



Recent Trends for Clinical Nephrology and Pharmacology Concerning Glomerular Filtration Rate (GFR)

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Abstract

Recently, chronic kidney disease (CKD), diabetic kidney disease (DKD), glomerular filtration rate (GFR) and related matters have been in focus. Estimated GFR (eGFR) has been usually calculated by serum creatinine and age corrected by body surface area (BSA). In contrast, Cockcroft-Gault formula is another way that is not corrected by BSA. When the patient's physique is significantly larger or smaller, BSA correction may remarkably change the value of eGFR. Based on the data of Japan Multi-institutional Collaborative Cohort (J-MICC) study, various factors influencing renal function were investigated. As a result, problem solving degree in men revealed inverse relationship with eGFR.

Keywords: *Chronic kidney disease (CKD); Diabetic kidney disease (DKD); Glomerular filtration rate (GFR); Body surface area (BSA); Cockcroft-Gault formula; Japan Multi-institutional Collaborative Cohort (J-MICC)*

Commentary Article

Recently, chronic kidney disease (CKD), diabetic kidney disease (DKD), glomerular filtration rate (GFR) and related matters have been in focus [1]. In Jan 2022, American Diabetes Association (ADA) announced the latest guideline for diabetes management [2]. Authors have continued medical practice and research for various patients with diabetes, CKD, DKD, hemodialysis (HD) and others [3,4]. Among them, discussion concerning estimated GFR (eGFR) and pharmacokinetics for CKD has been found [5]. For this field, several novel categories of diabetic agents were introduced to clinical practice. They include Glucagon-Like Peptide 1 receptor agonist (GLP-1RA), dipeptidyl peptidase-4 inhibitor (DPP-4i), and sodium/glucose cotransporter 2 (SGLT2) [6]. GLP-1RA, DPP-4i and SGLT2 have been evaluated to show beneficial effects to CKD, DKD, hypertension and others [7]. Some perspectives for these would be described in this article.

In the light of fundamentally medical knowledge, blood flow of humans has been well-known as follows [8]. For a normal person, the amount of blood pumped from the heart is 5 liters per minute. For 20% of them, 1 liter of blood comes to renal blood flow.

Since about half of the blood is plasma, the plasma volume flowing into the kidneys is calculated to be 500 ml/min. Among them, 100 ml/min is estimated for the glomerular filtration rate (GFR) that is equivalent of 20% of the flowing plasma. In the actual clinical practice, the estimated GFR (eGFR) has been used for long. It has been calculated from the serum creatinine (sCr), age, and sex that is corrected per 1.73 m² of body surface area (BSA).

Before calculating eGFR, sCr level has to be measured in all subjects and patients. It has been usually measured using an enzymatic method in the laboratories. The calculation equation is as follows: i) male: $eGFR (mL/min/1.73 m^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{Age}^{-0.287}$, and ii) female = i) $\times 0.739$ [9]. The creatinine clearance (Cr), which is an index of GFR, indicates how many mL of creatinine (Cr) in plasma is excreted in urine per minute. To be precise, the calculation is performed from serum Cr and Cr concentration in livestock urine for a certain period of time. However, in addition to glomerular filtration, some part of Cr is always secreted from the proximal tubule. Therefore, the measured values are slightly different, and then Cr shows a value about 10-20% higher than GFR.

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On the other hand, the Cockcroft-Gault (C-G) formula is known as another calculation way [10]. In this method, Ccr is calculated from sCr, age, sex, and body weight, and it may not be corrected by BSA. The C-G formula (1973) is as follows. $CCr = \{((140 - \text{age}) \times \text{weight}) / (72 \times \text{sCr})\} \times 0.85$ (if female). In the original calculation of C-G formula, sCr was measured by the Jaffe method and showed 0.2mg/dL higher value, due to the influence of contaminants in serum [11]. However, due to the small effect of such substances in urine, the Ccr value was lower than the actual Ccr value and close to the BSA-uncorrected GFR. Currently, sCr is measured by the enzymatic method. Since this is applied to the C-G formula, a value close to the actual Ccr can be obtained. Recently, a method including BSA amendment has been proposed [12].

In the clinical practice, many renal excretion-type drugs have been used for years. Each package insert supports dose adjustment by Ccr value. Actually, eGFR is often displayed automatically when sCr is measured. When considering the adjustment of drug dose from decreased renal function, it is appropriate to carry out based on GFR which is not corrected by BSA [13]. Consequently, the following two methods are recommended for evaluating renal function when administering a renal excretion-type drug. They are i) add 0.2 mg/dL to the sCr value created by the enzymatic method and substitute it into the C-G formula to calculate Ccr, ii) multiply eGFR by BSA/1.73 to obtain uncorrected GFR. The BSA calculation method uses $BSA (m^2) = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.00718$, that is from the DuBois formula.

The characteristic of these two methods is that they do not use the numerical values of weight and height. As renal function is almost normal and sCr is not high, the accuracy of these methods is rather low. When the patient's physique is significantly larger or smaller, the BSA correction may remarkably change the value. Then, it is recommended to use these two methods. In actual medical care, there is no strict response to the decline in renal function. If the renal function is mild, the dose is kept to the normal dose. When the renal function is moderate, the dose would be reduced to 1/2. If the renal function is severe, the dose has been usually reduced to about 1/3 to 1/4, or the dosing interval is lengthened. However, it is important to understand the principles of these calculations [14].

Latest impressive report was found. Concerning risk factors for renal dysfunction, lifestyle-related factors have been noted such as aging, diabetes, hypertension, obesity, smoking, drinking, and lack of exercise. Furthermore, psychological stress may be involved in decreased renal function, including depression and higher goal-striving stress [15,16].

For examining gene-environment interactions, the Japan Multi-institutional Collaborative Cohort (J-MICC) study was launched in 2005. Using these data, various factors influencing renal

function were investigated [17]. Protocol included 70642 subjects (male/female) with 56.0/55.2 years old and eGFR 76.3/80.0 mL/min/1.73 m². Various stress and coping strategies including problem solving, emotional support seeking, emotional expression, positive reappraisal, and disengagement were studied. As a result, problem solving degree in men revealed inverse relationship with eGFR. For reference, problem solving showed significantly positive correlation with grip strength [18]. As testosterone may decrease renal function, men associated with high problem-solving trend possibly show higher testosterone level and lower eGFR [19].

In summary, recent trends concerning nephrology were introduced. These informative perspectives will hopefully contribute for clinical practice for CKD, diabetes and cardiovascular diseases.

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