ORIGINAL ARTICLE

Estimation of Glomerular Filtration Rate Using Inverse of Serum Creatinine and Pulse × Mass Index - An Underestimated Tool

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ABSTRACT

Objective: In western world MDRD and Cockcroft & Gault equations (CG) are widely used for GFR estimation. Pulse×Mass Index (PMI) is known cardiovascular risk factor. In year 2005 Enrique J,Sanchez-Delgado suggested the calculation of GFR by using 1/S.Cr and PMI. He proposed that 1/S.Cr/PMI will not only calculate GFR but also predict cardiovascular mortality. The present study was undertaken to compare accuracy of GFR calculated by 1/S.Cr/PMI (GFR-PMI) with MDRD and CG equations.
Design: Prospective study
Place and duration of study: Nephrology Department, Sheikh Zayed Hospital, Lahore. Three months.
Patients and Methods: The study included 112 subjects between 15 to 70 years of age. Body weight and height and resting heart rate were measured. Serum sample was taken for analysis of creatinine, albumin, and urea nitrogen. Patients were divided into different groups based upon age, sex, albumin and serum creatinine level and GFR-PMI was compared with CG and MDRD equations using 2 sample t-tests.
Results: CG equation and GFR-PMI showed same results in all groups except when age was >60 years. When GFR-PMI was compared with MDRD-4 variable equation, similar results were found only at S.Cr less than 1 mg/dl and age less than 40 years.
Conclusion: The results determined both by GFR-PMI and CG equation were found to be similar. Although GFR-PMI equation has the edge that it not only estimates GFR but also predicts the cardiovascular mortality risk. As the MDRD equation has no proven validity in Pakistani population, its results are different from GFR-PMI and CG equations

Keywords: GFR, Pulse Mass Index, MDRD, Cockcroft and Gault

INTRODUCTION

In clinical practice inverse of Serum Creatinine (1/S.Cr) alone or creatinine clearance has been widely used for estimation of Glomerular Filtration Rate (GFR), which are unreliable and not widely accepted (1). In adults both European Best Practice Guide lines (EBPG) and National Kidney Foundation Dialysis Outcome Quality Initiative (K/DOQI) recommend the use of prediction equations to estimate the GFR from serum creatinine (S.Cr) (2, 3). In western world MDRD equation (Modification of Diet in Renal Disease) (4, 5) and CG equation (6) (Cockcroft and Gault equation) are widely used. However their applicability in South Asian population especially in Pakistan has never been validated (7).

In year 2000, Pulse × Mass Index (PMI) gained popularity as cardiovascular risk factor and the relation of 3:1 (72:24) between heart rate and body mass index was observed. So Pulse × Mass Index was calculated as Resting Heart Rate (RHR) × Body Mass Index (BMI) divided by 1730 (or 72×24). The PMI value of 0.7-1.0 was considered ideal (11). As we know the increase of 1 S.D in resting heart rate (10.1 bpm) plus an increase of 1 S.D in BMI (2.7 kg/m^2), they had a combined mortality of 1.28 (28%) in excess (12). Likewise the increase in PMI to value of 1.9 there is almost doubling of mortality (13).

Later in Jan. 2005 Prof. Enrique J. Sánchez-Delgado suggested the calculation of estimated GFR (eGFR) by using 1/S.Cr and PMI. He proposed that 1/S.Cr/PMI will not only calculate eGFR but also predict cardiovascular mortality risk (14).

As limited data was available on this proposition, the present study was undertaken to compare accuracy of eGFR calculated by

1/S.Cr/PMI (GFR-PMI) with MDRD and CG equations.

METHODS

This propective study consisted of 112 subjects with or without kidney disease. Patients were randomly selected from outpatient clinic of the nephrology department in 2006 (June – August) of Sheikh Zayed Hospital, National Institute of Kidney Disease, Lahore, Pakistan, where patients came directly or were referred by outpatient clinic of internal medicine and general practitioners for evaluation of renal status. All patients between 15 to 70 years presented first time were included in the study. Patients were excluded from study if (1) they had incomplete data (2) they were undergoing some form of dialysis therapy at or around the time of GFR measurement (3) they were requiring dialysis (4) they had unstable renal function, stability of renal function was defined as 15% or less change in S.Cr value with in 3 days of measurement of GFR (5) pregnancy and lactating mothers. The study was approved by ethical review committee at Sheikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore.

Age, gender, body weight and height were measured to calculate body surface area and body mass index (BMI). Serum sample were taken for analysis of creatinine, urea nitrogen. Resting heart rate (RHR) was noted after 5 minutes of rest.

Creatinine, urea, albumin were assayed in serum using an auto analyzer (Dade Dimension) by the department of biochemistry, Shaikh Zayed hospital Lahore.

GFR was estimated using the formulae identified in table (i). The MDRD equation containing four variables, described in abstract by levey at al [4], was used. The Cockcroft and Gault formula (CG) was used and adjusted for body surface area unless indicated. Measured GFR using Pulse ×Mass index (GFR-PMI) was calculated. As all subjects were of Pakistani origin (South Asian) ethnically was not a variable in this study.

Table 1: Predictions equations from MDRD study, by CG and GFR-PMI to calculate the GFR(ml/min)
MDRD (four variables) 186.3 × $SCr^{-1.154}$9md/dl)× $age^{-0.203}$(years)× (0.742, if female) × (1.212 black)
CG equation {[(140 - age) × weight]/[72×SCr(mg/dl)]} × (0.85 if female)
GFR-PMI BMI = body weight (kg) / height(m^2) PMI = Resting heart rate (RHR) × BMI GFR-PMI = 1 / S.Cr / PMI

Data are presented as mean± SD unless specified otherwise. Comparison among multiple groups was performed by using 2 sample t-tests. SPSS, Version 11.5 (SPSS Inc, Chicago, IL) was used for all statistical analysis and 2- tailed P value more than 0.05 is considered statistically similar groups.

RESULTS

Body surface area was calculated by Dubios formula.

On comparison of means of GFR calculated by different formulas, statistically no difference found (P value >0.05) as shown in table (iii).

When we compared the calculation of glomerular filtration rate by inclusion of Pulse × Body Mass Index (GFR-PMI) with all other equations in different age groups, no difference found up to 40 years of age. In age group 41-60 years only GFR-PMI and CG formula showed similar results. However in patients more than 60 years GFR-PMI does not correlate with any equation (table 3).

Table 2: Lists demographic characters of study group.

Table (ii). Demographic Characteristics of Study Population	
Sample size Age (years)	112 46.6 ±14.6
Male	53%
female	47%
Weight (kg)	67.8 ±13.9
Height (cm)	160.5 ±10.4
Body surface area (m^2)	1.7± 0.77
S.Cr (mg/dl) BUN (mg/dl)	2.1 ± 1.5 32.4 ± 21.7

When S.Cr was divided into different groups, GFR-PMI and CG equation similar results at all levels of S.Cr. In contrast when GFR-PMI was compared with MDRD equation, similar results were found only at S.Cr less than 1 mg/dl (table iii).

As a whole GFR-PMI and CG equation showed similar results, whereas MDRD-4 variable equation and GFR-PMI showed similar results at ages less than 40 years and S.Cr with in normal range.

Table 3: Renal function characteristics of study population

		GFR-PMI & CG(ml/min)	P value	GFR-PMI & MDRD (ml/min)	P value
Mean GFR (ml/min)		53.5+28.7 52.6+33.5	0.74	52.6+33.5 48.5+27.6	0.34
Age (years)	<40 41-60 >60	66.4+41.2 69.9+42.6 47.2+28.7 51.8+33.5 42.1+33.4 30.6+17.1	0.54 0.16 0.002	66.4+41.2 61.2+39 47.2+28.7 43.2+27.2 42.1+33.4 33.4+21	0.19 0.02 0.002
S.Cr (mg/dl)	<1 1-2 >2-3 >3	99.5+28.8 104.5+26.1 54.4+17.4 56.3+24.5 31+7.4 32+8.1 24.8+8.1 22.1+6.3	0.535 0.734 0.594 0.428	99.5+28.8 96.4+18.5 54.4+17.4 48.4+14 31+7.4 26.2+6.3 24.8+8.1 17+4.1	0.538 <0.05 <0.05 <0.05

DISCUSSION

For more than four decades clinicians and investigators recognized the need for rapid, accurate estimation of GFR, but it was not until 1976 when Cockcroft and Gault published their formula that clinicians found a fast and easy method to assess renal function (creatinine clearance) in adults (6). The advantage of this formula was that it incorporated variables other than serum creatinine known to affect GFR: age, gender, and size of the subject. The Cockcroft-Gault formula was developed from a primarily male inpatient population using Ccr as the reference method (6). The original model incorporated age

and weight but not race. The results were not normalized to body surface area (BSA) and were reported in ml/min. To extend the applicability of the formula to females, an arbitrary 85% adjustment was chosen. Nevertheless, recall that this method estimates Ccr, which is known to overestimate GFR due to the tubular secretion of creatinine (16, 17), particularly in the presence of proteinuria.

Its popularity was challenged by the 1999 publication of the more complex mathematical equations derived from a secondary analysis of data obtained from the Modification of Diet in Renal Disease (MDRD) study (4). An abbreviated form of the MDRD-derived equations was recommended and endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) to estimate GFR and classify patients into different “stages” of chronic kidney disease (CKD) (5,15).

The base population for these equations was outpatients with established CKD and a mean GFR, by 125I-iothalamate renal clearance, of 40 ml/min adjusted to a standard BSA of 1.73 m2. The determinants of BSA are pre-packaged in the equation and therefore not required.

Regarding the subjects of different race and ethnic origin, the current MDRD equation incorporates African- American race as a factor to account for the different creatinine metabolism in this population; hence its expected good performance when applied to an African-American population (18).

Estimation equations have also been tested in other populations with different degrees of performances (7, 21). Correction factors may be needed for other ethnic populations (*e.g.*, Asians). Two major concerns about the use of these formulas in Pakistani population are their use in detecting mild to moderate renal impairment or even in normal individuals and effect of racial difference on the results.

Many studies proved heart rate variability and obesity as major cardiovascular risk factor (22). Years ago the apparent relation of 3:1 (72:24) between resting heart rate and body mass index was observed. Based on these observations Pulse ×Mass index was developed, which reflected overweight, stress, sympathetic stimulation, oxidative metabolic rate, hyperinsulinemia, inflammatory activity, physical fitness and side effects of drugs like water retention, potent vasodilatation and tachycardia (23). Now a days Pulse ×Mass index is widely accepted predictor of both cardiovascular mortality. Pulse ×Mass index (PMI) is calculated as follows; Body Mass Index (BMI) multiplied by resting heart rate (RHR) and divided by 1730 (24×72). The PMI considers the height in meters (BMI=kg/m^2) and the RHR (bpm). The normal value of BMI (average 24) is similar in males and females. The normal value of PMI of 0.7-1.0 would be ideal (11). With the Pulse ×Mass index value of 1.9, there is almost doubling of mortality (13).

Later in 2005 Prof. Enrique J. Sánchez-Delgado gave the idea of estimation of GFR with inclusion of Pulse ×Mass index. He proposed to investigate usefulness and accuracy of inverse of serum Creatinine (1/S.Cr) divided by PMI (1/S.Cr/PMI). For example, for a normal S.Cr of 1.1 mg/dl and a normal PMI of 1.0, the eGFR would be 0.9 or 90% of normal. For a S.Cr of 1.5, it would be 0.66. If the PMI was 1.3, which is common in patients with a high global cardiovascular risk according to the Framingham Risk Equation, the eGFR would be 0.7 (70 % of normal) in the case of 1.1 mg S.Cr or 0.51 (less than 60 % of normal) for a S.Cr of 1.5 mg. The higher the PMI, the lower the expected eGFR for a giver value of S.Cr (14).

In this study when we compared the CG equation and MDRD equation with GFR-PMI, CG equation and GFR-PMI showed similar results at all levels of serum creatinine and different age groups except when age was more than 60 years but the number of individuals in this age group was small (no.) So wherever we use CG equation, GFR-PMI can be used reliably.

However MDRD equation didn’t show similar results as a whole. Because the MDRD equation was not originally designed for this population, that’s why the results were different.

Further studies with larger population size needed both at indoor and outdoor patients to verify the results in different ethnic groups. Secondly we have to verify the original CG and MDRD equation in our population by using gold standard Inulin or radiolabelled Iothalamate clearances.

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