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Original Research Article

Chronic kidney disease in elderly – Fact or fiction?

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ABSTRACT

Introduction: Chronic kidney disease (CKD) affects up to 10% of modern societies and its prevalence increases with age. In most epidemiological reports CKD is diagnosed based mainly or exclusively on estimated glomerular filtration rate (eGFR) assessment. Since no ''gold standard'' or reference method of eGFR calculation exists and other diagnostic criteria of CKD are rarely employed, the true prevalence of clinically significant CKD seems to be lower than reported in large epidemiological studies.

Aim: We aimed to analyze the prevalence of CKD and its clinical significance in the cohort of patients aged 65 years and older in general practice, applying all recommended criteria.

Material and methods: 108 consecutive patients (40 men and 68 women) aged 65 years and older (mean age 72 ± 5.2 years; range 65–87 years) were analyzed. Biochemical tests available in general practice with eGFR calculation using modification of diet in renal disease (MDRD), CKD epidemiology collaboration (CKD-EPI), Cockcroft–Gault formula and renal ultrasound were performed.

Results and discussion: 50% of patients were characterized with significantly reduced MDRD/CKD-EPI-eGFR (<60 mL/min/1.73 m^2). Detailed analysis revealed that patients with low eGFR do not differ from those with eGFR more than or equal to 60 mL/min/1.73 m^2 in terms of serum biochemical parameters (except for urea and creatinine), proteinuria/albuminuria, urinalysis, renal ultrasound, blood pressure or history of cardiovascular disease.

Conclusions: Stage 3 CKD (eGFR < 60 mL/min/1.73 m^2) in patients aged 65 years or older seems to be a ''benign'' finding with no important clinical consequences. It should be emphasized that these results apply to ambulant elderly patients with relatively low co-morbidities.

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1. Introduction

Estimating renal function is essential in medicine. Knowing glomerular filtration rate (GFR) is important in planning sophisticated procedures (such as imaging tests with use of contrast media) and for ''common'' purposes (such as drug dose adjustment in everyday practice). Choosing the method of GFR assessment is a matter of debate. Three most popular formulas – namely, Cockcroft–Gault (C–G), modification of diet in renal disease (MDRD), and most recent chronic kidney disease (CKD) epidemiology collaboration (CKD-EPI) – produce different results in different populations and do not strictly correlate with each other and reference methods. In addition doubts arise concerning the true significance of ''borderline'' CKD, i.e. stage 2 and stage 3.[1–3] Several prospective studies suggest that many patients with eGFR between 30 mL/min and 60 mL/min do not progress to end-stage renal disease (ESRD), nor have worse outcome in terms of cardiovascular (CVS) morbidity and mortality, unless other co-morbid conditions contribute.[4,5] Last but not least, it seems that accepting definition of CKD stage 3 based solely on eGFR as a ''true'' disease would create ''artificial'' epidemics of CKD and result in unnecessary referral to specialized renal care.[6]

Older patients appear the fastest-growing group in health-care system. This is also the case for CKD – patients over 65 years are the leading age category starting renal replacement therapy. Mean values of eGFR in elderly population approximate 50–60 mL/min/1.73 m^2 and are lower than 60 mL/min/1.73 m^2 in 20%–70% of individuals.[7,8] A long-lasting and ongoing debate – whether lower GFR in elderly is just a sign of aging, or reflects clinically significant renal damage – seems to be unresolved to date.[9]

General practitioners (GP) remain the first-line medical professionals to diagnose diseases with significant population burden. They also serve as gatekeepers, limiting referral to specialized care. Hence it is important to recognize the real significance of CKD criteria at the GP practice level, especially in the population with the higher risk of this disease, i.e. elderly.

2. Aim

The aim of this study was to calculate eGFR using different formulas (C–G, MDRD and CKD-EPI) in unselected group of patients aged 65 years and older who attended single GP office. We compared prevalence of CKD when using different formulas and analyzed other parameters of kidney damage in patients with different ranges of GFR.

3. Material and methods

In total, 298 consecutive patients aged 65 years and older visiting GP practice for any reason were invited to participate (except for those unable to read and understand information for patient and sign informed consent due to cognitive impairment). Only 108 patients agreed to participate, which corresponds to ~30% of all subjects aged 65 years and older supervised in the practice. None of the patients visited GP due to emergency or acute illness and all were clinically stable. The population can be considered as socially underprivileged, with only 2 persons with academic and 13 with high school education level; 104 patients were on retirement salary and 4 patients on disability living allowance; 21 participants were the residents of a small city (30 000 inhabitants) and remaining 83 – of the rural region.

In all patients physical examination was performed and medical history was collected. Blood pressure was measured according to the present ESH/ESC standards, using certified Omron M6 Comfort equipment (Omron, Kyoto, Japan). Body weight and height were measured and BMI was calculated. We measured serum creatinine, urea, lipid profile, glucose, sodium, potassium calcium, phosphate, urine creatinine and albumin (Olympus Life and Material Science Europe GmbH, Clare, Ireland; enzymatic method used for creatinine assays), studied blood morphology (ADVIA 2120) and performed urinalysis (Clinitec Atlas, Siemens Healthcare Diagnostics Inc., Tarrytown, USA). In all patients abdominal ultrasound was performed (General Electric Logiq 7 with 3.5C convex transducer; GE Healthcare Technologies, Milwaukee, USA) with special attention paid on size and structure of kidneys. C–G, abbreviated MDRD and CKD-EPI formulas were used to calculate eGFR.[10]

3.1. *Statistical analysis*

Statistical analysis was performed using Statistica 9 (StatSoft, Tulsa, OK, USA). W Shapiro–Wilk and Kolomogorow–Smirnow tests were used to check the data. All results were presented as mean and standard deviation. Pearson test was used to find correlation between variables; inter-group comparisons were performed with Student's *t*-test. *P* value of less than or equal to 0.05 was considered statistically significant.

4. Results

The mean age of patients equaled 72 ± 5.2 years (range 65–87); there were 40 men (37%) and 68 women (63%), with no age difference between the two sexes. Table 1 displays their

Table 1 – Prevalence of chronic diseases in the study group.[a]

Underlying chronic disease	Number of cases
Arterial hypertension	99 (91.7)
Chronic arthrosis	53 (49.1)
Coronary artery disease	30 (27.8)
Benign prostatic hypertrophy	23 (21.3)
Diabetes type 2	21 (19.4)
Thyroid disease	14 (13)
History of stroke	8 (7.4)
Kidney disease (any renal impairment in medical records)	7 (6.5)
History of renal stones	6 (5.6)
Carotid atherosclerosis	6 (5.6)
Peripheral artery disease	2 (1.9)

[a] Values are given as no. (%).

Table 2 – eGFR values and prevalence of CKD stages depending on formula.

Formula	Mean ± SD	Patients with GFR				P
		Less than 60 mL/min/1.73 m^2		More than or equal to 60 mL/min/1.73 m^2		
		N (%)	Mean ± SD	N (%)	Mean ± SD	
MDRD	61.2 ± 12.8	54 (50)	50.6 ± 5.8	54 (50)	71.8 ± 8.2	<.001
CKD-EPI	59.1 ± 13.0	59 (54.6)	49.3 ± 6.4	49 (45.4)	70.8 ± 8.3	<.001
C–G	83.3 ± 23.2	11 (10.4)	51.3 ± 5.7	95 (89.6)	86.6 ± 21.5	<.001

co-morbid conditions. None of the participants had eGFR below 30 mL/min/1.73 m^2 and in one patient it exceeded 90 mL/min/1.73 m^2 (calculated with MDRD formula). The mean values of MDRD and CKD-EPI eGFR did not differ between each other and their application resulted in identical distribution of patients with eGFR less than 60 mL/min/1.73 m^2 and more than or equal to 60 mL/min/1.73 m^2. Mean eGFR according to C–G formula was significantly higher as compared to remaining two methods and changed the distribution of patients between the two groups (Table 2).

Mean and median albuminuria for the whole group equaled 12.4 ± 12.0 mg/L and 6.2 mg/L, and urinary albumin-to-creatinine ratio (UAER) – 11.8 ± 26.7 mg/g and 4.9 mg/g of creatinine, respectively. No correlation was found between eGFR (regardless of the formula used) and albuminuria. Patients with eGFR less than 60 mL/min/1.73 m^2 and more than or equal to 60 mL/min/1.73 m^2 did not differ in urinary albumin loss. They also did not differ in none of the tested demographic and anthropometric parameters (distribution of men and women, age, BMI, waist circumference) regardless of the formula applied.

Patients with eGFR less than 60 mL/min/1.73 m^2 were characterized with lower values of hematocrit (39.4% ± 3.3% vs. 40.8% ± 3.0%, $P = 0.02$) and RBC ($4.6 \pm 0.4 \times 10^6$ mm^{-3} vs. $4.7 \pm 0.35 \times 10^6$ mm^{-3}, $P = 0.04$) when MDRD formula was considered. Hematocrit, but not RBC differed when CKD-EPI formula was applied (39.5% ± 3.3% vs. 40.8% ± 2.9%, $P = 0.04$, lower vs. higher eGFR range). Hemoglobin did not differ between patients within two ranges of eGFR. Remaining parameters of peripheral blood morphology were within normal range and did not differ between eGFR ranges (data not shown).

Table 3 – Presence of any urinalysis or ultrasound abnormality depending on eGFR value and calculation method.

Formula	Patients with GFR[a]		P
	Less than 60 mL/min/1.73 m^2	More than or equal to 60 mL/min/1.73 m^2	
Any urinalysis abnormality			
MDRD	35 (64.8)	30 (55.6)	0.57
CKD-EPI	39 (66.1)	26 (53.1)	0.68
C–G	10 (90.9)	55 (57.9)	0.85
Any ultrasound abnormality			
MDRD	49 (90.7)	49 (90.7)	0.32
CKD-EPI	52 (89.7)	47 (95.9)	0.39
C–G	9 (81.9)	87 (91.6)	0.32

[a] Values are given as no. (%).

Our patients did not suffer from abnormalities in lipid profile (total cholesterol equaled 190.0 ± 49.0 mg/dL, LDL-cholesterol 107.6 ± 43.4 mg/dL, HDL-cholesterol 53.3 ± 12.8 mg/dL and triglycerides 141.4 ± 71.5 mg/dL). This may reflect effective treatment with statins (67.6% of subjects were on statin – 2/3 on simvastatin and 1/3 on atorvastatin). Quite paradoxically, LDL-cholesterol was lower in patients with lower eGFR according to CKD-EPI (101.0 ± 41.9 mg/dL vs. 117.5 ± 41.4 mg/dL, $P = 0.045$), whereas triglycerides were higher in those with lower eGFR according to MDRD and CKD-EPI formulas (157.4 ± 86.9 mg/dL vs. 125.4 ± 47.3 mg/dL and 155.8 ± 84.5 mg/dL vs. 124.2 ± 47.0 mg/dL, respectively; $P = 0.02$ for both differences).

Any abnormality in urinalysis (including pH out of normal range or specific gravity below 1.018) was abundant seen slightly more frequently in patients with low eGFR (especially when C–G formula was considered); nevertheless this difference was not significant (Table 3). When clinically important abnormalities were considered (such as erythrocytes and leukocytes more than 3 and 10, respectively, casts in sediment or protein), they did not exceed 10% and differences remained insignificant (data not shown).

Blood pressure was well controlled, with mean systolic, diastolic and pulse blood pressures of 142.2 ± 19.2 mmHg, 79.1 ± 8.0 mmHg and 63.2 ± 16.0 mmHg, respectively. No difference in blood pressure or heart rate could be noticed between patients with eGFR less than 60 mL/min/1.73 m^2 and more than or equal to 60 mL/min/1.73 m^2 (regardless of the formula used). In Table 4 we listed the antihypertensive treatment used in our patients (shown in subgroups according to the MDRD formula) – blockade of the renin-angiotensine-aldosteron system (RAAS) was the favorite approach. None of the patients received double RAAS blockade. The values of eGFR and UACR did not differ between users and non-users of RAAS blocking agents.

CKD is considered the powerful of CVS morbidity and mortality. Our patients were relatively healthy, with only 30 having history of coronary artery disease (including myocardial infarction), 8 with the history of stroke and 7 with clinically significant peripheral artery disease (Table 1). Patients with and without respective co-morbidities had equal values of eGFR (regardless of the formula applied).

Prevalence of any abnormality in renal ultrasound was high but equally distributed in both eGFR categories (Table 3). Most of the abnormalities could be categorized as ''benign'' – none of the patients was diagnosed with advanced real damage. None of the parameters (including the thickness of renal parenchyma, cortico-medullary differentiation, kidney size, number of stones or cysts, presence of hydronephrosis, rough or bumpy contours, etc.) differed between patients with higher vs. lower eGFR, regardless the formula used. Length of the right and left

Table 4 – Type of blood-pressure lowering medications in the study group.

Blood-pressure lowering medication	Patients with GFR[a]		P
	Less than 60 mL/min/1.73 m^2	More than or equal to 60 mL/min/1.73 m^2	
	54 (50)	54 (50)	
ACEi	36 (66.7)	34 (63.0)	0.69
Angiotensin II receptor antagonist	10 (18.5)	4 (7.4)	0.09
β-Blocker	40 (47.1)	24 (44.4)	0.002
Calcium channel blocker	12 (22.2)	17 (31.5)	0.28
Thiazide	25 (46.3)	12 (22.2)	0.008
Loop diuretic	6 (11.1)	2 (3.7)	0.14
Indapamide	4 (7.4)	2 (3.7)	0.4
α-Blocker	3 (5.6)	4 (7.4)	0.66

[a] Values of eGFR were calculated according to MDRD formula and given as no. (%).

kidney correlated with age ($r = -0.28$, $P = 0.004$ and $r = -0.15$, $P = 0.12$, respectively) but not with eGFR. Only in 7 patients (6.5%) an increased echogenicity of renal parenchyma (stage 1) was found and those with higher echogenicity had the same value of eGFR (using any formula) as compared to those with normal ultrasound. Patients with at least 1 cyst (32 cases) did not differ from those without cysts in terms of age and mean eGFR (regardless the formula used). Number of cysts in both kidneys ranged between 1 and 15 (there were 25 patients with 1 cyst and 6 with 10 or more cysts) and did not correlate with any anthropometric, demographic or lab parameter, except for age ($R = 0.35$, $P = 0.03$).

There were 21 patients with type 2 diabetes. Interestingly, they were similar to non-diabetics in terms of all analyzed parameters, including eGFR (regardless of formula), age, BMI, prevalence of renal ultrasound abnormalities, urinalysis, blood pressure and lab profile (except for triglycerides, higher in diabetics – 190.2 ± 110.6 mg/dL vs. 129.7 ± 52.9 mg/dL in non-diabetics, $P = 0.02$). Of note, UAER was only marginally higher among diabetics (31.0 ± 56.8 mg/g vs. 7.4 ± 8.0 mg/g in non-diabetics, $P = 0.09$).

5. Discussion

In 50% of study patients MDRD or CKD-EPI eGFR was less than 60 mL/min/1.73 m^2, although only a few reported any history of kidney disease. In the population-based study on elderly completed recently in Poland (Polsenior) 21.4% of subjects aged 55 years and more were characterized by eGFR below 60 mL/min/1.73 m^2 (calculated using MDRD formula); this number increased to 27.7% when subjects aged 65 years and more were considered.[11] In other studies CKD stage 3–5 was found in 20%–56% of subjects aged 65 years and more, with prevalence increasing with age.[7,8,12–14] Percentage of individuals with low GFR in our study should be considered high but consistent with available reports. Important selection bias should be acknowledged – our patients were ambulant, in good general status and with low co-morbidity, which eliminated those disabled and severely ill. Nursing home residents and disabled elderly tend to have lower GFR as compared to their non-institutionalized peers.[7]

Differences between eGFR results obtained using different formulas are frequently reported in the literature. All popular formulas (including those used in this study) are characterized with poor reproducibility and their accuracy differs depending on degree of renal dysfunction.[1] MDRD and CKD-EPI formulas seem to underestimate GFR and thus – overestimate the number of CKD patients. Many authors suggest higher precision of CKD-EPI in estimation of GFR. The largest available research project on CKD epidemiology (CKD Prognosis Consortium) demonstrated that using CKD-EPI formula leads to reclassification in CKD prevalence and improves precision of CKD diagnosis in stages 1–3a; CKD-EPI formula classifies patients to lower CKD stage as compared to MDRD in all age groups, except for patients older than 70 years.[15] This however was not the case in our study, in which MDRD and CKD-EPI produced virtually the same results. The choice of formula seemed to have no impact on prevalence of any risk factor, biochemical abnormality or finding on renal ultrasound.

Albuminuria is considered a key marker of kidney damage, although some authors argue that it should rather be considered renal manifestation of endothelial dysfunction, especially in its lower ranges (i.e. below 30 mg/g of creatinine), and not a true indicator of kidney disease.[16,17] In our study albuminuria was mild and there was no association between urine albumin excretion and eGFR calculated with neither formula. ''Dissociation'' between albuminuria and GFR has been noticed by many investigators and this notion supports the hypothesis that albuminuria and low GFR may reflect different pathologic processes.[16] In large population-based study UAER 30–300 mg/g creatinine was increasing with age decades of 60–69, 70–79, and 80 years and over from 10.9% through 16.4% to 24.2% (and UAER ≥ 300 mg/g – 3.3%, 4.9% and 8.5%, respectively). This study however included large proportion of diabetics (namely 15.1%, 15.9% and 13.1%, respectively). Prevalence of microalbuminuria in younger age (<60 years) was low and equaled 5.5%.[13] These figures are higher as compared to our study sample, although almost 20% of our patients also suffered from type 2 diabetes. As mentioned before, diabetics were comparable to non-diabetics in terms of eGFR and UAER. Despite advanced age of our population, median value of UAER (4.9 mg/g) was similar to values found in large population-based studies, such as PREVEND (median 6.1 mg/L, with 95% of results between 2.3 mg/L and 28.7 mg/L), NHANES III (mean 12.3 mg/g of creatinine) or MONICA (median 5.9 mg/g and 6.5 mg/g for men and women, respectively).[18–20] It should be mentioned that high percentage of patients in our

study were using angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor antagonists. This may explain low UAER, but also – relatively low GFR. Although RAAS blockade is considered nephroprotective, these drugs may lower GFR due to lowering of filtration pressure, and their discontinuation sometimes leads to transient GFR increase. Blood pressure was well controlled, which also might contribute to low UAER.

Reduced GFR is a widely accepted predictor of death and CVS events.[15] Our study is cross-sectional in nature, so outcome analyses could not be performed. Nevertheless, lower GFR was not linked to parameters suggesting increased risk of CVS complications (distribution of past CVS events, lipid profile, blood pressure values etc. were largely the same in patients with lower vs. higher eGFR).

Key diagnostic criteria of CKD include structural abnormalities of the kidneys detected by imaging techniques. In large, population-based studies this criterion is almost universally abandoned. High percentage of patients in our study (>90%) revealed multiple abnormalities on renal ultrasound. The nature and prevalence of these abnormalities however did not differ between patients with eGFR below or above 60 mL/min/1.73 m^2 (regardless eGFR calculation method). Many authors indicated that renal size does not change with age until sixth–seventh decade of life, unless no pathologic process develops. Significant decrease in renal size can be expected however after this age.[21] Echogenicity of the kidney remains a very subjective parameter – due to inter-observer variability, variable echogenicity of comparator organs and variable quality of equipment used. No difference in renal echogenicity could be found between study participants with eGFR less than 60 mL/min/1.73 m^2 and more than or equal to 60 mL/min/1.73 m^2. Some authors pointed into the inverse correlation between parenchymal thickness and renal function.[22] Such a difference in renal parenchymal thickness could not be observed between patients with eGFR less than 60 mL/min/1.73 m^2 and more than or equal to 60 mL/min/1.73 m^2. Concerning the significance of renal cysts, the milestone study was published by Caglioti et al. who examined 1526 patients aged 18 years and more, searching for correlations between prevalence of cysts and clinical manifestations of kidney damage. The results showed that 17% of all subjects had at least one cyst in one kidney. The number of cysts was increasing with age and was generally higher in men than in women (22.8% vs. 12.3%, respectively). In our population this percentage was much higher and equaled 69.5%. Patients with cysts in the study of Caglioti et al. more frequently suffered from arterial hypertension, but proteinuria, hematuria nor GFR did not differ between those with and without cysts.[23] This is in agreement with our results – there was no relationship between presence and number of cysts and blood pressure, GFR or albuminuria. Paradoxically, patients with cysts had even slightly higher MDRD-eGFR (62.3 ± 13.8 mL/min/1.73 m^2 vs. 59.3 ± 10.3 mL/min/1.73 m^2; P = NS). This may suggest that renal cysts are non-specific findings and are not related to kidney function but rather reflect age-related degenerative lesions (unless no underlying polycystic kidney disease is present). Urinalysis also did not differ between patients with different eGFR.

Our study has certain limitations; the results can be applied only to ambulant, relatively healthy elderly (the healthiest, i.e. those who did not need GP consultation at all, and the sickest, i.e. those who were bed-ridden or institutionalized were not included). The study sample was relatively small and the criterion of more than three months duration of abnormalities before diagnosis of CKD is established was not fulfilled (although due to stable general condition of subjects acute kidney injury was unlikely). On the other hand, we employed into our analysis the detailed and standardized ultrasound – the data which are not available in large, cohort studies. We consider it a major strength of the study, since the presence of renal structure abnormalities remains the key criterion of CKD diagnosis, but is rarely reported in clinical studies. The same applies to urinalysis; although urinalysis abnormalities are key diagnostic criteria of CKD, they are rarely mentioned (except for proteinuria) in the literature. Our study shows that diagnostic armamentarium available in GP practice is sufficient to detect or exclude clinically important CKD.

Despite criticism on diagnosing CKD based solely on eGFR less than 60 mL/min/1.73 m^2 (regardless of other criteria) the recently published KDIGO recommendations supported such a definition.[24] Since no age-specific definitions of CKD are available, current standards continue to recommend diagnosing CKD in all age groups if eGFR falls below this threshold.

6. Conclusions

1. In elderly patients with relatively low morbidity, receiving intensive pharmacological treatment as the primary or secondary prevention eGFR less than 60 mL/min/1.73 m^2 is not associated with adverse risk profile and reflects rather ''physiological'' aging than the true renal damage.
2. Our data suggest that CKD-EPI formula does not add new value in recognizing clinically important CKD in patients aged 65 years and over.

Conflict of interest

None declared.

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