

# Serum Creatinine versus Corrected Cockcroft-Gault Equation According to Poggio Reference Values in Patients with Arterial Hypertension

## Abstract

**Introduction:** Serum creatinine is not enough sensitive marker for the evaluation of glomerular filtration rate (GFR). Cockcroft-Gault (CG) formula is often used to assess GFR, but it is necessary to correct original one for body surface area (BSA), adipositas, and the creatinine tubular secretion. The values of the estimated creatinine clearance and GFR are considered to Poggio reference ones according to biological parameters (age and gender). The aim of the study was to determine the difference in renal function estimation between serum creatinine and corrected CG equation according to the Poggio reference values in the arterial hypertension patients. **Materials and Methods:** The research included 124 patients of both gender with arterial hypertension, excluding ones with the already verified chronic kidney disease. We estimated creatinine clearance and GFR by CG method corrected for the BSA, body mass index (BMI), and the creatinine tubular secretion according to Poggio reference values. **Results:** There was no significant difference in both age and gender groups among patients with physiological and pathological values of the renal function determined by the serum creatinine and estimated creatinine clearance by CG equation corrected for BMI, BSA. In both age and gender groups there was significant difference among subjects with physiological and pathological values of the renal function determined by serum creatinine and estimated GFR by CG method corrected for BMI, BSA, and creatinine tubular secretion. **Conclusion:** There is the most striking difference in the assessment of renal function between serum creatinine and estimated GFR by CG method with three corrections (BSA, BMI, the creatinine tubular secretion). Estimated GFR by CG method with three corrections can help in the early diagnosis of renal dysfunction and optimal treatment in patients with arterial hypertension.

**Keywords:** Chronic kidney disease, creatinine, glomerular filtration rate, hypertension

## Background

In clinical practice, serum creatinine is used to assess renal function. However, serum creatinine as a marker is not sensitive enough for evaluation of glomerular filtration rate (GFR) and it may be reduced in addition to serum creatinine reference values. The authors examined the incidence of “hidden” renal failure due to the use of serum creatinine to assess renal function.<sup>[1,2]</sup> There is often a correlation between moderate or even severe renal dysfunction, with serum creatinine at reference values indicating that GFR should be calculated systemically.<sup>[3-5]</sup> Chronic kidney disease (CKD) is more common than it was previously thought and has been established as a major independent contributor to mortality.<sup>[6,7]</sup> Given the above, formulas that assess creatinine clearance or

glomerular filtration have been introduced in clinical practice. They are most often based on serum creatinine, gender, age, and body weight. One of the first formulas was Cockcroft-Gault (CG) which actually estimates creatinine clearance based on the above-mentioned parameters.<sup>[8]</sup> Assessment of renal function is more sensitive using formulas based on serum creatinine than individual values of serum creatinine.<sup>[7]</sup> The incidence of patients with impaired renal function was higher if formulas were used compared to using serum creatinine alone. For this reason, higher prevalence of renal dysfunction in essential hypertension was proven.<sup>[9,10]</sup>

CG formula is often used to assess glomerular filtration, but its use for extreme body mass values is questionable.<sup>[11,12]</sup> Using modification of diet in renal disease (MDRD) formula in obese patients is also questionable.<sup>[13,14]</sup> With obese

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**Table 1: The difference between the number of patients with physiological (F) and pathological (P) values of renal function based on: serum creatinine, estimated Cockcroft-Gault creatinine clearance corrected for body mass index, Estimated Cockcroft-Gault creatinine clearance corrected for body mass index and body surface area<sub>1,73</sub> and estimated creatinine clearance rate by Cockcroft-Gault method corrected for body mass index and body surface area<sub>1,73</sub> according to reference values by Poggio *et al.***

Name	Serum creatinine		eCrCl <sub>CGBMI</sub>		eCrCl <sub>CGBMI,73</sub>		eGFR <sub>CGBMI,73</sub>	
	Female, n (%)	Male, n (%)	Female, n (%)	Male, n (%)	Female, n (%)	Male, n (%)	Female, n (%)	Male, n (%)
Age								
35-65								
Physiological	27 (73)	34 (87)	22 (59)	36 (92)	21 (57)	29 (74)	4 (11)	20 (51)
Pathological	10 (27)	5 (13)	15 (41)	3 (8)	16 (43)	10 (26)	33 (89)	19 (49)
66-85								
Physiological	16 (70)	17 (68)	16 (70)	20 (80)	13 (57)	18 (72)	5 (22)	5 (20)
Pathological	7 (30)	8 (32)	7 (30)	5 (20)	10 (43)	7 (28)	18 (78)	20 (80)
Total number of patients	n=124 (female [60], male [64])							

eCrCl<sub>CGBMI</sub>: Estimated Cockcroft-Gault creatinine clearance corrected for body mass index; eCrCl<sub>CGBMI,73</sub>: Estimated Cockcroft-Gault creatinine clearance corrected for body mass index and body surface area; eGFR<sub>CGBMI,73</sub>: Estimated creatinine clearance rate by Cockcroft-Gault method corrected for body mass index and body surface area

patients, an increase in adipose tissue leads to a decrease in the amount of excreted creatinine in the urine relative to body weight, and then there is a false increase in creatinine clearance values obtained by the CG formula. The formula has been proposed to correct the values of the estimated creatinine clearance obtained by the CG; BMI corrected CG creatinine clearance = CG clearance (1.25-0.012·BMI).<sup>[15]</sup> Manabe *et al.* measured inulin clearance and compared it with formulas for assessing creatinine clearance in obese and nonobese patients. In the group of obese patients, the standard error was smaller if a correction for actual body weight was used, which was a very important factor for assessing creatinine clearance.<sup>[16,17]</sup> Luke *et al.* compared inulin clearance, creatinine clearance with five formulas for assessing creatinine clearance and glomerular filtration, which use gender, age, body height, body weight. According to these authors, the ratio of inulin clearance as a measure of glomerular filtration can be related to creatinine clearance by the formula Inulin clearance = 1.12·creatinine clearance-20.6.<sup>[18]</sup> Problem with an appropriate equation for estimation of creatinine clearance and GFR is existing.<sup>[19,20]</sup>

The aim of this research was to determine the difference in the assessment of renal function with serum creatinine in relation to the corrected CG formulas according to the Poggio reference values in patients with arterial hypertension.

## Materials and Methods

### Patients and study design

Cross-sectional research was conducted on Clinic for Heart, Rheumatism and Blood Vessels, Clinical Center University of Sarajevo, from May to April 2019. The research included 124 patients of both genders, aged 35–85 years, who have arterial hypertension. Data about gender, age,

body height, and weight, serum creatinine were taken from the official medical history of patients on the Clinic for Heart, Rheumatism, and Blood Vessels.

We excluded patients from our study if they were already verified CKD, patients on renal replacement therapy, with peripheral arterial disease, and pregnant women. Ethical approval was obtained from the Ethical Committee, Clinical Center University of Sarajevo.

### Methods

Creatinine values were measured spectrophotometrically in serum samples. Physiological values of serum creatinine for females are 45–90 μmol/L, and for males 60–110 μmol/L.

CG formula is a noninvasive method that uses: serum creatinine, gender, age, and body weight for the estimation of creatinine clearance, estimated creatinine clearance by CG formula (eCrCl<sub>CG</sub>),

$$eCrCl_{CG} = (140 - \text{years}) \times \text{body mass} \times 1,2 \text{ (if males) / creatinine}_{\text{serum}}^{[8]}$$

According to CG creatinine clearance values were corrected for body mass index (BMI) according to the following formula:

$$eCrCl_{CGBMI} = eCrCl_{CG} (1.25 - 0.012 \cdot \text{BMI})^{[15]}$$

To compare the clearance values, formulas were calculated on a body surface area (BSA) of 1.73 m<sup>2</sup>. The BSA was determined based on the Gehan-Georg formula

$$PT = 0,0235 \cdot \text{body weight}^{0,51456} \cdot \text{body height}^{0,42246}$$

The formula used to estimate GFR according to the CG method, which takes into account creatinine tubular secretion, corresponds to the original formula published by Luke *et al.*, eGFR<sub>CGBMI,73 m<sup>2</sup></sub> = 1,12·eCrCl<sub>CGBMI,73</sub>-20,6 (estimated GFR by CG formula corrected for BMI and BSA-eGFR<sub>CGBMI,73 m<sup>2</sup></sub>).<sup>[18]</sup>

All the values of the estimated creatinine clearance and estimated GFR are considered pathological if values were lower than 5<sup>th</sup> percentile according to Poggio reference values.<sup>[21]</sup>

### Statistical analysis

The results of the research were processed using descriptive and inferential statistics. The Chi-square test of exact probability evaluated the association of categorical variables. All results of the statistical analysis at the level of  $P < 0.05$  were accepted as statistically significant.

### Results

The research was conducted among 124 patients, of whom 60 (48.4%) were female, of an average age of  $63.1 \pm 8.2$ , and 64 (51.6%) male, of an average age of  $63.2 \pm 11.0$  years.

In the age groups 35–65 and 65–85 years of patients of both genders, there was no significant difference in the number of patients with physiological or pathological values of renal function, determined by serum creatinine and estimated creatinine clearance by CG Equation corrected for BMI ( $eCrCl_{CGBMI}$ ) [Table 1].

In addition, comparing male and female patients in the age groups 35–65 and 65–85 years, there was no significant difference of patients with physiological and pathological values of renal function between those assessed by creatinine clearance by CG Equation corrected for BMI and standardized BSA of  $1.73 \text{ m}^2$  ( $eCrCl_{CGBMI,1.73}$ ) and serum creatinine.

In the age group 35–65 years in women, there was a significant difference ( $\chi^2 = 26.9$   $P \leq 0.001$ ) among patients with physiological and pathological values of renal function as assessed by the rate of glomerular filtration by CG Equation corrected for secerning at the level of tubules, BMI, a standardized BSA of  $1.73 \text{ m}^2$  ( $eCrCl_{CGBMI,1.73}$ ) with that particular serum creatinine.

In men of the same age group, 35–65 years, there was a significant difference ( $\chi^2 = 10.2$   $P \leq 0.001$ ) among patients with physiological and pathological values of renal function, among patients with estimated glomerular filtration by CG Equation, corrected for BMI, tubular secretion, and standardized BSA of  $1.73 \text{ m}^2$  ( $eCrCl_{CGBMI,1.73}$ ) with that particular serum creatinine.

In the age group 66–85 years, in female patients, there was a significant difference ( $\chi^2 = 8.7$   $P \leq 0.01$ ) among patients with physiological and pathological values of renal function, determining serum creatinine and estimated glomerular filtration by CG Equation, corrected for BMI, tubular secretion, and standardized BSA of  $1.73 \text{ m}^2$  ( $eCrCl_{CGBMI,1.73}$ ).

Furthermore, in the same age group, 66–85 years, in male patients, there was a significant difference ( $\chi^2 = 8.6$

$P \leq 0.001$ ) among patients with physiological and pathological values of renal function, between patients with estimated glomerular filtration by CG Equation, corrected for BMI, tubular secretion, and a standardized BSA of  $1.73 \text{ m}^2$  ( $eCrCl_{CGBMI,1.73}$ ) with that particular serum creatinine.

### Discussion

It is a well-known fact that renal dysfunction most often occurs as a consequence of long-standing diabetes mellitus and/or arterial hypertension. In practice, serum creatinine is unjustifiably used to assess renal dysfunction instead of appropriate formulas that estimate creatinine clearance or GFR based on, most commonly, serum creatinine, sex, age, body weight, body height, and race. The two most commonly used formulas are the MDRD<sup>[22]</sup> and the CG formula or CG Equation.<sup>[8]</sup> If we use the CG Equation, to get more reliable results, it is necessary to make a correction for BMI among other parameters. With this method without correction for BMI in overweight patients, we obtain increased values of the estimated creatinine clearance at the expense of adipose tissue, and due to the logic of the results, correction for BMI was used.<sup>[15]</sup>

In the age group of 35–65 years, we see that there was no significant difference in either men or women in the number of patients with pathological serum creatinine values compared to the estimated creatinine clearance by CG BMI-corrected method ( $eCrCl_{CGBMI}$ ) using Poggio reference values. Similar values were found in the older age group of 66–85 years. The assumed reasons for the absent difference are the lack of standardization for the BSA of  $1.73 \text{ m}^2$  and the noninclusion of correction for secerning at the level of tubules as well as the relatively small number of patients in subgroups. According to studies serum creatinine in reference values often corresponds to moderate or severe renal dysfunction with estimated creatinine clearance by the CG method corrected for a BSA index of  $1.73 \text{ m}^2$ .<sup>[3,4]</sup> The difference from our results was most likely due to the use of KDIGO reference values of 60 ml/min for all age groups. However, the KDIGO criteria that define CKD are a subject of a very intense debate in the current nephrology literature, with recommendations for the introduction of an age-specific limit for GFR.<sup>[23-26]</sup>

Comparing the estimated creatinine clearance corrected for two criteria, BMI and BSA ones ( $eCrCl_{CGBMI,1.73}$ ) with serum creatinine values in men and women in the age group 35-65 years, there is found a nominally higher number of patients with pathological values in the group where  $eCrCl_{CGBMI,1.73}$  was determined, but they did not have statistical significance, probably due to the relatively small number of patients in the mentioned subgroups, as well as the nonuse of corrections for creatinine secerning at the level of tubules. In addition, in the older age group 66–85 years in the category of both male and female patients we also noticed a nominally higher number of patients with pathological values estimated by CG Equation

compared to serum creatinine, but this value was also not statistically significant probably for the same reason as in younger age group. Serum creatinine is a deficient screening test for renal dysfunction in elderly patients, leading to significant nonrecognition of renal dysfunction in this population.<sup>[27,28]</sup> The CG Equation is calculated based on total body weight and therefore overestimates eGFR in patients with obesity.<sup>[29]</sup> A significant proportion of patients with heart failure have prognostically significant renal dysfunction despite normal serum creatinine. Such patients represent a high-risk group and can be more accurately identified by a CG formula corrected for BSA than by MDRD.<sup>[30]</sup> There is no ideal formula for assessing glomerular filtration in highly adipose patients, however, the adjusted body weight incorporated in the CG formula may be helpful in these patients.<sup>[20]</sup>

The most interesting was the comparison of pathological values of the renal function obtained by serum creatinine and the estimated value of glomerular filtration obtained by CG Equation with corrections for BMI, BSA of 1.73 m<sup>2</sup>, and creatinine secretion at the level of tubules. In the younger age group, 35–65 years with pathological values of the renal function obtained by serum creatinine in relation to renal function obtained by estimating the GFR by the CG Equation corrected for tubular secretion ( $eCrCl_{CGBMI,73}$ ), with the previous 2 corrections, for BMI and BSA. It is evident that only after 3 corrections do these differences become significant. In women, the percentage with renal dysfunction rises from 27% to 89%, while in men, this percentage increases from 13% to 49%. From this, it can be concluded how important all three corrections of the stated CG Equation are to obtain the expected values since CKD is most common in patients with hypertension and diabetes mellitus.

In the older age group of 66–85 years, similar values were obtained, which was expected after three corrections (for secreting at the level of tubules, BMI, and BSA of 1.73 m<sup>2</sup>). There was a significant difference in both men and women between the pathological values of renal function between those obtained by serum creatinine and those assessed as the GFR by the CG Equation with the above three corrections. In women, the percentage with renal dysfunction rose from 30% to 78%, while in men, this percentage increased from 32% to 80%, if patients with serum creatinine were compared to  $eGFR_{CGBMI,73}$ , which included three corrections. Fernández-Fresnedo *et al.* obtained similar results, even in the group of patients with normal renal function determined by serum creatinine which was <115 μmol/L in the group of women there was a relatively high percentage with  $CrCl_{CG}$  values <50 ml/min and 22% (60–70y), 35% (70–80y) and 57% (>80y), while in the group of male respondents, this percentage was 11.3% (70–80y) and 33.3% (>80y).<sup>[2]</sup> Similar results were found in Huynh *et al.* in patients without clinically present renal dysfunction, both creatinine and eGFR assessed by the

CG Equation predict additional mortality, but eGFR was a much stronger predictor in patients with thoracoabdominal aortic surgery.<sup>[31]</sup> According to the CG Equation, mild renal failure was found in 38.2% and moderate renal failure in 16.9% of patients with normal serum creatinine. The stated lower percentage in Fiseha *et al.* can be explained by the fact that no correction formulas were used in the calculation.<sup>[19]</sup> The prevalence of CKD is high, with almost 80% of patients undergoing primary percutaneous coronary intervention, despite normal serum creatinine. This is very important in patients with hidden renal dysfunction and normal serum creatinine, at an increased risk of contrast nephropathy.<sup>[32]</sup>

The limitations of this study relate to the relatively small sample of patients, as well as the fact that this was not a randomized controlled trial, which could specifically evaluate the impact of each variable.

Further studies are needed to elucidate the relationship between serum creatinine and chronic renal disease, especially from the perspective of logical age criteria for GFR limits.

## Conclusion

There was a significant percentage of renal dysfunction in outpatients with normal serum creatinine levels. The most striking difference in the assessment of renal function determined by serum creatinine and the formula for estimating the GFR by the CG Equation is found in the group where three corrections were included. A large proportion of the younger and older population with arterial hypertension will not be recognized if clinicians rely on serum creatinine values as evidence of normal renal function. The CG Equation, but with three corrections in patients with arterial hypertension in routine laboratory reporting, can help in the early diagnosis of renal dysfunction and the optimal treatment of these patients.

## Patients consent form

All patients included in this study were officially informed about it.

## Ethical clearance

The study was approved by the Ethics Committee of Faculty of Medicine, University of Sarajevo (Approval No 100-85/18).

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## Conflicts of interest

There are no conflicts of interest.

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