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Estimating Glomerular Filtration Rate in Overweight and Obese Malaysian Subjects

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Abstract

Background and Aims: Overweight and obesity are significant risk factors for chronic kidney disease (CKD). Glomerular filtration rate (GFR) is the best index of renal function. We evaluated the accuracy of the Cockroft-Gault, MDRD and modified MDRD formulae in predicting GFR in overweight and obese subjects and also determined the relationship between Body Mass Index (BMI), weight and GFR.

Methods: Healthy volunteers with BMI ≥23kg/m² were recruited and subjected to blood and urine investigations, renal ultrasonography and ^{99m}Tc-DTPA renal scan. The correlation, accuracy and precision of the eGFR derived from each formula were compared with reference GFR as determined by ^{99m}Tc-DTPA.

Results: A total of 101 subjects with a median weight of 74.0kg (68.0-84.7) and median BMI of 29.6 kg/m² (27.2-33.2) were recruited. Their mean GFR ^{99m}Tc-DTPA was 120.3± 24.5ml/mm/1.73m². Although the eGFRs derived from all formulae correlated with GFR ^{99m}Tc-DTPA, only those derived from the MDRD and modified MDRD had small biases and better precision in estimating GFR. While GFR significantly correlated with the subjects' weight (p=0.036), it didn't with their BMI (p=0.302).

Conclusions: The MDRD-based formulae were better in estimating GFR in overweight and obese Malaysian subjects. GFR correlated with subjects' weight rather than BMI.

Keywords: eGFR, Overweight, Obese, CKD, Cockcroft-Gault, MDRD

Introduction

Chronic kidney disease (CKD) is a universal public health problem, with increasing prevalence, poor outcomes and high costs. Hence, The Kidney Disease Outcomes Quality Initiative (K/DOQI) was developed to provide guidelines to physicians for monitoring their progress (1). These guidelines have established a five-stage classification of patients with CKD based on the level of the glomerular filtration rate (GFR). Therefore, an accurate estimation of kidney function is important in the management of these patients.

Glomerular filtration rate (GFR) provides an excellent measure of the filtering capacity of the kidneys

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and is considered to be the best index of renal function (2, 3). Inulin clearance has long been regarded as the gold standard for measuring GFR, but the procedure is costly, time consuming and difficult to perform (3). Creatinine has many advantages as a filtration marker and its measurement is cost effective (3). Since the early 1970s, several formulae for estimating creatinine clearance and GFR from serum creatinine have been developed. Although there have been many studies validating each formula, selecting the best in a given patient remains a topic of debate (4). Additionally, measurement of creatinine clearance by using timed urine collection e.g. 24-hour urine collection, does not provide a more accurate estimate of GFR than do prediction equations (4, 5).

The Cockcroft-Gault (CG) formula remains the most widely used method for estimating GFR in clinical practice. A more recently developed formula is that of the Modification of Diet in Renal Disease (MDRD 1) study in the U.S (6). It automatically estimates body surface area (BSA)-indexed GFR in units of ml/min/1.73m^2 as opposed to the results with the CG formula. In 2002, Levey and coworkers proposed a modified MDRD equation (MDRD 2) using less variables and this correlated well with MDRD 1 (7).

The MDRD 1 and MDRD 2 formulae have been evaluated in various subgroups such as African Americans with CKD, Caucasian patients with kidney disease and normal serum creatinine, type 1 diabetics without nephropathy, type 2 diabetics with and without nephropathy, newly diagnosed type 2 diabetics, elderly patients with CKD, patients with chronic heart failure, potential renal transplant donors and recipients as well as in normal subjects (8-16). Whether the MDRD 1 and MDRD 2 formulae are applicable to other populations require further evaluation.

Serum creatinine is affected by many factors such as age, gender, race, muscle mass, protein intake, nutritional status, hydration status, drugs and renal disease (2, 3). On the other hand, measurement of creatinine clearance by 24-hour urine collection may overestimate GFR since creatinine is secreted as well as filtered by the renal tubules (3). The delay for the collection and analysis and the difficulties in ensuring complete urine collection are other disadvantages of this approach to GFR estimation. Various radioisotopic filtration markers for estimating GFR have also been studied (17, 18). Perrone et al concluded that the urinary clearance of exogenous radioactive markers such as 125I-iothalamate and ^{99m}Tc-DTPA also provided accurate measures of GFR (18). However, these methods are invasive, time consuming, expensive, not readily available and expose subjects to radiation.

Obesity is a common, chronic and complex metabolic disorder with multifactorial aetiologies occuring throughout the world. The Asia Pacific Guidelines define overweight as a body mass index (BMI) between 23.0-24.9 kg/m^2 and obese as a BMI over 25.0 kg/m^2 (19). The rates of obesity in developing countries have tripled over the past 20 years (20). Several studies have demonstrated obesity as a risk factor for CKD and end stage renal disease (ESRD) (21, 22).

Using serum creatinine to calculate GFR can be misleading as obese and overweight individuals can have disproportionately lower serum creatinine compared to the body weight as fat does not secrete creatinine. The application of these formulae to this cohort is again limited by the lack of validation. Hence, this study was conducted to evaluate the accuracy of these formulae in these subjects in our country.

Our primary objective was to evaluate the accuracy of the estimated GFR (eGFR) derived from the various formulae compared to the reference GFR as measured by the ^{99m}Tc-DTPA radioisotope scan in overweight and obese Malaysian subjects. These formulae included Cockcroft-Gault corrected for the

body surface area BSA (CGBSA), original MDRD (MDRD 1) and modified MDRD (MDRD 2). Our secondary objective was to study the association between true GFR with subjects' weights and BMI.

Materials and Methods

This was a cross-sectional, single centre study involving overweight and obese Malaysian subjects. The study protocol was approved by the Medical Research and Ethics Committee of the Faculty of Medicine, Universiti Kebangsaan Malaysia (Research Grant FF-160-2006). Healthy volunteers aged 18-55 years with BMI > 23 kg/m^2 were eligible for this study. Subjects with the following conditions were excluded: acute and chronic medical illnesses, history of hospital admission within one month prior to the study, history of taking traditional medications and/or non-steroidal anti-inflammatory drugs (NSAIDs) and/or angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) within one month prior to the study, pregnant women, lactating mothers and those with eGFR of ≤ 30ml/min on baseline investigations.

The study population was selected from volunteers who fulfilled the study criteria and gave informed consent. A full history and physical examination were performed. Subjects with underlying diseases, on medications or taking herbal or food supplements were excluded. Selected subjects were scheduled for two visits. Prior to the first visit, subjects were advised to fast and to avoid smoking and drinking alcohol or caffeinated beverages from 12 midnight. At the first visit, a full history and physical examination were performed and baseline fasting blood and urine investigations were done. Their heights were recorded they were weighed in a standing position with a digital weighing scale (SECA 954, Germany) five minutes after emptying their bladder. The blood pressure (BP) was measured with an appropriately-sized cuff on the right upper arm using a mercury sphygmomanometer after resting in a sitting position for at least five minutes.

At the second visit, a repeat measure of the subjects' height, weight, BP and renal profile was performed and urine samples for microscopic examination and microalbuminuria-creatinine ratio were collected. Serum creatinine was measured using the latest generation of the Jaffé method. On the same day, baseline ultrasound imaging of the kidneys and ^{99m}Tc-DTPA nuclear scan were conducted consecutively. The ^{99m}Tc-DTPA nuclear scans were performed following a standard procedure and the GFR measurements were standardized to BSA of 1.73m^2. Patients would be referred to the appropriate subspecialty clinic should any abnormality be detected.

Formulae:

1. Cockcroft & Gault formula (CG) (23):

a) Creatinine clearance for male subjects =

$$\frac{(140\text{-age}) \times \text{body weight (kg)} \times 1.2}{\text{Serum Creatinine (mmol/L)}}$$

b) Creatinine clearance for female subjects =

$$\frac{(140\text{-age}) \times \text{body weight (kg)} \times 1.2 \times 0.85}{\text{Serum Creatinine (mmol/L)}}$$

2. Cockcroft & Gault formula corrected for body surface area (CGBSA) (16):

Creatinine clearance x 1.73m^2/BSA

3. MDRD formula (MDRD 1) (6):

eGFR (mL/min/1.73m^2) = 170 x creatinine (*mg/dL)$^{-0.999}$ x age (years)$^{-0.176}$ x urea (mg/dL)$^{-0.170}$ x albumin (g/dL)$^{+0.318}$ x constant.

The constant is 1 for a male, 0.762 if female and 1.80 for African American.

4. Modified MDRD formula (MDRD 2) (7):

eGFR (mL/min/1.73m^2) = 1.86 x creatinine (*mg/dL) $^{-1.154}$ x age (years) $^{-0.203}$ x constant.

The constant is 1 for a male, 0.742 if female and 1.21 for African American.

5. BMI calculation:

BMI = weight (kg)/ height (m^2)

Statistics

Based on the approximate prevalence of impaired kidney function in an overweight and obese population of 2.5%, it was calculated that 100 patients were needed for a power of study of 80% with a confidence interval of 95%. To provide a slight margin of error given the possibility of subject attrition, we targeted to recruit 130 subjects. The SPSS version 12.0 (SPSS Inc., Chicago, 1L) was used for statistical analysis. All normally distributed numerical data were expressed as mean ± SD (standard deviation). Non-normally distributed data were subjected to non-parametric tests and the median (interquartile range) was used. Correlation (r) between any two parameters was determined by the Pearson coefficient for normally distributed data and by the Spearman rho coefficient for non-normally distributed data.

The mean difference (ΛGFR) between estimated GFR (eGFR) and reference GFR using ^{99m}Tc-DTPA nuclear scan, was used to estimate the bias of the formulae (4). The wider the standard deviation (SD) of the mean difference leads to the lower the precision. The ΛGFR of each formula was then plotted against the average GFR obtained between the eGFR and measured GFR for each patient to give a further estimate of the agreement using Bland-Altman plot. Limits of agreement were calculated as mean difference ± 2SD of the difference. A p value < 0.05 was considered significant.

Results

From August 2006 to February 2007 a total of 180 volunteers were screened. Of these, only 130 subjects satisfied the study criteria. However, 29 dropped out for various reasons - three became pregnant prior to the DTPA scan, three moved elsewhere and 23 withdrew after the baseline blood investigations. Hence, only 101 subjects completed the study. Their baseline socio-demographic characteristics are as shown in Table 1. The subjects' median weight was 74.0 kg (68.0-84.7) and median BMI was 29.6 kg/m² (27.2-33.2). Although their mean BP was normal, seven subjects had a BP > 130/85 mmHg. The median fasting blood sugar (FBS) was 5.0 mmol/L (4.7-5.5) with 23 subjects having FBS > 5.6 mmol/L. The median urinary albumin creatinine ratio was 0.4 mg/mmol creatinine (NR 0.2-0.6) and three subjects had microalbuminuria. The mean GFR measured by ^{99m}Tc-DTPA in this cohort was 120.3± 24.5 ml/min/1.73m². There were 44 subjects with a GFR of ≥120ml ml/min/1.73m², 53 with 90-120 ml/min/1.73m² and four with 60-90 ml/min/1.73m².

Table 1. Baseline characteristics and demographic data

Age (years)*	28 (25-34)
Ethnicity (Malay/Chinese/Indian)	94/4/3
Gender (male/female)	31/70
Height (cm)	158.6±7.4
Weight (kg)*	74.0 (68.0-84.7)
Body Mass Index (kg/m²)*	29.6 (27.2-33.2)
Waist-Hip ratio (cm)	0.84±0.07
Systolic Blood Pressure (mmHg)	124.7±12.3
Diastolic Blood Pressure (mmHg)	71.4±9.0
Mean Arterial Pressure (mmHg)	91.3±10.7

Values are given in mean ± SD or *median (interquartile range)

We found that the eGFR from all the formulae correlated significantly with true GFR as measured by ^{99m}Tc-DTPA (Figure 1). However, the difference between the eGFR by CGBSA formula and the true GFR (Λ GFR) was 20.8 ± 35.1 ml/min/1.73m² and the 95% limits of agreement was between -42.2 to 97.3. These wide limits indicate that these differences were highly inaccurate (p=0.0001).

The difference between eGFR by the MDRD 1 formula and the true GFR (Λ GFR) was 2.2 ± 27.6 ml/min/1.73m² with the 95% limits of agreement

between -47.3 to 52.3. The 95% limits of agreement for the MDRD 2 formula were between -51.2 to 52.2. These narrow limits indicate that MDRD 1 and 2 equations were more accurate (p=0.43, p=0.65 respectively).

Although there was a positive correlation between GFR 99mTc-DTPA and BMI, this was not significant (p=0.302). In contrast, true GFR statistically correlated with the subjects' weights (p=0.036; Figure 2).

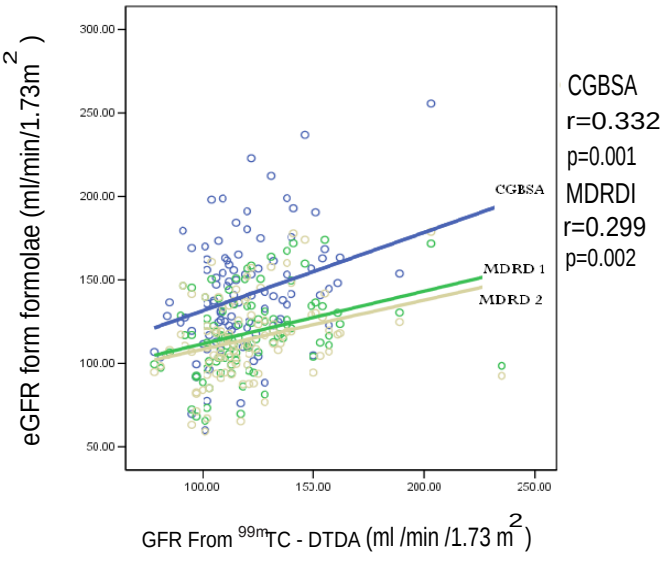

Figure 1. Correlation between various formulae with GFR from ^{99m}Tc-DTPA

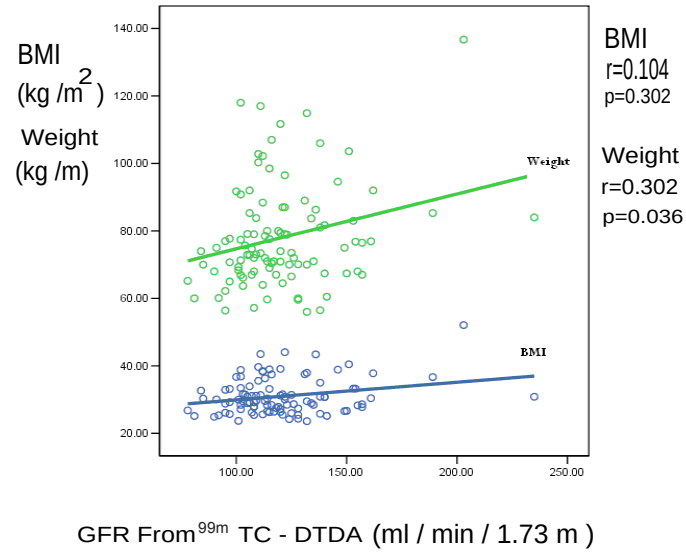

Figure 2. Correlation between GFR from ^{99m}Tc-DTPA with BMI and weight

Discussion

The rising incidence of CKD and the epidemic of overweight and obesity are major public health issues worldwide. Several epidemiological studies have confirmed that the latter two are significant but eminently modifiable risk factors for CKD (22, 23). In Malaysia, our two most recent 10-year consensus have also shown that the prevalence of overweight, obesity and diabetes have risen from 20%, 5% and 8% in 1996 to 29%, 14% and 12% respectively in 2006 (24). Hence early and accurate assessment of renal function in these subjects is very important.

Majority of the formulae for GFR estimation, including the CG and MDRD formulae, have been developed in study populations consisting predominantly of patients with renal insufficiency and reduced GFR (6, 24). Ideally, a formula should be developed from a population that includes many individuals who vary widely with regards to GFR, age, race, ethnicity, body composition, health status, risk factors for CKD and types of CKD. Although an equation developed in one population is generally adopted for use in other populations, validation in the latter should ideally be performed.

To our knowledge, this present study is the first to examine the accuracy of the eGFR formulae in overweight and obese Malaysian subjects compared to the measured GFR using the ^{99m}Tc-DTPA. The eGFR obtained with each formula showed significant correlation with the GFR ^{99m}Tc-DTPA. However, the eGFR by CGBSA may lead to overestimation of the GFR by 20 ml/min/1.73m² and introduced significant biases and lacked precision. Hence the CGBSA was not as accurate in our study cohort.

In contrast, the eGFR obtained by the MDRD 1 and MDRD 2 formulae showed greater accuracies and precisions when compared to the reference GFR

derived from ^{99m}Tc-DTPA. These two formulae underestimated the measured GFR only slightly - by 2 - 5 ml/min/1.73m² and their biases were not significant. Several previous studies on the performance of the CG and MDRD formulae in estimating GFR have reported conflicting results i.e. underestimation of eGFR in some and overestimation of eGFR in others (8-16).

Our results concur with many of the published reports in the literature. Vervoot (9), Poggio (10), Froissart (11), Rigalleau (13) and Lin (16) et al were amongst the investigators who showed that the CG formula persistently overestimated the measured GFR whereas the MDRD formula persistently underestimated the measured GFR in both healthy and CKD subjects. Poggio et al (10) and Froissart et al (11) have also reported that the MDRD formula was less accurate and less precise in patients without CKD. They reasoned that the MDRD formula, which was developed in a population with CKD, had limited application in a population without CKD. They also showed that the CGBSA was accurate but not precise in the population without CKD.

Lin et al studied the predictive performance of eGFR by the MDRD and CG equations in 100 healthy subjects by allocating 45 to ^{99m}Tc-DTPA and 55 to 125I-iothalamate (16). They reported that the eGFR by MDRD 1 and MDRD 2 in the ^{99m}Tc-DTPA group were more precise (i.e. highly correlated) but were also more biased and less accurate (i.e. significantly under-estimated measured GFR) than the CG formula.

Scientifically, the CG formula overestimates GFR because it was originally derived to predict creatinine clearance instead of GFR (24). Creatinine is secreted by the distal renal tubule as well as filtered by the glomerulus - thus the creatinine clearance exceeds the GFR (3). To overcome this error, adjustment of the formula to convert creatinine clearance to GFR prediction had been proposed (7, 9, 16). However, other researchers had verified that correcting the original CG formula to estimate GFR does not improve the predictive ability of the CG equation (16). The inclusion of weight as a measure of muscle mass in the C-G formula is another important erroneous factor. Since GFR is proportional to body weight in the CG formula, CG would overestimate GFR in patients who are overweight and obese even though most of the excessive body weight in obesity is derived from fat mass and not the lean mass that produces creatinine. The 20 ml/min/1.73m² overestimation of GFR that we found by the CGBSA in our overweight and obese subjects almost certainly reflects this influence of weight.

The MDRD based prediction equations have also been shown to underestimate GFR in various groups of patients, especially those with normal serum creatinine concentrations (8, 9-14, 16). This was probably because the equation was developed in a population with CKD in whom the relationship of serum creatinine to GFR differs from that in healthy people. The increase in serum creatinine levels caused by GFR reduction in patients with CKD may be attenuated by their muscle atrophy, reduced dietary protein intake and compensatory increase in tubular creatinine secretion. In general, the application of the CG formula may underestimate the prevalence of CKD, giving a false sense of security in this at-risk population. On the other hand, the use of the MDRD formula may increase health awareness especially in this at-risk obese population.

We found that GFR was positively correlated with our subjects' body weights. This finding is consistent with those of previous studies which also reported that GFR is elevated in obese patients (25, 26). The presence of glomerular hyperfiltration in the overweight and obese subjects does not indicate that they have 'super' kidneys. On the contrary, it represents glomerular hypertension which has been postulated to be the primary mechanism leading to subsequent structural changes in the kidney (27-29). This is but one of multiple aetiopathogenetic factors which has

been implicated in the predisposition of obesity to CKD and ESRD even in the absence of diabetes and hypertension (30, 31).

Our study population was biased towards young, obese, Malay females only and thus may not reflect the true composition of the Malaysian population. Therefore, the obtained findings may not be generalizable to the elderly, males, lean individuals and other ethnic groups. Nonetheless, our study does shed some light on the prevalence of overweight and obesity amongst our young Malaysian adults and should spur the Health Authorities to perform a more comprehensive study of this problem and its associated complications.

Conclusions

In conclusion, both the MDRD 1 and the MDRD 2 formulae have better accuracy and precision in estimating GFR in overweight and obese Malaysian subjects with normal serum creatinines. Nonetheless, the eGFR should not be taken in isolation but be considered in conjunction with other indicators of CKD such as microalbuminuria, proteinuria, haematuria and/or ultrasonographic abnormalities.

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Conflict of interest

There was no conflict of interest in all the authors in this study.

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