom za HBB je uključeno u analizu: 75 bolesnika sa DM2 sa zadovoljavajućom glikoregulacijom i bez hipertenzije, 130 sa hipertenzijom i 80 osoba >60 godina bez dijabetesa i hipertenzije su grupisani u kategorije HBB prema jačini glomerulske filtracije (JGF) i albuminuriji kao klasifikacionim kriterijumima.
Rezultati. Šest bolesnika sa DM2, 15 sa hipertenzijom i 12 starih imali su JGF<60 ml/min/1.73m2 sa optimalnom albuminurijom. Visoka albuminurija je nađena kod jednog bolesnika sa DM2, četiri sa hipertenzijom, i 28 starih osoba. Predvideni rizici za glavne ishode HBB su bili sledeći: umereni rizik kod 41,2% starih, 9,3% bolesnika sa DM2 i 16,9% sa hipertenzijom, i visok rizik kod 8,8% starih, nijednog bolesnik sa DM2 i 4,6% bolesnika sa hipertenzijom.

Zaključak. Većina ispitanika nije imala HBB, a među osobama sa sniženom JGF većina nije imala albuminuriju >30mg/g. Najveći rizik za mogući ishod HBB nađen je kod starijih osoba.

Ključne reči: bolesnici sa rizikom za HBB, procenjena JGF, albuminurija, HBB kategorije, ishod bolesti

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