Underestimation of Impaired Kidney Function with Serum Creatinine

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Abstract Serum creatinine (SCr) levels are frequently used as a screening test to assess impaired renal function; however, patients can have significantly decreased glomerular filtration rate (GFR) with normal SCr values and making the recognition of kidney dysfunction more difficult. Hence, this study was designed to determine the extent of misclassification of the patients who have significantly reduced GFR as calculated by reexpressed four variable modification of diet in renal disease (MDRD) equation but, normal range of SCr. The study included 1040 in and out patients referred by physicians for serum creatinine measurement. When an exclusion criterion was applied 928 patients were qualified for the study. SCr was measured in 928 patients by a Roche kinetic compensated Jaffe's assay. GFR was calculated using reexpressed four variable MDRD study equation. Of the 928 patients 270 (29.1%) had renal dysfunction on the basis of eGFR (<60 ml/min/1.73 m²). However, with SCr only 162 (17.5%) patients had abnormal renal function (>1.5 mg/dl) and SCr values misrepresented (108) 11.6% patients with impaired kidney function. In addition, more females, about 15% were failed to detect by SCr method in contrast to males of 9%. This study documented that, a large proportion of patients with impaired renal function are not diagnosed if clinicians rely solely on normal SCr as evidence of normal renal function. Inclusion of eGFR calculated by re-expressed 4 variable MDRD equation may facilitates the early identification and intervention of patients with renal impairment.

Keywords Serum creatinine · Renal failure · eGFR · MDRD · Jaffe's assay

Introduction

Kidney function is assessed in clinical practice to screen for kidney disease, to adapt dosage of medications for renal clearance, and to follow the evolution of known kidney disease. It is important to assess kidney function as accurately as possible, because renal disease has different clinical presentations and patients are often asymptomatic [1].

Glomerular filtration rate (GFR) is a useful index to assess the kidney function [2]. GFR can be measured directly by clearance studies of exogenous markers, such as iothexol, iothalamate, and Cr51-EDTA. However, these procedures are costly, time consuming and are not suited to the routine detection of kidney disease. Even to measure the clearance of endogenous substances, such as urea and creatinine, requires both serum and an accurately timed urine collection. So efforts have been directed at more convenient "urine-free" estimates of GFR [3]. Although not routinely reported by laboratories, prediction equations such as Cockcroft and Gault (CG) [4] or modification of diet in renal disease (MDRD) [5] equations provides a rapid method of assessing GFR from serum creatinine (SCr) and routine data.

Currently, SCr is the most widely used method of assessing renal function in clinical practice; however, SCr levels remain within the normal range even when renal function is significantly impaired [6]. Despite the fact that SCr alone may not be well correlated with true GFR [7], many clinicians continue to rely solely on SCr as a measure of renal function and interpret a normal SCr as

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indicating normal renal function. However, many patients with impaired kidney function are failing to notice when relying on SCr alone [8]. But how many patients with impaired kidney function are missed when relying on SCr alone? Do women have the same risk of misclassification as men?

To counter this, the present study was designed to determine the magnitude of misrepresentation of patients who had significantly abnormal GFR values as calculated but SCr is within the normal range, which may make the recognition of renal dysfunction more difficult.

Materials and Methods

Patients

The study included 1040 out patients and inpatients of PSG Hospitals, Coimbatore, India. Patients with age <20 years, were excluded from the study as MDRD equation is not applicable. Renal transplant patients and who were received dialysis also excluded from the study. After applying, an exclusion criteria only nine hundred and twenty eight (928) patients were qualified for the study. No specific inclusion criteria were used. Retrospective SCr concentrations were obtained from the laboratory database. Age, sex, weight, height, and other relevant particulars were also obtained from the database. The clinical indications for ordering SCr is available; however, the racial background of the patients was not available. All the data was maintained anonymously. Ethical clearance for this study was obtained from Institutional Human Ethics Committee.

Laboratory Data

SCr was estimated by kinetic compensated Jaffe assay on an Integra 400 analyser (cat. no. 20764345, Roche Diagnostics Ltd, UK). This is a rate assay without deproteinization, measuring the increase in absorbance at 512 nm between 55 and 70 s after initiation of the reaction. Absorbance blanking at 583 nm is used. The assay is calibrated with a lyophilized human serum calibrator (C.f.a.s., Roche Diagnostics Ltd) in which the creatinine concentration (normally ~3.61 mg/dl) is traceable to an Isotope Dilution Mass Spectrometry (IDMS) determination. Water is used as the zero standard. To compensate for non-creatinine chromogens, values are automatically corrected by subtracting 0.2 mg/dl. Twice daily quality control checks were done. The between-day coefficients of variation were 3.2 and 2.7% at concentrations of 1.73 and 5.24 mg/dl, respectively. No significant interference with hemoglobin up to 800 mg/dl and with bilirubin 5 mg/dl.

Calculations

GFR was calculated using the reexpressed four variable MDRD formula [9] in which the constant 186 is replaced by 175. $GFR = 175 \times \text{standardized SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times 0.742$ (if female); (standardized SCr—Recalibration of Scr methods to be traceable to the reference method for creatinine which is IDMS). Abnormal renal function was defined as calculated GFR is <60 ml/min/1.73 m² and Scr >1.4 mg/dl.

Statistical Analysis

Descriptive statistics are reported as medians and ranges. Student's "t" test was used to assess the significance. A *P* value of <0.05 was considered statistically significant. Correlations were calculated using the Pearson's correlation test (*r*). Independent associations between one dependent variable and more than two independent variables were assessed using linear regression analysis. Data were analyzed using the statistical software, SPSS-Version 11.5.

Results

The population consisted of 378 (40.7%) women and 550 men (59.3%). Median age was 49 years (range 20–85 years), median weight 52 kg (range 23–115 kg), and median SCr concentration 1.04 mg/dl (range 0.40–6.32 mg/dl). Estimated median GFR with MDRD 52.3 ml/min/1.73 m² (range 6.4–152.3 ml/min/1.73 m²).

Of the 928 patients, 270 (29.1%) had abnormal GFR calculated by abbreviated MDRD equation, while 162

Table 1 Prevalence of abnormal eGFR and SCr values by age and sex in study group patients

	Total	eGFR (<60 ml/min/ 1.73 m ²)	SCr (>1.3 mg/dl)	Difference
Subjects	928 (100)	270 (29.1)	162 (17.5)	108 (11.6)
Males	550 (59.3)	151 (27.4)	100 (18.2)	51 (9.0)
Females	378 (40.7)	119 (31.5)	62 (16.4)	57 (15.0)
Age (years)				
20–29	106 (11.4)	17 (16.0)	11 (10.3)	6 (5.6)
30–39	139 (15.0)	23 (16.5)	16 (11.5)	7 (5.0)
40–49	192 (20.7)	47(24.4)	31 (16.1)	16 (8.3)
50–59	223 (24.0)	58 (26.0)	37 (16.5)	21 (9.4)
60–69	155 (16.7)	67 (43.2)	39 (25.1)	28 (18.0)
>70	113 (12.2)	58 (51.3)	28 (24.7)	30 (26.5)

Data are number (%) of patients

(17.5%) had overtly abnormal renal function with Scr values. Interestingly, 108 (11.6%) patients had normal Scr levels, but their GFR was <60 ml/min/1.73 m² (covert renal dysfunction). More female patients, about 15% were

misrepresented when compared to male patients of 9% with SCr method. The discordance between SCr and MDRD calculated GFR values were most pronounced in the older age groups with 8.3% of 40–49 years, 9.4% of

Table 2 Patient classification according to stages of CKD using abbreviated MDRD study equation

	Total	Stages of CKD using abbreviated MDRD equation				
		I	II	III	IV	V
Subjects	928 (100)	195 (21.0)	463 (49.8)	145 (15.6)	51 (5.5)	74 (7.9)
Males	550 (59.3)	115 (20.9)	266 (48.3)	88 (16.0)	35 (5.8)	46 (8.3)
Females	378 (40.7)	80 (17.4)	197 (50.2)	57 (19.5)	16 (4.2)	28 (8.4)

Data are number (%) of patients

MDRD modification of diet in renal disease

Fig. 1 Relationship of SCr concentration to GFR with the abbreviated MDRD equation among male (a) and female (b) patients

50–59 years, 18% of 60–69 years and 26.5% over the age of 70 years or older with normal SCr having abnormal MDRD GFR values (Table 1).

Patients were classified according to the five stages of chronic kidney disease (CKD) as defined by the American National Kidney Foundation [2] from values calculated with the re-expressed MDRD equation. Of the 928 patients 195 (21.0%), 463 (49.8%), 145 (15.6%), 51 (5.5%) and 74 (7.9%) were in stages I, II, III, IV and V, respectively (Table 2). More patients (49.8%) were at stage II with the GFR between 89 and 60 ml/min. Figure 1a and b shows the relationship between SCr and eGFR calculated using abbreviated MDRD equation. There is a hyperbolic inverse relationship between SCr and eGFR and the correlation coefficient being -0.44 which is statistically significant.

Discussion

Recently there has been emphasis on appropriate treatment and timely referral of patients with renal disease [10]. SCr concentration is the most widely used method of assessing renal function; however, in the present study SCr concentration method misplaced (108) 11.6% patients with impaired function. Our study is in harmony with Duncan et al. [8] study reported that (13.9%) patients had misplaced with SCr concentration method. Yet another Indian study also forwarded similar results [11]. For this study, we chose a cut-off for abnormal renal function of <60 ml/min to reduce the likelihood of elderly patients being erroneously classified as having abnormal renal function. It has been suggested that renal function decreases over time as a part the normal ageing process [6]. In this study also, as subsequent to 40 years of age there is a gradual decline in GFR. Furthermore, the age related GFR reduction in males is superior over females with the ratio of 1:0.65. However, a major short coming of the study is lack of “gold standard” for measurement of GFR; however, the problem is ameliorated by using more appropriate revised MDRD equation with standardized creatinine assay.

There have been no randomised controlled trials (RCTs) comparing the effect of SCr concentration versus other measures of kidney function on relevant clinical outcomes, such as detection or prevention of CKD, prevention of cardiovascular disease (CVD) or reduction in medication-related adverse events. Iseki et al. [12] group reported that for each 0.2 mg/dl (18 μ mol/l) rise in SCr above the level, i.e., >1.4 mg/dl in men and >1.2 mg/dl in women, the risk of end stage renal disease (ESRD) is increased by 5.31% in men and 3.92% in women. Consequently, SCr concentration method is usually considered as inadequate for detecting mild-to-moderate kidney failure, such that patients may lose up to 50% or more of their kidney

function before the SCr value rises above the upper limit, depending on how close a patient's baseline SCr is to the upper reference limit [7, 13]. The critical SCr concentration range over which CKD patients are often misclassified as having normal renal function is in the general vicinity of 0.9 mg/dl (80–120 μ mol/l) [13]. Moreover, SCr is affected by many factors other than the level of GFR such as age, gender, race, body size, diet, certain drugs and laboratory calibration bias (of the order of 0.2 mg/dl) [14]. So far, no SCr cut-off points have been developed, which effectively identify patients with CKD with acceptable sensitivity and specificity.

Increasing use of eGFR has re-focused the attention of the scientific community on the shortcomings of SCr methodology. GFR estimates appear to provide substantial improvements over the measurement of SCr alone in the clinical assessment of kidney function [15]. Several glomerular filtration rate (GFR) prediction equations have been shown to generate sufficiently precise, unbiased and accurate estimates of GFR (eGFR) to be clinically useful for evaluating kidney function in a broad range of clinical settings. Among 46 different predicted equations the most commonly used is a CG and MDRD equation. Current evidence demonstrated that revised 4 variable MDRD study equation is superior over CG equation [16]; as CG equation having several practical limitations [5]. While, extensive evaluation of the MDRD Study equation showed good performance in populations with lower levels of GFR but variable performance in those with higher levels [17]. Variability among clinical laboratories in calibration of SCr assays [18] introduces error in GFR estimates, especially at high levels of GFR [19]. Thus, the National Kidney Disease Education Program (NKDEP) has initiated a creatinine standardization program to improve and normalize SCr results used in estimating equations [14].

For this purpose, in this study the constant factor in revised four variable MDRD equation has been changed from 186 to 175 for creatinine methods that have been calibrated to be traceable to a reference method based on IDMS [20]. It requires the use of revised MDRD equation with a 6% change in the calculation factor from 186 to 175 to ameliorate the bias between methods and laboratories [9]. It was subsequently suggested by the UK National External Quality Assessment Service (UKNEQAS) that slope and intercept adjusters for the creatinine methods could be used to approximate non-IDMS traceable creatinine results to an IDMS standardized method [21].

Currently, international recommendations also suggest that measurement of SCr should be supplemented with an estimate of the GFR and the revised MDRD equation [13] is generally thought to be the least biased and most accurate method of achieving this [22]. With, the ease of use of appropriate calibrator materials from NIST (SRM 967) and

trueness control materials from the College of American Pathologists (LN24 Linearity Survey), clinical laboratories can establish and maintain standardized SCr assays (should become traceable to a reference method based on IDMS) and use reexpressed four variable MDRD equation, to report GFR estimates.

In conclusion, this study demonstrates a large proportion of patients with impaired renal function were not diagnosed if clinicians rely solely on normal SCr as evidence of normal renal function. Estimated GFR is potentially an excellent method of detecting and monitoring renal failure, as it is quick, cheap and simple. Thus, inclusion of reexpressed four variable MDRD study equation with the standardized SCr assay, clinical laboratories can report more accurate GFR estimates which facilitates the identification of patients with kidney disease at a time sufficient to ensure proactive care to delay progression of further damage.

Conflict of interest None.

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