Which glomerular filtration rate estimation formula should be used for nephrological evaluation in patients with common variable immune deficiency?

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Abstract

Background: Common variable immunodeficiency (CVID) is the most common primary immunodeficiency in adults. In addition to renal complications of the disease, there may be an increased likelihood of renal dysfunction due to sucrose in immunoglobulin replacement therapies or other drugs used in treatment. In CVID patients, it is important to monitor patients for renal complications at routine intervals. We compared creatinine-based calculation methods for estimated glomerular filtration rate (eGFR) such as Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) with 24-hour urine creatinine clearance measurement. We aimed to investigate which calculation method was more reliable and consistent in this patient population.

Methods: The records of 14 patients who had clinical follow-up at our hospital were retrospectively reviewed. Patients' eGFR values were measured by three different methods (CKD-EPI, MDRD , and CG formulas). The 24-hour urinary creatinine clearance of all patients and e-GFR calculated by the formula were compared.

Results: The eGFR calculated using the MDRD formula was 122.99±41.22 mL/min/1.73 m2, whereas the eGFR measured using the 24-hour urinary creatinine clearance was 99.64(83.35-156.58) mL/min/1.73 m2. Moreover, eGFR calculated by CKD-EPI formula was 113.83±26.46 mL/min/1.73 m2, while eGFR calculated by CG formula was 133.52±45.35 mL/min/1.73 m2. 24-hour urinary creatinine clearance was positively correlated with MDRD, CKD-EPI and CG formulas (r=0.726, p=0.003, r=0.634, p=0.015, r=0.806, p=0.001, respectively).

Conclusions: We found that all creatinine-based formulas used in clinical practice for eGFR measurement correlate with 24-hour urine creatinine clearance in patients with CVID. In addition, we have shown that eGFR calculated with the formula CKD-EPI is more closely related to 24-hour urinary creatinine clearance. Therefore, we believe that the eGFR measurement calculated with CKD-EPI is more useful for nephrological follow-up of patients with CVID. It should be noted that our study has some limitations due to the small number of patients.

Keywords: Common Variable Immune Deficiency, Chronic Kidney Disease Epidemiology Collaboration, Cockcroft-Gault, Glomerular Filtration Rate, Modification of Diet in Renal Disease.

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INTRODUCTION

In the adult population, common variable immunodeficiency (CVID) is the most common primary immunodeficiency. It is characterized by recurrent upper respiratory tract infections and chronic lung diseases such as bronchiectasis and interstitial lung disease, inflammatory bowel disease, granulomatous disease, autoimmunity, immune dysregulation, and a predisposition to lymphomalignancies (1,2). Although many diseases such as renal granulomas, focal segmental glomerulosclerosis (FSGS), membranous glomerulonephritis (MGN), membranoproliferative glomerulonephritis (MPGN), renal amyloidosis, nephrotic syndrome, various tubulopathies, and end-stage renal disease have been described in CVID patients, there are no comprehensive prospective studies investigating renal complications in this patient population (3-6). Data are generally based on case reports and brief literature reviews. In addition to renal complications of the disease, there may be an increased likelihood of renal dysfunction due to sucrose in immunoglobulin replacement therapies or other drugs used in treatment (7, 8). With advances in treatment and increasing life expectancy in these patients, issues such as management of disease-related complications and quality of life have become more important. For this reason, it is important to monitor patients for renal complications at regular intervals. The most commonly used parameter in monitoring renal functions is creatinine, while the gold standard parameters are inulin clearance, 51Cr-EDTA, 99mTC-DTPA, 125I-thalamate, and iohexol clearance, but they are expensive and impractical to use (9). Although measurement of renal function with 24-hour urine is the most widely used method, creatinine-based glomerular filtration rate (GFR) calculation methods such as Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are practical methods that can be used instead of measuring urea creatinine clearance in 24-hour urine. The serious limitations of the 24-hour urine creatinine clearance method, such as urine collection in one day and erroneous urine collection, necessitate alternative measurement methods. In this study, we compared creatinine-based estimated glomerular filtration rate (e-GFR) calculation methods such as Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) with 24-hour urine creatinine clearance measurement. We aimed to determine which calculation method was more reliable and consistent in this patient population.

MATERIALS AND METHODS

This study was approved by the clinical research ethics committee of the Necmettin Erbakan University Meram Faculty of Medicine (Date: 21.02.2020 number: 2020/2322), and all participants signed a written informed consent form. The records of 14 patients who were followed-up in our hospital were retrospectively analyzed. Patients were diagnosed with CVID according to the European Society for Immunodeficiency (ESID) criteria (10). Inclusion criteria for the study: 1) CVID patients according to ESID criteria. 2) Patients over 18 years old 3) Patients not taking medications that affect 24-hour urinary creatinine excretion or serum creatinine level measurement. As exclusion criteria: 1) Patients under 18 years old 2) Patients taking medications that may affect 24-hour urinary creatinine excretion or serum creatinine level measurement. 3) Presence of urinary tract infection. All of our patients received intravenous immunolobulin (IVIG) treatment, but none of them received sucrose-containing IVIG.

Data on age, height, and current body weight were recorded, and their body mass index (BMI) was calculated using this equation: BMI (kg/m^2) = weight (kg)/height (m). Blood samples were obtained from all patients by venipuncture. All creatinine measurements were performed in the same laboratory using the method of Jaffe.

The e-GFR values of the patients were measured by three different methods (Table 1). In addition, 24-hour urinary proteinuria values were recorded for all patients in the system.

Table 1. e-GFR Calculation Formulas

MDRD	$186 \times \text{Serum Cr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if the patient is black) $\times 0.742$ (if female)
Cockcroft-Gault	CrCl ml/min = $(140 - \text{age}) \times (\text{weight, kg}) \times (0.85$ if female$) / (72 \times \text{Cr})$
CKD-EPI	$141 \times \min (\text{Scr}/\kappa$ **(0.7 for females and 0.9 for males))** α (-0.329 for females and -0.411 for males) $\times \max(\text{Scr}/\kappa)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.159$ (if black)

eGFR: Estimated glomerular filtration rate, MDRD: The Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Statistical analysis was performed using the software package IBM SPSS Statistics version 22. Normally distributed parameters were presented as mean ± standard deviation, and skewed parameters were expressed as median (interquartile range [minimum/ maximum]). Descriptive data were presented as frequencies and percentages and compared with the chi-square test. Baseline characteristics were compared with an independent Student's t test, Mann-Whitney rank sum test, Fisher's exact test, or chi-square test where appropriate.

RESULTS

Demographic, clinical characteristics, and biochemical parameters of 14 patients with CVID were depicted in Table 2. We studied 14 patients with CVID, 8 (57.1%) females and 6 (42.9%) males. The mean age of the patients was 40.61 ± 13.73 years. As shown in Table 2, the mean serum creatinine level was 0.72 ± 0.20.
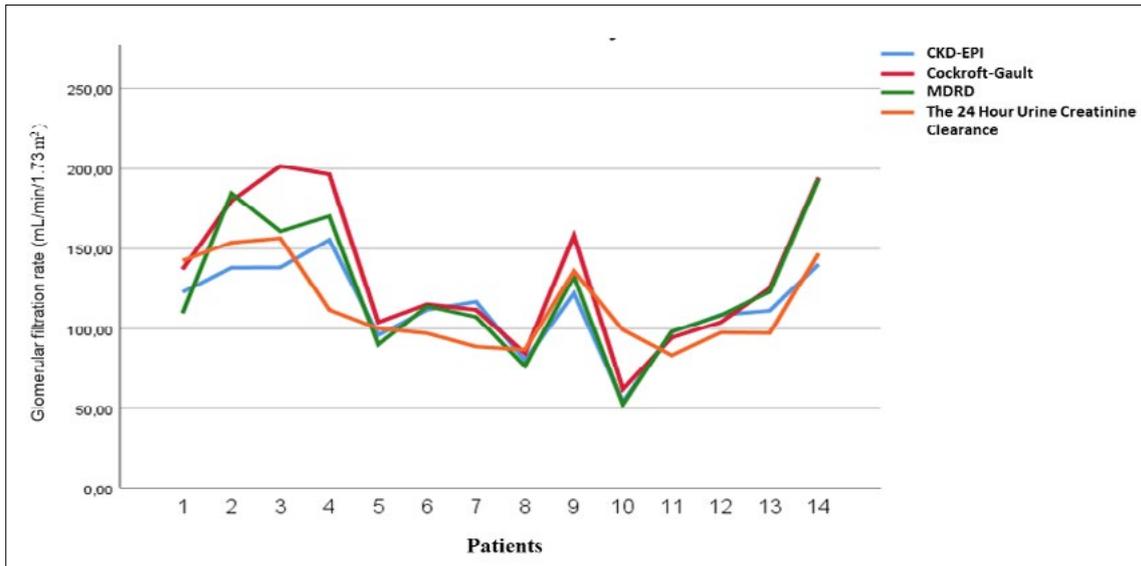
Table 2. Demographic, clinical characteristics, and biochemical parameters of 14 patients

Parameters	
Gender (F/M)	8/6
Currrent age, years	40.61 ± 13.73
Height (cm)	166.07 ± 8.34
Body weight, kg	72.14 ± 12.95
Age at diagnosis, years	32.64 ± 15.92
Diagnostic delay, months	81 (0-294)
Body surface area, (m²)	1.82 ± 0.20
Creatinine, (mg/dl)	0.72 ± 0.20
Urea (mg/dl)	28.43 ± 22.38
24-Hour Creatinine Clearance (ml/min)	99.64 (83.35-156.58)
CKD-EPI, ml/min/1.73 m²	113.83 ± 26.46
Cockcroft-Gault, ml/min	133.52 ± 45.35
MDRD, ml/min/1.73 m²	122.99 ± 41.22
Serum Albumin, (g/dL)	4.26 ±0.45
>150 mg/day 24-hour urine Proteinuria, n (%)	6 (42.8)
Mean proteinuria of all patients (mg/dL)	130.14 (223.98)

MDRD: The Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration F/M: Female/Male,

e-GFR calculated by the MDRD formula was 122.99 ± 41.22 mL/min/1.73 m², while e-GFR measured by 24-hour urinary creatinine clearance was 99.64 (83.35-156.58) mL/min/1.73 m². In addition, e-GFR calculated by the CKD-EPI formula was 113.83 ± 26.46 mL/min/1.73 m², while e-GFR calculated by the CG formula was 133.52 ± 45.35 mL/min/1.73 m². On average, there were differences of 23.9, 43.5, and 14.8 mL/min/1.73 m² in e-GFR calculated by the MDRD, CG, and CKD-EPI formulas, respectively, when compared with the 24-hour urine creatinine clearance (Figure 1).
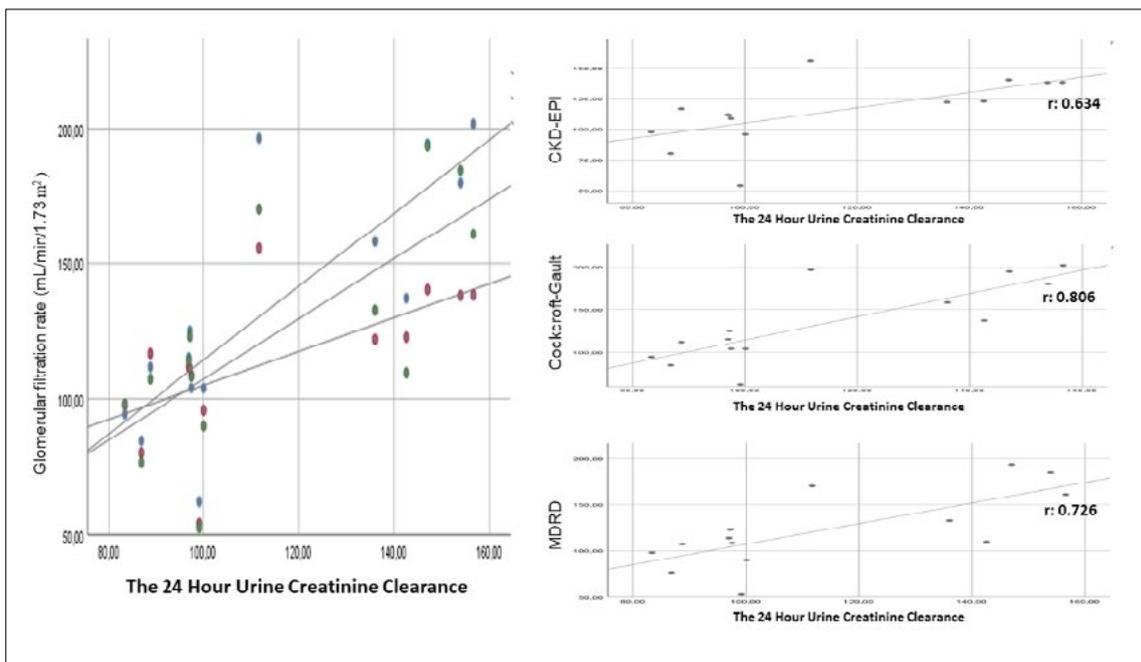
Figure 1. eGFR calculated with the formulas MDRD, CG, and CKD-EPI compared with 24-hour urinary creatinine clearance.

We also performed correlation analysis between 24-hour urinary creatinine clearance and other formulas. 24-hour urinary creatinine clearance was positively correlated with MDRD, CKD-EPI and CG formulas (r = 0.726, p = 0.003, r = 0.634, p = 0.015, r = 0.806, p = 0.001, respectively) (Figure 2).

Figure 2. Correlation analysis of 24-hour urinary creatinine clearance and e-GFR calculated with MDRD, CKD-EPI and CG formulas.

DISCUSSION

Although CVID is estimated to affect 1 in 25,000 people, it is the most common form of severe antibody deficiency in both children and adults (11). As life expectancy increases due to improved medical care for CVID patients, the number of patients presenting to nephrology clinics for renal complications is also increasing. Small changes in serum creatinine in CVID patients with progressively decreasing muscle mass, both as a result of chronic inflammation and as a result of gastrointestinal involvement, may indicate serious alterations in renal function. In other words, serum creatinine levels alone are not sufficient to assess the incidence and stage of renal disease in immunocompromised patients. At this point, evaluation and monitoring of renal function estimation with e-GFR is of great importance for early diagnosis and follow-up (12). To date, the optimal formula for calculating glomerular filtration rate in patients with common variable immunodeficiency is not known, but an indication of chronic renal impairment based on creatinine elevation alone is insufficient to detect renal impairment, especially in lean patients or patients with low muscle mass. Moreover, even minor increases in creatinine levels can lead to a serious decrease in e-GFR. Therefore, it is not appropriate to diagnose chronic kidney disease based on creatinine levels alone. In our study, glomerular filtration rate calculated from 24-hour urinary creatinine clearance in patients with common variable immunodeficiency correlated with all three formulas, but there were large differences among the three formulas in terms of calculated mean e-GFR values. The e-GFR value that was closest to 24-hour urine creatinine clearance was obtained using the CKD-EPI formula.

The prevalence of acute kidney injury, which is one of the side effects of IVIG replacement therapy commonly used in CVID patients, is approximately 1%. The addition of sugar components such as sucrose to IVIG formulas has also increased the incidence of acute kidney injury (13). Patient age and the presence of renal impairment before treatment are the most important risk factors for IVIG-induced renal injury. Identification of these risks allow early diagnosis of possible renal injury and early precautions to be taken, thereby reducing morbidity and mortality (14). CVID patients have tubular dysfunction, which is mainly related to impaired urine acidification and decreased concentration capacity. In CVID patients, the decreased urine concentrating ability in particular can lead to hypovolemia and dehydration under stress conditions (8).

The MDRD (expressed as mL/min/1.73m^2) was developed primarily for hospitalized patients with chronic kidney disease. It is a formula calculated using 4 variables such as age, sex, serum creatinine, and race. It provides more accurate results in patients with a GFR < 60 mL/min. The GFR > 60 mL/min/1.73m^2 leads to an overestimation of glomerular filtration rate in individuals. The current formula underestimates the GFR value much lower than it actually is, especially in young women and patients with severe nutritional problems (15-17). Because none of the patients in our study had chronic kidney disease and all had a GFR greater than 60 mL/min, we believe that there is a significant difference between clearance calculated by the MDRD formula and creatinine clearance.

The CG formula (expressed in mL/min) determines approximate GFR by formulating ideal weight and serum creatinine. It reduces the variability of serum creatinine in estimating GFR due to sex and age-related differences in muscle mass. Because the formula does not account for differences in creatinine production due to variations in muscle mass, it overestimates the GFR when there is an imbalance between muscle mass and weight (in people with low muscle mass, obesity, edematous disease, chronic disease) (16,18). Absorption disorders due to gastrointestinal effects in patients with immunodeficiency and decrease in muscle mass due to chronic diseases may mask the decrease in GFR. Despite the decrease in GFR, serum creatinine remains at normal levels, or because creatinine remains low as a result of the decrease in muscle mass, very high GFR values can occur in calculation methods that formulate body mass, such as CG. We consider this to be one of the reasons why the formula CG has such a large difference compared to the other two formulas when compared to 24-hour urine creatinine clearance.

The CKD-EPI equation was developed because of the limitations of the MDRD and CG equations. It is a recognized calculation method that provides more accurate and precise results than the MDRD equation, particularly for estimating GFR in individuals with GFR greater than 60 mL/min/1.73m^2 (16,19). The sensitivity of

the CKD-EPI equation for detecting a glomerular filtration rate of less than 60 mL/min/1.73 m² is 91% and the specificity is 87%; the sensitivity of the MDRD equation is 95% and the specificity is 82% (20). The GFR of our entire study patient group was greater than 60 mL/min, and the results closest to 24-hour urine creatinine clearance were found with the CKD-EPI equation. The only study in the literature with a similar patient group states that the e-GFR formulation that contains the results closest to the patients' expected renal clearance is the CKD-EPI equation (21). This was said by the authors to be more appropriate because the CKD-EPI formula relatively accounts for differences in creatinine production due to changes in muscle mass in CVID patients who often suffer from gastrointestinal disease and protein malnutrition and does not overestimate the GFR relative to weight in individuals with low muscle mass. Another feature that makes the CKD-EPI formula more useful is that it accounts for variations due to extrarenal creatinine clearance and tubular secretion and is designed for use with standard serum creatinine concentrations. For all these reasons, there is a strong argument not to use the CG formula (21). The main limitations of our study are that methods such as inulin clearance or scintigraphic methods, which are considered the gold standard in calculating renal function, were not used and the entire patient group consisted of patients with GFR greater than 60 mL/min and were of the same ethnicity.

In summary, we found that all creatinine-based formulas used in clinical practice for e-GFR measurement correlate with 24-hour urine creatinine clearance in patients with CVID. In addition, we have shown that e-GFR calculated with the formula CKD-EPI is more closely related to 24-hour urine creatinine clearance. Therefore, we believe that e-GFR measurement calculated using CKD-EPI is more useful for nephrological follow-up of patients with CVID.

The limited number of patients in our study group was one of the most important limitations. Another significant limitation was that only six patients had 24-hour urinary protein excretion above the physiological limit, so statistics were impossible. The last limitation of our study was that the history of acute kidney injury was not known in the patients included in the study.

Declarations

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