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Formulas for calculating glomerular filtration rate: advantages and disadvantages

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ABSTRACT

In conformity with the guidelines of the Kidney Disease | Improving Global Outcomes (KDIGO) and the National Kidney Foundation (NKF), since the beginning of 2012, chronic renal disease (CKD) staging has been based on the **cause**, **eGFR values and albuminuria**. In the early stages of renal impairment, when the clinical picture is very poor, both laboratory markers - albuminuria and glomerular filtration rate - are particularly important. In recent years, the calculation of **eGFR** is based mainly on creatinine values, which have both advantages and disadvantages. In recent decades, the marker **cystatin C** has been studied as an alternative to creatinine. Since 2009, different formulas for calculating glomerular filtration (**eGFR**), including either creatinine or cystatin C alone, or both, have been proposed. In Bulgaria, the **eGFR** is mainly determined by the MDRD creatinine-based formula.

KEYWORDS:

chronic kidney disease, type 2 diabetes mellitus, essential hypertension, glomerular filtration, MDRD and CKD-EPI

INTRODUCTION

Glomerular filtration rate (**GFR**) is a major marker for assessing kidney function and is particularly important for the detection, assessment and management of chronic kidney disease (CKD) (10, 17, 24). GFR is the basis for classifying the CKD in 5 stages (I, II, III, IV and V stage). In conformity with the guidelines of the KDIGO and the NKF, in the beginning of 2012, VI stage was introduced in the classification of CKD by subdividing stage III into IIIa and IIIb stages, which is based on the triad **cause, eGFR and albuminuria** (10, 17, 24). In case of albuminuria A2 and GFR <60 mL/min/1.73 m2 lasting over 3 months, chronic renal failure (CRF) is considered. The use of exogenous markers, such as inulin, is considered the "gold standard," but is limited for a number of reasons (cost, undesirable allergic reactions, and invasiveness of the procedure). For many years in Bulgaria and around the world, glomerular filtration (GF) has been calculated, based on creatinine. Recently, this approach has been criticized for analytical and physiological problems (interference of the methods and creatinine dependence on muscle mass, protein intake, tubular excretion, etc.) (1, 2, 5, 21). In the course of searching for and testing new endogenous markers over the past decades, the use of the new marker **cystatin C** (1, 2) has been proposed for estimating the GF. The formulas for calculating the GF, MDRD (Modified Diet of Renal Disease) and CKD-EPI (Chronic Kidney Disease-Epidemiology), based on either creatinine or cystatin C alone, or on both biomarkers, are continuously modified and refined by including the age, gender, race and the concentration of the marker (6, 11, 12, 20).

DISCUSSION

Glomerular filtration rate is a critical predictor of renal insufficiency. As a threshold for the diagnosis of initial CRF, GFR <60 mL/min/1.73 m2 with albuminuria A2 lasting over 3 months is considered. Direct GF measurement is difficult and therefore, endogenous and exogenous markers are used. The search for a new way to assess the GF stems from the limitations of plasma creatinine alone, the cost and complexity of determining the GF with inulin or radionuclides, and the inaccuracies associated with the collection of 24-hour diuresis for creatinine clearance (6, 9, 17). Creatinine levels depend on muscle mass, diet, gender, age, and ethnicity. These limitations are the reason to search for new GF biomarkers and new formulas for its calculation. Cystatin C is a possible alternative to creatinine, due to its direct dependence on **eGFR** and less analytical interference: it is synthesized at a constant rate and is freely filtered from the glomeruli, is not excreted in the urine, but is absorbed and metabolised in the proximal tubules (1, 2, 4, 7, 14, 16). After the introduction of cystatin C, the modification of the old and the introduction of the new formulas started. The widely used creatinine-based MDRD formula (Modification Diet of Renal Disease) underestimates the renal function in patients with estimated normal GFR >90 ml/min/1.73 m2. This is one of the reasons for the implementation of CKD-EPI (Chronic Kidney Disease Epidemiology) equation, suggested in 2009, which is currently showing significantly higher accuracy (24). Recently developed CKD-EPI equations are based on either creatinine or cystatin C alone, and the combination of creatinine + cystatin C (2, 7, 8, 21). The qualities of these equations are extensively studied and consistent with the gender, age, ethnicity, and the plasma concentration of the marker (2, 5, 21, 23).

The present study discusses the following formulas:

1. MDRD, based on creatinine alone
eGFR (mL/min/1.73 m2) = 175 × (SCR) - 1,154 × (age) – 0.203 x 0.742 (for women only)

2. CKD-EPI, based on creatinine alone
- eGFR (mL/min/1.73 m2) = 144 x (sCr/0.7) - 0.329 x (0.993) age (for women with creatinine ≤0.7)
- eGFR (mL/min/1.73 m2) = 144 x (sCr/0.7) - 1.209 x (0.993) age (for women with creatinine >0.7)
- eGFR (mL/min/1.73 m2) =141 x (sCr/0.9) -0.411 x (0.996) age (for men with creatinine ≤0.9)
- eGFR (mL/min/1.73 m2) =141x (sCr/0.9) -1.209 x (0.996) age (for men with creatinine >0.9)

3. CKD-EPI, based on cystatin C alone (for men and women) with cystatin C ≤0.8)
- eGFR (mL/min/1.73 m2) =133 x (sCys/0.8) -0.499 x (0.993) age x 0.932 (for women with cystatin C ≤0.8)
- eGFR (mL/min/1.73 m2) =133 x (sCys/0.8) -1.328 x (0.993) age x 0.932 (for men with cystatin C >0.8)

4. CKD-EPI, based on creatinine and cystatin C
- eGFR (mL/min/1.73 m2) =130 x (sCys/0.7) -0.248 x (sCys/0.8) -0.375 x 0.995 age (for women with creatinine ≤0.7 and cystatin C ≤0.8)
- eGFR (mL/min/1.73 m2) =130 x (sCr/0.7) -0.248 x (sCys/0.8) -0.711 x 0.995 age (for women with creatinine >0.7 and cystatin C >0.8)
- eGFR (mL/min/1.73 m2) =135 x (sCr/0.9) -0.207 x (sCys/0.8) -0.375 x 0.995 age (for men with creatinine ≤0.9 and cystatin C ≤0.8)

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The studies conducted in Bulgaria on the diagnostic reliability of cystatin C for the diagnosis of initial CRF, whether alone or in combination with creatinine, as well as in different formulas, have confirmed the general literature data (1, 2, 3, 8, 10, 16). Following the KDGIO and NKF recommendations that CKD stages are determined by the triad (9, 10, 15) cause, GF and albuminuria, and given the high standardization of microalbumin testing, the calculation of eGFR becomes a key point in the early diagnosis and follow-up of CRF. The studies conducted in Bulgaria and some other countries have shown the difference between the two formulas, MDRD and CKD-EPI, based on either creatinine or cystatin C alone (8, 9, 10, 11, 12, 13). The second equation, CKD-EPI, gives more reliable results, both in the studies conducted by our authors and in those outside Bulgaria (6, 21). It is considered more universal and accurate, but is also criticized for the problems related to creatinine. The CKD-EPI formula based on cystatin C alone is only suitable under certain conditions, including the so-called "blind" area of creatinine, in overweight patients, and particularly in outpatients (4). This formula is also criticized because new data suggest that the synthesis of cystatin C is influenced by hyperthyroidism and hypothyroidism, corticosteroid intake, etc. The last, fourth CKD-EPI formula, based on both creatinine and cystatin C, is the most hopeful because it uses two endogenous markers, thus eliminating the disadvantages of the individual use of creatinine or cystatin C (2, 5, 20). It could be assumed that the data obtained with this formula are the most reliable (7, 8, 9, 10, 11, 13, 16, 17, 21).

In the literature, it is argued which formula is to be used for calculating the GF on the basis of the diagnostic strategy – for screening, for a specific clinical indication, for secondary testing based on creatinine test results, or for comparing to creatinine-based GF (5, 10, 11, 12, 13, 15). Most authors give an advantage to the combined equation (2, 6, 7, 8). It best calculates the glomerular filtration across the entire range. It is believed to be the equation of the future for calculating the GF. In a meta-analysis, Shlipak et al. (20) have found that cystatin C-based equations have advantages over creatinine-based ones in classifying patients with CKD. **The KDIGO (10, 15) recommends the use of cystatin C in patients, whose creatinine-based GF is within the range of 45 to 60 ml/min/1.73m2 and have no other symptoms of chronic kidney disease, such as microalbuminuria**. The cystatin C-based equations, according to the authors, are the best way to predict CRF and end-stage CKD.

In Bulgaria, the creatinine-based MDRD formula is used for estimating the GF. Despite the advantages of the cystatin C-based formula, it cannot completely replace the "gold standard" for estimating the GF, but can help to more accurately select the patients in need of invasive and costly procedures. It is good to have a well-established strategy for screening patients with CKD. The two creatinine-based equations overestimate the incidence of CKD. It is expected that some of these problems will be solved when using the combined equation. Creatinine correlates insignificantly with GF in conditions, associated with increased tubular secretion or outside renal elimination, as is the case with severe CKDs. In the end, all GF equations are essentially mathematical abstractions that refer to individual cases from where these equations have been derived. It is impossible for an equation to be ideal and appropriate for all cases, and the clinicians should be acquainted with and involved in all potential constraints when interpreting the results (17, 18, 19). All recent studies conclude that cystatin C is superior to creatinine when calculating the GF across the entire range (5, 14, 18, 19). In 2014, Tsai et al. (25) published data on the average GF levels, based on either creatinine or cystatin C alone, without giving any advantage to either of the markers. In their view, **neither creatinine nor cystatin C are perfect filtration markers, because both have determinants that are not dependent on glomerular filtration**. This still requires their simultaneous use (2, 14, 22, 23, 24). We have found an inverse correlation between the GF and the age of the individuals, cystatin C and serum creatinine. Inker et al. checked the alternative marker, cystatin C. By using a cross-sectional analysis of 5,353 participants from 13 studies, the authors examined cystatin C and creatinine as single and combined markers for estimating the GF. The average GF was 68 and 70 ml/min/1.73 m2. When the data were verified, it was found that **the use of the combined creatinine-cystatin C equation was more effective** than the use of the formulas, based on either creatinine or cystatin alone.

Following the recommendations of the KDIGO and the NKF and international experience, it is necessary to improve the laboratory diagnosis of CKD by using both endogenous markers (creatinine and cystatin C) and the new compound formula.

Cystatin C, along with creatinine, expands and improves the estimation of GF, and in combination with albuminuria (A1, A2 and A3) is an extremely good diagnostic model for the early diagnosis of CKD.

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