ORIGINAL PAPER

Estimated glomerular filtration rate in elderly patients with type 2 diabetes

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ABSTRACT

INTRODUCTION: People in old age with diabetes are at high risk of kidney damage. Data regarding optimal methods for estimation glomerular filtration rate (eGFR) in this group of patients are limited.

MATERIAL AND METHODS: The purpose of the study was to check the results of eGFR calculated using 9 selected formulae based on serum creatinine or cystatin C in clinically stable, outpatient people aged ≥ 70 years with diabetes and to compare the classification to chronic kidney disease (CKD) stages based on different eGFR equations. TIPCO Statistica version 13.3 and Origin Pro 2022 statistical software were used for statistical analysis. According to the data distribution the Student's *t*-test or the Mann-Whitney *U* test were used for intergroup comparison. The non-parametric Friedman ANOVA test of dependent variables was also performed. $P < 0.05$ was considered as statistically significant.

RESULTS: The study group consisted of 132 patients (83 women and 49 men) with a mean age of 75.4 years and mean glycated haemoglobin 7.8%. 71.2% of patients had eGFR < 60 ml/min/1.73 m^2. No significant differences were found between eGFR calculated by The Modification of Diet in Renal Disease (MDRD) formula and The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (SCr), and the Perkins and Ma formulae. Significant differences were found between the eGFR MDRD formula and the CKD-EPI (SCys), CKD-EPI (SCr,SCys) and Rule formulae. The CKD-EPI (SCr) overestimated, while CKD-EPI (SCys) underestimated eGFR compared to MDRD.

CONCLUSIONS: The results of eGFR calculations according to the studied equations are not consistent, hence a single calculation of eGFR does not allow to provide a clear classification of patients into CKD stages.

KEY WORDS: estimated glomerular filtration rate, chronic kidney disease stage, elderly people, type 2 diabetes.

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Introduction

The aging of the body is a physiological process leading to morphological and functional changes in all systems and organs, including the kidneys. With age, the mass of the kidneys decreases, just like the number of active nephrons and the thickness of Bowman's capsule, while the basement membrane and the volume of the mesangium increases, the number and length of renal tubules decreases, interstitial tissue increases in volume and undergoes fibrosis, and fibrosis of the renal vessels occurs. Co-occurring functional changes include decreased renal blood flow and increased resistance of efferent arterioles. Already around the age of 35–40 years, a constant decrease in glomerular filtration by approximately 0.8–1.0 ml/min/1.73 m^2 *per* year is observed, and this process significantly accelerates in people over 65 years of age. It is therefore not surprising that in the elderly population, a chronic reduction in glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2 is often found, meeting the current guideline criteria for chronic kidney disease (CKD) [1, 2]. Clinical observations clearly indicate that CKD significantly worsens the prognosis of patients, contributing not only to the deterioration of the quality of life, but also to premature mortality [3, 4]. Therefore, it is important to diagnose CKD as early as possible and provide adequate treatment to delay the progression of the complications [3].

It was found that a greater decrease in GFR compared to the healthy population occurs in elderly patients with risk factors such as diabetes, generalized atherosclerosis, arterial hypertension, heart failure, recurrent urinary tract infections, urinary stasis, systemic diseases and nicotine addiction [3, 5–7]. Renal function is also impaired in these patients as a result of taking nephrotoxic drugs or not adjusting drug dose to the degree of kidney damage. In patients with risk factors for development of CKD, screening tests should be routinely performed, including determination of serum creatinine concentration and estimation of GFR as well as a urinalysis with the detection of albuminuria or overt proteinuria [8].

The primary measure of kidney function is GFR. Techniques for its assessment based on the assessment of renal clearance of various substances, including inulin, are inconvenient for patients, time-consuming and expensive.

Hence, simplified equations estimating glomerular filtration based on measurements of serum creatinine and/or cystatin C concentrations and basic demographic/anthropometric data of patients (age, gender, race, body weight) are commonly used in practice.

These equations have numerous limitations [9]. One of them is because to the fact that they were tested on limited, selected patient populations. Therefore, optimising the choice of method for calculating estimated glomerular filtration for specific subpopulations of patients, including those at high risk of comorbidities, remains a current topic.

Such a specific group of patients are old people suffering from diabetes diagnosed based on current diabetic guidelines.

In a unit dedicated to the treatment of patients with diabetes and kidney diseases, research on this topic is carried out in many ways. One of the preliminary elements of the analysis was to check the differences in the estimated GFR calculated on the basis of various formulae in an outpatient clinically stable population of elderly people suffering from diabetes, because the choice of formula may be important for the clinical practice. Here we present our preliminary results of this study.

The purpose of the study was to analyse the estimated glomerular filtration rate (eGFR) calculated according to 9 different formulae known from the literature, based on the serum concentration of creatinine and/or cystatin C, in a population of people with diabetes aged 70 years and over, taking into account the impact of metabolic control of diabetes. Because staging of CKD is very important in practice, CKD- stage qualifications according to the eGFR results calculated with different formulae was also subject of the research.

The primary goal of the study was to make doctors aware of the need for caution in the interpretation of estimated GFR results and the need to individualise it and perhaps also to notice indication to verify eGFR by measuring GFR.

Material and methods

The study group consisted of patients with diabetes mellitus in the age ≥ 70 years under the care of the Diabetes Clinic consecutively attending routine check-ups, who gave written consent to participate in the study.

The study protocol was approved by the Bioethics Committee of the Medical University of Silesia in Katowice.

During routine outpatient visit height, weight and blood pressure were measured, and 5 ml of venous blood was taken for laboratory determi-

nations (serum creatinine, cystatin C, glycated haemoglobin). Patients were asked to provide information on comorbidities, in particular regarding hypertension, coronary heart disease, history of myocardial infarction, stroke or peripheral atherosclerosis. Using available medical documentation as an source, information about the course of diabetes and its micro- and macroangiopathic complications (as listed above), as well as the treatment regimen were collected. Serum creatinine, cystatin C, and glycated haemoglobin (HbA_{1c}) concentrations were determined for each patient with laboratory methods generally accepted as certified. Based on these results and demographic data, the estimated GFR was calculated for each of 9 equations as follow (when SCr – serum creatinine [mg/dl], SCys – serum cystatin C [mg/l]) [10–17].

MDRD, Modification of Diet in Renal Disease

$$eGFR = 186 \times (SCr/88.4)^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female})$$

CKD-EPI (SCr), Chronic Kidney Diesease Epidemiology Collaboration (based on serum creatinine)

$$\text{For females } eGFR = 144 \times (SCr/0.7)^{-0.329\ (-1.209 \text{ if } SCr > 0.7)} \times 0.993^{age}$$

$$\text{For males } eGFR = 141 \times (SCr/0.9)^{-0.411\ (-1.209 \text{ if } SCr > 0.9)} \times 0.993^{age}$$

CKD-EPI (SCys), CKD-EPI (based on serum cystatin C)

$$eGFR = 133 \times (SCys/0.8)^{-0.499\ (-1.328 \text{ if } SCys > 0.8)} \times 0.996^{age} (\times 0.932 \text{ if female})$$

CKD-EPI (SCr, SCys), CKD-EPI (based on serum creatinine and cystatin C)

For females if serum cystatin C ≤ 0.8 and serum creatinine ≤ 0.7

$$eGFR = 130 \times (SCr/0.7)^{-0.248} \times (SCys/0.8)^{-0.375} \times 0.995^{age}$$

For females if serum cystatin C > 0.8 and serum creatinine ≤ 0.7

$$eGFR = 130 \times (SCr/0.7)^{-0.248} \times (SCys/0.8)^{-0.711} \times 0.995^{age}$$

For females if serum cystatin C ≤ 0.8 and serum creatinine > 0.7

$$eGFR = 130 \times (SCr/0.7)^{-0.601} \times (SCys/0.8)^{-0.375} \times 0.995^{age}$$

For females if serum cystatin C > 0.8 and serum creatinine > 0.7

$$eGFR = 130 \times (SCr/0.7)^{-0.601} \times (SCys/0.8)^{-0.711} \times 0.995^{age}$$

For males if serum cystatin C ≤ 0.8 and serum creatinine ≤ 0.9

$$eGFR = 135 \times (SCr/0.7)^{-0.207} \times (SCys/0.8)^{-0.375} \times 0.995^{age}$$

For males if serum cystatin C > 0.8 and serum creatinine ≤ 0.9

$$eGFR = 135 \times (SCr/0.7)^{-0.207} \times (SCys/0.8)^{-0.711} \times 0.995^{age}$$

For males if serum cystatin C ≤ 0.8 and serum creatinine > 0.9

$$eGFR = 135 \times (SCr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$$

For males if serum cystatin C > 0.8 and serum creatinine > 0.9

$$eGFR = 135 \times (SCr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$$

Stevens *et al.*

$$eGFR = 177.6 \times (SCr/88.4)^{-0.65} \times SCys^{-0.57} \times age^{-0.20} \times (0.82 \text{ if female})$$

Ma *et al.*

$$eGFR = 169 \times (SCr/88.4)^{-0.608} \times SCys^{-0.63} \times age^{-0.157} \times (0.83 \text{ if female})$$

Rule *et al.*

$$eGFR = 66.8 \times SCys^{-1..30}$$

Perkins *et al.*

$$eGFR = 100/SCys$$

Macisaac *et al.*

$$eGFR = (88.7/SCys) - 4.2$$

Statistical analysis

Analysis was performed using TIPCO Statistica version 13.3 statistical and Origin Pro 2022 software. The normality of the distribution of individual variables was checked using the Shapiro-Wilk test. Descriptive statistical parameters were characterised by means and standard deviations (in the case of normality of distribution) and median and min/max quartile (in other cases). Comparison between groups of patients were done using Student *t*-test or respectively Mann-Whitney *U* test. Because to the fact that the research was carried out on the same group of patients using different methods, the obtained variables (eGFR values) were treated as dependent variables. Because variables with no normal distribution prevailed, the non-parametric Friedman ANOVA test of dependent variables was selected for comparative analysis. Correlation analysis between selected variables was also performed. Results for p less than 0.05 were considered statistically significant.

Results

The study group consisted of 132 patients – 83 women (63%) and 49 men (37%) – with an average age of 75.4 (SD ±4.6) years, suffering from diabetes for a mean of 18.4 (SD ±8.3) years.

The mean time from the diagnosis of diabetes to the initiation of insulin therapy was 8.2 (SD ±6.8) years, while the average concentration of HbA_{1c} in the entire study group was 7.8% (SD ±1.1, min 4.9 – max 11.6).

Most of the patients had comorbidities: 82 people (62%) suffered from hypertension for an average 21.2 (SD ±10.0) years, 49 patients (37%) were diagnosed with coronary heart disease, 27 people (20%) had a history of a heart attack, 17 (13%) had a stroke, and 7 people had both a heart attack and stroke. Based on the eGFR results calculated according to the MDRD equation, 71.2% of patients had reduced glomerular filtration below 60 ml/min/1.73 m^2. Table 1 presents the characteristics of patients with < 60 ml/min/1.73 m^2 and ≥ 60 ml/min/1.73 m^2 GFR estimated with the MDRD formula.

The literature data are indicate metabolic control as an important factor that influences the GFR. Therefore for the purposes of further analyses, the entire study group was divided into subgroups according to the concentration of HbA_{1c} ≤ 7% and > 7%. Most patients had poor metabolic control and belonged to the second group (73.49% of women and 69.39% of men).

The statistical analysis did not show any significant differences between women or men with HbA_{1c} ≤ 7% or > 7% in terms of age, body mass index, serum creatinine and cystatin C levels, as well as in terms of eGFR calculated on the basis of the tested equations (Tables 2, 3).

For all patients with diabetes and each of the studied subgroups, eGFR results calculated using various formulae were analysed.

Density plots of the eGFR are presented in Figure 1, and box plots of eGFR for the study groups are presented in Figure 2.

Comparing eGFR results, the values from the MDRD formula most widely available in outpatient practice, were taken as reference.

Independently from HbA_{1c} value ≤ 7% or > 7%, the Friedman *post hoc* test showed no significant differences between eGFR calculated using the MDRD formula and the CKD-EPI (SCr), Perkins and Ma formulae. However, there were significant differences between eGFR calculated using the MDRD formula and both the CKD-EPI (SCys), CKD-EPI (SCr,SCys) and Rule formulae.

Moreover, in the entire group and subgroups separated by gender with HbA_{1c} > 7%, significant differences between eGFR calculated using the MDRD formula and eGFR according to the Stevens formula were found. In men, regardless of the HbA_{1c} range, differences in the eGFR calculated by the McIsaac formula were revealed.

In summary, in patients with HbA_{1c} > 7% comparing to those with HbA_{1c} ≤ 7%, a greater number

Table 1. Characteristics of the study group: all patients and subgroups with estimated glomerular filtration rate < 60 and estimated glomerular filtration rate ≥ 60 (based on modification of diet in renal disease equation)

Parameters	All patients	Patients with eGFR < 60	Patients with eGFR ≥ 60
Number of patients, *n* (%)	132 (100)	38 (28.8)	94 (71.2)
Female/male	83/49	31/7	52/42
Age (year)	75.41 ±4.567	76.29 ±4.459	75.05 ±4.585
BMI [kg/m^2]	29.77 ±4.929	29.66 ±5.552	29.82 ±4.685
HbA_1c (%)	7.804 ±1.109	7.776 ±1.268	7.815 ±1.045
Serum creatinine [mg/dl]	0.9894 ±0.6548	1.363 ±1.123	0.8383 ±0.1482
Serum cystatin C [mg/l]	1.649 ±0.7503	1.754 ±0.720	1.607 ±0.7685
DM duration (year)	18.42 ±8.330	17.82 ±7.490	18.67 ±8.673
The interval between DM diagnosis and start of insulin therapy (year)	8.172 ±6.815	7.639 ±5.592	8.380 ±7.255
Daily insulin dose [j.]	57.07 ±36.86	63.86 ±47.76	54.32 ±31.31
HA, *n* (%)	82 (62.1)	21 (55.3)	61 (64.9)
HA duration (year)	21.21 ±9.961	24.05 ±13.32	20.23 ±8.427
CHD, *n* (%)	49 (37)	14 (36.8)	35 (37.2)
Post cardiac infarction patients, *n* (%)	27 (20.4)	9 (23.7))	18 (19.1)
Post stroke patients, *n* (%)	17 (12.9)	6 (15.8))	11 (11.7)
Post cardiac infarction and post stroke patients, *n* (%)	7 (5.3)	2 (5.3)	5 (5.3)

BMI – body mass index, CHD – coronary heart disease, DM – diabetes mellitus, eGFR – estimated glomerular filtration rate, HA – hypertension, HbA_1c – glycated haemoglobin

Table 2. Comparison between women with glycated haemoglobin ≤ 7% and glycated haemoglobin > 7%

Women	HbA_{1c} ≤ 7%			HbA_{1c} > 7%			*p*-value
	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	
Age (year)	75.50	71.00	78.00	76.00	73.00	79.00	0.4847
Body mass index [kg/m^2]	27.97	25.71	31.65	28.84	26.40	32.45	0.8648
Serum creatinine [mg/dl]	0.950	0.800	1.100	0.900	0.700	1.000	0.1715
Serum cystatin C [mg/l]	1.493	1.196	1.918	1.387	1.057	1.825	0.2375
CKD-EPI (SCr)	79.41	78.37	82.69	80.96	77.89	84.43	0.4762*
CKD-EPI (SCys)	39.51	27.98	51.32	41.32	29.18	61.71	0.2543
CKD-EPI (SCr, SCys)	45.81	38.97	51.86	53.16	39.90	67.63	0.1230*
MDRD-Levey	60.98	51.75	74.32	65.42	57.61	84.94	0.2067*
eGFR-Perkins	67.06	52.14	83.59	72.08	54.80	94.60	0.2375
eGFR-MacIsaac	53.94	41.01	68.27	58.30	43.31	77.82	0.2375
eGFR-Rule	39.75	28.65	52.92	43.65	30.56	62.15	0.2375
eGFR-Stevens	49.38	43.95	54.20	56.30	44.04	70.07	0.1333
eGFR-Ma	54.77	48.03	62.40	64.36	49.74	80.70	0.1530

CKD-EPI – chronic kidney disease epidemiology collaboration, eGFR – estimated glomerular filtration rate [ml/min/1.73 m^2], HbA_{1c} – glycated haemoglobin, MDRD – modification of diet in renal disease, SCr – serum creatinine, SCys – serum cystatin C

*Mann-Whitney U test, * Student t-test*

Table 3. Comparison between men with glycated haemoglobin ≤ 7% and glycated haemoglobin > 7%

Men	HbA_{1c} ≤ 7%			HbA_{1c} > 7%			*p*-value
	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	
Age (year)	75.00	72.00	79.00	73.00	70.00	75.0	0.1027
Body Mass Index [kg/m^2]	29.41	29.00	33.14	28.84	25.20	32.8	0.2005
Serum creatinine [mg/dl]	1.000	0.900	1.200	0.900	0.800	1.10	0.3116
Serum cystatin C [mg/l]	1.949	1.461	2.342	1.536	1.317	1.91	0.1684
CKD-EPI (SCr)	76.99	60.05	83.25	84.10	69.09	90.5	0.1648
CKD-EPI (SCys)	29.03	23.30	43.62	40.61	30.49	51.1	0.1491
CKD-EPI (SCr, SCys)	44.47	39.84	55.58	52.52	47.65	66.7	0.367*
MDRD-Levey	78.29	62.73	86.74	87.32	70.34	100.7	0.2500
eGFR-Perkins	51.31	42.69	68.47	65.11	52.45	75.9	0.1684
eGFR-Macisaac	40.29	32.81	55.16	52.25	41.27	61.6	0.1684
eGFR-Rule	28.06	22.09	40.82	38.25	28.87	46.7	0.1684
eGFR-Stevens	51.66	44.16	61.48	57.77	51.33	69.5	0.1684
eGFR-Ma	56.37	48.87	67.81	64.37	56.86	77.8	0.1822

CKD-EPI – chronic kidney disease epidemiology collaboration, eGFR – estimated glomerular filtration rate [ml/min/1.73m^2], HbA_{1c} – glycated haemoglobin, MDRD – modification of diet in renal disease, SCr – serum creatinine, SCys – serum cystatin C

*Mann-Whitney U test, * Student t-test*

of statistically significant differences were observed in terms of eGFR calculated according to the 9 tested formulae. In the group of women it concerned respectively 4 vs. 3 formulae while in the men it was 5 vs. 4.

In the next step of the analysis, for each of the 9 eGFR formulae patients were assigned to stages 1–5 of CKD, as defined by kidney disease: improving global outcomes: Stage 1 eGFR ≥ 90 [ml/min/1.73 m^2], Stage 2 eGFR 60–89 [ml/min/1.73 m^2], Stage 3 eGFR 30–59 [ml/min/1.73 m^2], Stage 4 eGFR 15–29 [ml/min/1.73 m^2], Stage 5 eGFR < 15 [ml/min/1.73 m^2].

The obtained results of staging are presented in Figure 3 and Table 4 for the entire study group, while the results of subgroups divided by gender and HbA_{1c} values ≤ 7% or > 7% are presented in Tables 5 and 6.

Referring to the MDRD and CKD-EPI (SCr) formulae, as currently widely used in practice, signif-

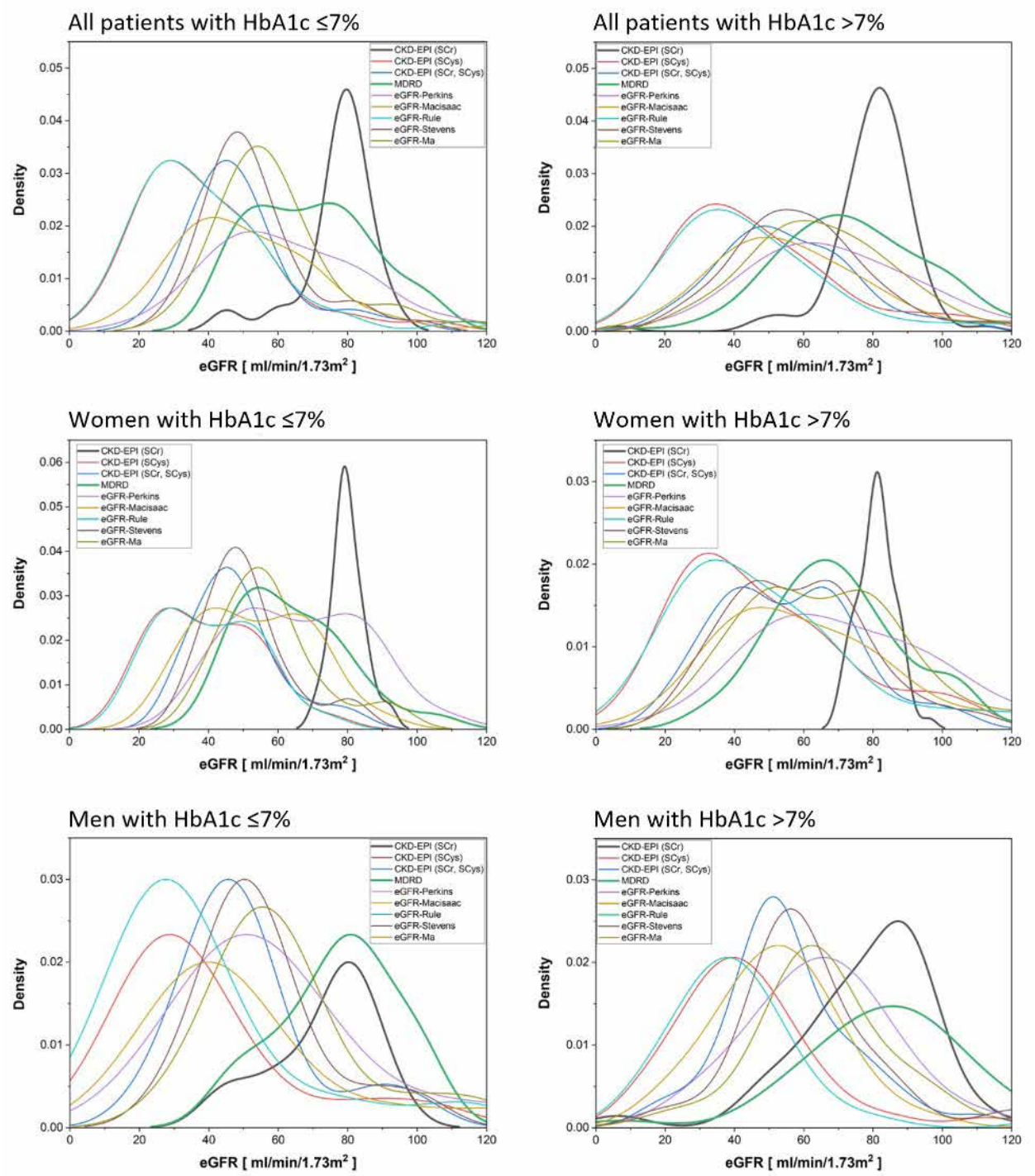

Fig. 1. Distribution of estimated glomerular filtration rate calculated with various equations demonstrated as a kernel density plot

icant differences were found in the allocation of patients to CKD stage groups.

When dividing all patients with diabetes into CKD stages basing on the results of the CKD-EPI (SCr) formula, more people compared to MDRD were classified into CKD Stage 2 (83.33% vs. 53%, disagreement + 30.33%), underestimating the number of patients mainly in CKD Stage 3 (5.30% vs. 28.03%, disagreement – 22.73%) (Table 4). These indicate overestimation in the GFR range close to 60 ml/min/1.73 m².

This tendency was particularly clear in the group of women. In this case, the qualification to Stage 2 CKD based on the CKD-EPI (SCr) results was 95.45% in relation to MDRD 45.45% (i.e. + 50%) in the subgroup with HbA_{1c} ≤ 7%, while in patients with HbA_{1c} > 7% it was respectively: 96.72% vs. 54.1% (that is + 42.62%) (Table 5).

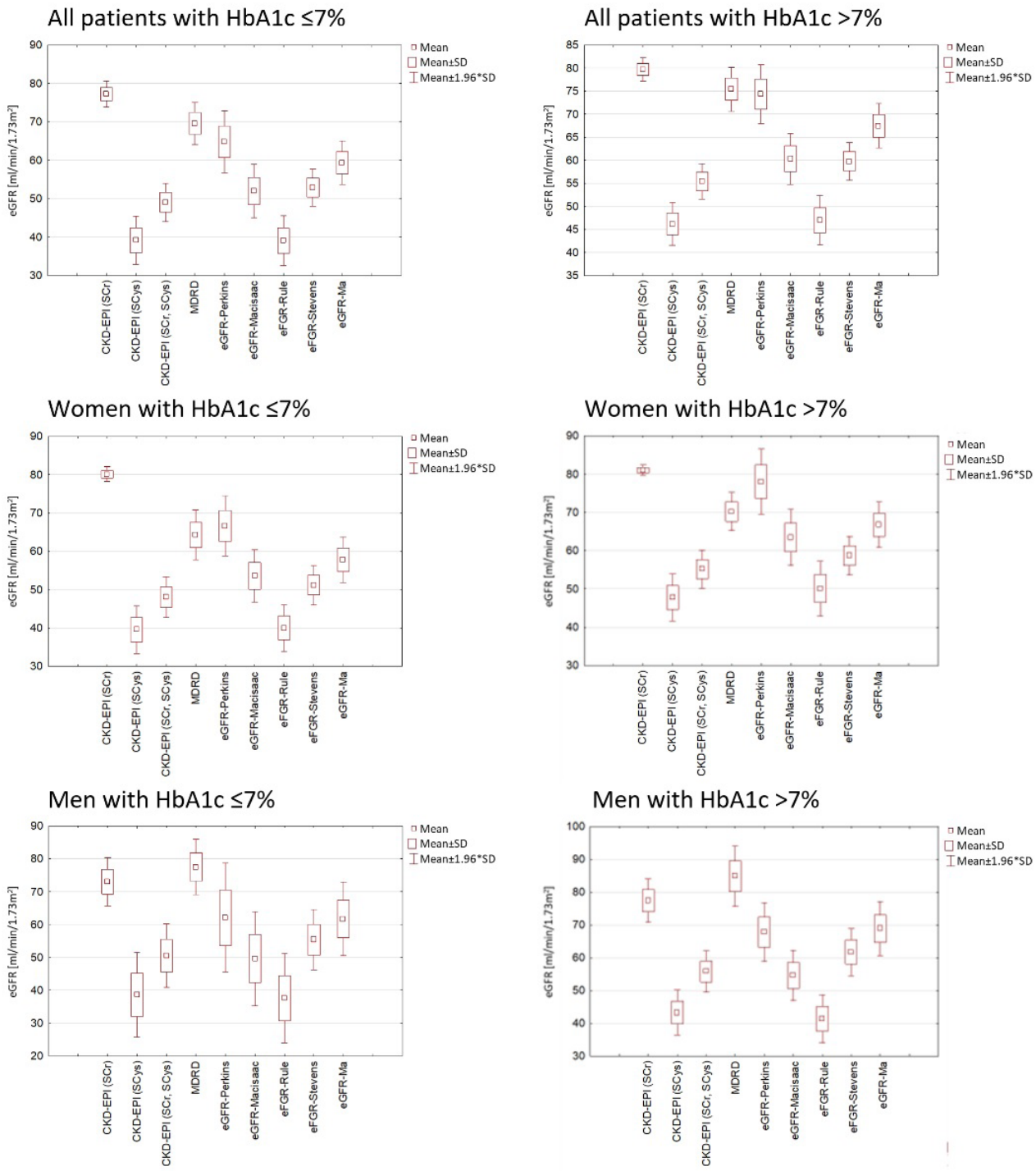

Fig. 2. Box plots of estimated glomerular filtration rate for various equations

When we compared the qualification for CKD stages using formula MDRD based on the serum creatinine and formulae based on the serum cystatin C, i.e. CKD-EPI (SCys) and CKD-EPI (SCr, SCys), a shift in the size of groups towards higher stages of CKD was observed. It suggests an overestimation of eGFR by MDRD, which appears as early as Stage 2 CKD. Interestingly, this was most visible, regardless of gender, in patients with better metabolic balance and HbA_{1c} ≤ 7% (Table 5).

Here, for example, for women with HbA_{1c} ≤ 7%, the percentage of patients in Stage 2 according to MDRD and CKD-EPI (SCys) results was 45.45% vs. 4.45% (disagreement – 41%), and for men 66.67% vs. 6.67% (disagreement – 60%). In the case of Stage 4 according to MDRD and CKD-EPI (SCys), the percentage of assigned patients was 0% vs. 36.36 (i.e. + 36.36%) for women, and respectively – 0% vs. 40.00% (that is + 40%) for men.

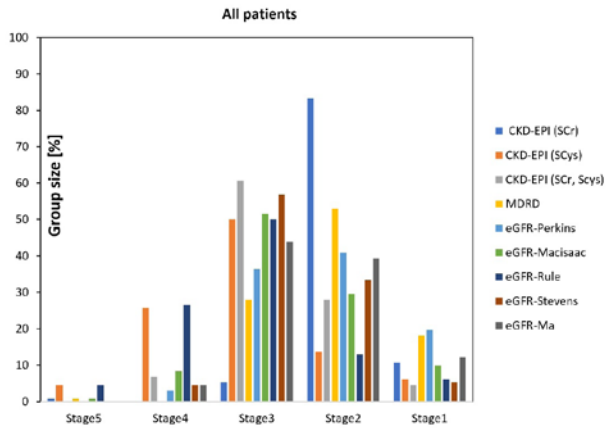

Fig. 3. Distribution of chronic kidney disease stages based on estimated glomerular filtration rate calculated with various equations

Discussion

Assessment of kidney function, commonly obtained through evaluation of the renal GFR, has important clinical value. In everyday practice GFR is widely used to optimize drug dosing. It is also tool for kidney damage diagnosis. The disclosure of reduced GFR is not limited to disclosure the pathology of the kidneys themselves. For the patient, it reveals the risk of development and/or progression of multi-organ complications, mainly cardiovascular complications, which worsen the prognosis and increase the risk of mortality. This risk is particularly high in elderly people with serious comorbidities, including diabetes and cardiovascular diseases [18]. Diabetes predisposes to kidney damage itself. Epidemiological data indicate that it may affect approximately 30–50% of patients, particularly those with type 2 diabetes. Because both diabetes and ageing are accompanied by numerous additional diseases, the incidence of kidney damage is higher in old people with diabetes. The prognosis in this group of patients is also

Table 4. Estimated prevalence of chronic kidney disease stages in all study group based on estimated glomerular filtration rate calculated according to various formulae

Stages of CKD considering eGFR [ml/min/1.73 m²]	CKD-EPI (SCr) (%)	CKD-EPI (SCys) (%)	CKD-EPI (SCr, Scys) (%)	MDRD (%)	eGFR-Perkins (%)	eGFR-Macisaac (%)	eGFR-Rule (%)	eGFR-Stevens (%)	eGFR-Ma (%)
Stage 1: eGFR ≥ 90	10.61	6.06	4.55	18.18	19.70	9.85	6.06	5.30	12.12
Stage 2: 60 ≤ eGFR ≤ 89	83.33	13.64	28.03	53.03	40.91	29.55	12.88	33.33	39.39
Stage 3: 30 ≤ eGFR ≤ 59	5.30	50.00	60.61	28.03	36.36	51.52	50.00	56.82	43.94
Stage 4: 15 ≤ eGFR ≤ 29	0.00	25.76	6.82	0.00	3.03	8.33	26.52	4.55	4.55
Stage 5: eGFR < 15	0.76	4.55	0.00	0.76	0.00	0.76	4.55	0.00	0.00

CKD-EPI – chronic kidney disease epidemiology collaboration, eGFR – estimated glomerular filtration rate, MDRD – modification of diet in renal disease

Table 5. Estimated prevalence of chronic kidney disease stages in women based on estimated glomerular filtration rate calculated according to various formulae

Stages of CKD considering eGFR [ml/min/1.73 m²]	CKD-EPI (SCr) (%)	CKD-EPI (SCys) (%)	CKD-EPI (SCr, Scys) (%)	MDRD (%)	eGFR-Perkins (%)	eGFR-Macisaac (%)	eGFR-Rule (%)	eGFR-Stevens (%)	eGFR-Ma (%)
Women with HbA_{1c} ≤ 7%									
Stage 1: eGFR ≥ 90	4.55	0.00	0.00	4.55	4.55	0.00	0.00	0.00	4.55
Stage 2: 60 ≤ eGFR ≤ 89	95.45	4.55	18.18	45.45	54.55	36.36	4.55	18.18	27.27
Stage 3: 30 ≤ eGFR ≤ 59	0.00	59.09	81.82	50.00	40.91	54.55	59.09	81.82	68.18
Stage 4: 15 ≤ eGFR ≤ 29	0.00	36.36	0.00	0.00	0.00	9.09	36.36	0.00	0.00
Stage 5: eGFR < 15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Women with HbA_{1c} > 7%									
Stage 1: eGFR ≥ 90	3.28	9.84	6.56	13.11	31.15	14.75	9.84	6.56	13.11
Stage 2: 60 ≤ eGFR ≤ 89	96.72	19.67	37.70	54.10	34.43	32.79	19.67	40.98	40.98
Stage 3: 30 ≤ eGFR ≤ 59	0.00	44.26	45.90	32.79	31.15	45.90	45.90	47.54	40.98
Stage 4: 15 ≤ eGFR ≤ 29	0.00	22.95	9.84	0.00	3.28	4.92	21.31	4.92	4.92
Stage 5: eGFR < 15	0.00	3.28	0.00	0.00	0.00	1.64	3.28	0.00	0.00

CKD-EPI – chronic kidney disease epidemiology collaboration, eGFR – estimated glomerular filtration rate, HbA_{1c} – glycated haemoglobin, MDRD – modification of diet in renal disease

Table 6. Estimated prevalence of chronic kidney disease stages in men based on estimated glomerular filtration rate calculated according to various formulae

Stages of CKD considering eGFR [ml/min/1.73m^2]	CKD-EPI (SCr) (%)	CKD-EPI (SCys) (%)	CKD-EPI (SCr, Scys) (%)	MDRD (%)	eGFR-Perkins (%)	eGFR-Macisaac (%)	eGFR-Rule (%)	eGFR-Stevens (%)	eGFR-Ma (%)
Men with HbA_{1c} ≤ 7%									
Stage 1: eGFR ≥ 90	6.67	6.67	6.67	20.00	13.33	13.33	6.67	6.67	13.33
Stage 2: 60 ≤ eGFR ≤ 89	73.33	6.67	6.67	66.67	26.67	6.67	6.67	20.00	26.67
Stage 3: 30 ≤ eGFR ≤ 59	20.00	33.33	80.00	13.33	53.33	66.67	33.33	66.67	53.33
Stage 4: 15 ≤ eGFR ≤ 29	0.00	40.00	6.67	0.00	6.67	6.67	40.00	6.67	6.67
Stage 5: eGFR < 15	0.00	13.33	0.00	0.00	0.00	6.67	13.33	0.00	0.00
Men with HbA_{1c} > 7%									
Stage 1: eGFR ≥ 90	29.41	2.94	2.94	35.29	11.76	5.88	2.94	5.88	14.71
Stage 2: 60 ≤ eGFR ≤ 89	55.88	11.76	26.47	50.00	50.00	29.41	8.82	35.29	50.00
Stage 3: 30 ≤ eGFR ≤ 59	11.76	61.76	64.71	11.76	35.29	52.94	58.82	52.94	29.41
Stage 4: 15 ≤ eGFR ≤ 29	0.00	17.65	5.88	0.00	2.94	11.76	23.53	5.88	5.88
Stage 5: eGFR < 15	2.94	5.88	0.00	2.94	0.00	0.00	5.88	0.00	0.00

CKD-EPI – chronic kidney disease epidemiology collaboration, eGFR – estimated glomerular filtration rate, HbA_{1c} – glycated haemoglobin, MDRD – modification of diet in renal disease

worse. Therefore, it is so important to reliably access their kidney function [19].

However measurement of inulin clearance still remains the gold standard for reliable assessment of the GFR, but it is not technically easy or cheap and is therefore limited to clinical trials. In everyday practice, the so-called estimated GFR is used, which is calculated with mathematical formulae based on the serum concentration of creatinine and/or cystatin C. The current literature points to the challenges and disadvantages of eGFR. As numerous observations indicate, today there is no universal formula that perfectly correlates with actual glomerular filtration and can be used for each patient. Reliable estimation of renal function in old people suffering from multiple diseases has many difficulties [20], hence our project to evaluate the results of measured eGFR in the high-risk elderly diabetics population using different equations.

We selected for preliminary analysis formulae based on serum creatinine concentration and those based on cystatin C serum concentration or both measurements together. We deliberately did not include the Cockcroft-Gault formula in our research although it has been used for many years, among others for the purpose of optimising drug dosage. This was because the aim of the study was to compare easy to carry out methods of eGFR calculation that are used in outpatient practice, where sometimes we do not have access to complete patient data. Meanwhile, to calculate eGFR using the Cockcroft-Gault formula, it is necessary to know the patient's current body weight.

Considering the still widespread use of the MDRD formula, we adopted its results as a reference point. We found significant differences in the eGFR when comparing formulae based on serum creatinine i.e. MDRD and CKD-EPI (SCr), and also those based on serum creatinine and serum cystatin C i.e. CKD-EPI (SCys) and CKD-EPI (SCr, SCys). A weakness of our study that prevent full conclusions is the lack of the reference to measured GFR, although it was the intended to be subject of our research. The aim of our study was mainly to indicate what doubts may be encountered with eGFR in everyday outpatient practice.

In our study we evaluated the classification of patients to CKD stages according to eGFR obtained for each of the tested equations. As a result, we found out that the CKD-EPI (SCr) formula overestimated eGFR in the GFR range close to 60 ml/min/1.73 m^2. It resulted in overestimation of the percentage of patients in 2 stages of CKD by as much as 30%.

Similar observations but with smaller differences were made by other authors. For example in by Drion *et al.* the CKD-EPI (SCr) equation (2009) provided higher eGFR values than MDRD particularly in patients with higher levels of GFR and in women, and this tendency was observed throughout the total range of renal function [21]. CKD-EPI is considered as the best tool for the detection of hyperfil-

tration, which is known as an important risk factor of kidney damage progression [22].

When we compared formulae based on serum creatinine and cystatin C, i.e. MDRD vs. CKD-EPI (SCys) and CKD-EPI (SCr, SCys), a shift in the size of groups towards higher stages of CKD was observed in formulae using serum cystatin C. This result indicate an overestimation of eGFR by MDRD formula, which appears from Stage 2 CKD. It was most pronounced in patients with better metabolic control and HbA_{1c} ≤ 7%. It is known that serum cystatin C concentration progressively increased in parallel with GFR decline. Its diagnostic accuracy is estimated as significantly better in patients with diabetes than those of serum creatinine [23] Some study results even indicate it can be useful in detecting the early stage of diabetic nephropathy [24].

We suspect multiple causes of the observed discrepancies, ignoring the imperfections of the same equations initially tested on different populations. One of the potential causes could be the serum creatinine concentrations itself having well-known limitations. Creatinine is a product of muscle protein creatine and phosphocreatine metabolism. Its concentration in blood serum is influenced by many different factors, mainly diet (protein supply) and muscle mass. An increase in the serum creatinine concentration occurs, for example, as a result of physical exercise or following a high-protein diet. What is more, an increase in serum creatinine is not a sensitive indicator of deterioration of renal function and it occurs when approximately 60% of nephrons are damaged. It is because creatinine is not only filtered in the renal glomeruli but can also be secreted by the renal tubules (in physiology it is approximately 10%) which is particularly important, e.g. in diabetes or when using certain medications, e.g. famotidine. With a decrease in glomerular filtration, tubular creatinine secretion may increase by up to 50%. It is estimated that in patients with end-stage renal failure, up to 66% of creatinine may be excreted or metabolised in a non-renal way, including the participation of intestinal flora. In people of different age, gender, body weight and muscle mass, with the same creatinine concentration in blood serum, kidney function may be completely different. In old age, falsely lowering creatinine concentration is often caused by reduced muscle mass and a low-protein diet. In certain pathological conditions, for example certain cardiovascular diseases, it could be also secondary to renal hyperfiltration. Hyperfiltration risk increases in the case of coexistence of old age with diabetes, which is caused also by poor metabolic control, hyperglycaemia and glucosuria [25–27]. This condition may change over time and vary in severity, and hence it may unpredictable disturb the eGFR results.

Cystatin C is an alternative endogenous marker used to assess the GFR. Its characteristic points cause it is better than creatinine indicator of renal function. Cystatin C is an inhibitor of cysteine proteases – a low molecular weight protein produced by all nucleated cells of the body, which is circulates in the blood and is eliminated from the body 99% by the kidneys. It is neither reabsorbed into the blood nor secreted through tubules into the urine. Its concentration in serum is not significantly influenced by gender, height, body weight, muscle mass, use of stimulants (alcohol, tobacco), ethnicity or diet. However it changes during inflammation, thyroid dysfunction, cancer and, for example, when using large doses of glucocorticosteroids. It is also influenced by the patient's age. In people over 50 years of age, an increase in the concentration of cystatin C in the blood is observed. It becomes particularly pronounced after the age of 80 years.

Summing up, in old patients with diabetes we can expect eGFR discrepancies caused by lowering serum creatinine secondary to changes in body composition with predominance of adipose tissue at the expense of muscle atrophy and secondary to glycaemic control. While the influence of the patient's diet on serum creatinine is not clear both serum creatinine understatement and overstatement may then occur. Cystatin C is better than creatinine but is still an imperfect indicator of GFR because of its variability with age [23, 24]. Also, the higher cost of cystatin C testing limits its introduction as a routine outpatient practice.

Considering the limitations mentioned above, it is not surprising that the results of estimated GFR based on the selected formulae may be inconsistent and far from real GFR values [28].

Is there any optimal solution? The results of numerous analyses have proven that CKD-EPI equations based on both serum cystatin C and serum creatinine measurements are currently the best tool for estimation GFR for the entire population, among them also for old patients and those with diabetes [28–32]. Based on the current American Diabetes Association recommendations, the CKD-EPI equation using serum cystatin should be used for checking/confirming purposes in cases of

doubtful GFR estimation based on serum creatinine with no matching clinical picture [8].

Considering the results of our study, it should also be mentioned that the revealed discrepancies in eGFR measurements could also be caused by the overlapping of age and diabetes with other diseases affecting kidney function, e.g. primary glomerulopathy or tubulopathy. It is highly reliable in the terms of kidney biopsy results where diagnosis of diabetic nephropathy is not common.

Summarising our research in terms of practical clinical indications, we believe the following:

Each conclusion about renal function based on the result of eGFR should be cautious and taking into account clinical data.

An individual approach to the interpretation of eGFR results is necessary, especially in conditions that may affect serum creatinine concentration (e.g. obesity, cachexia, poor diabetes control, significant kidney damage).

In the cases of discrepancies in eGFR results obtained from equations based on the serum creatinine concentration, it should be verified by calculating the eGFR from a formula basing on the serum cystatin C concentration.

In doubtful cases and situations requiring high accuracy in glomerular filtration assessment, it is necessary to perform measured GFR.

Emphasising the benefits of our work, we showed that it is difficult to reliably assess renal function (glomerular filtration) in elderly people with diabetes by estimation of GFR even with formula commonly used in practice.

However, although our project has many limitations, we believe that it will make doctors aware of the discrepancies they encounter in outpatient practice.

Keeping in mind the problem of limiting the performance of mGFR in outpatient practice, for the purpose of increasing inference about GFR estimation it would be advisable to expand the study protocol assessing eGFR to include performing the body weight composition and basic kidney imaging tests, e.g. ultrasound and testing the proteinuria and comparing the study group with the control one. This remains the focus of our further research.

Conclusions

In elderly patients with diabetes the results of eGFR calculations according to the equations most often used in practice, i.e. MDRD, CKD-EPI (SCys) and CKD-EPI (SCr,SCys), are not consistent; hence a single eGFR calculation does not allow to provide a clear classification of patients into CKD stages.

Disclosures

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