ORIGINAL ARTICLE

Predictive performance of 12 equations for estimating glomerular filtration rate in severely obese patients

Desempenho preditivo de 12 equações para estimativa da taxa de filtração glomerular em pacientes gravemente obesos

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ABSTRACT

Objective: Considering that the Cockcroft-Gault formula and the equation of diet modification in renal disease are amply used in clinical practice to estimate the glomerular filtration rate, although they seem to have low accuracy in obese patients, the present study intends to evaluate the predictive performance of 12 equations used to estimate the glomerular filtration rate in obese patients. **Methods:** This is a cross-sectional retrospective study, conducted between 2007 and 2008 and carried out at a university, of 140 patients with severe obesity (mean body mass index 44 ± 4.4 kg/m^2). The glomerular filtration rate was determined by means of 24-hour urine samples. Patients were classified into one or more of the four subgroups: impaired glucose tolerance (n = 43), diabetic (n = 24), metabolic syndrome (n = 76), and/or hypertension (n = 66). We used bias, precision, and accuracy to assess the predictive performance of each equation in the entire group and in the subgroups. **Results:** In renal disease, Cockcroft-Gault's formula and the diet modification equation are not precise in severely obese patients (precision: 40.9 and 33.4, respectively). Sobh's equation showed no bias in the general group or in two subgroups. Salazar-Corcoran's and Sobh's equations showed no bias for the entire group (Bias: -5.2, 95% confidence interval (CI) = -11.4, 1.0, and 6. 2; 95%CI = -0.3, 12.7, respectively). All the other equations were imprecise for the entire group. **Conclusion:** Of the equations studied, those of Sobh and Salazar-Corcoran seem to be the best for estimating the glomerular filtration rate in severely obese patients analyzed in our study.

Keywords: Glomerular filtration rate; Obesity; Kidney; Creatinine; Weight loss

RESUMO

Objetivo: Considerando que a fórmula de Cockcroft-Gault e a equação de modificação da dieta em doença renal são amplamente utilizadas na prática clínica para estimar a taxa de filtração glomerular, de aparente baixa acurácia em pacientes obesos, o presente estudo procura avaliar o desempenho preditivo de 12 equações utilizadas para estimar a taxa de filtração glomerular em pacientes obesos. **Métodos:** Estudo transversal, retrospectivo, realizado entre 2007 e 2008 em uma universidade, com 140 pacientes com obesidade grave (índice de massa corpórea médio de 44 ± 4,4 kg/m^2). A taxa de filtração glomerular foi determinada por meio de amostras de urina de 24 horas. Os pacientes foram classificados em um ou mais dos quatro subgrupos: intolerância à glicose (n = 43), diabéticos (n = 24), síndrome metabólica (n = 76) e/ou hipertensos (n = 66). Viés, precisão e acurácia foram usados para avaliar o desempenho preditivo de cada equação no grupo como um todo e nos subgrupos. **Resultados:** A fórmula de Cockcroft-Gault e a equação de modificação da dieta em doença renal são imprecisas em pacientes gravemente obesos (precisão de 40,9 e 33,4, respectivamente). A equação de Sobh não apresentou viés no grupo geral e em dois subgrupos. As equações de Salazar-Corcoran e Sobh não apresentaram viés em todo o grupo (viés: -5,2, intervalo de confiança (IC) 95% = -11,4, 1,0 e 6,2; IC95% = -0,3, 12.7, respectivamente). Todas as outras equações foram imprecisas no grupo como um todo. **Conclusão:** Das equações estudadas, a de Sobh e a de Salazar-Corcoran parecem ser as melhores para estimar a taxa de filtração glomerular em pacientes gravemente obesos analisados no estudo.

Descritores: Taxa de filtração glomerular; Obesidade; Rim; Creatinina; Perda de peso

INTRODUCTION

Severe obesity is associated with high renal plasma flow (RPF)[1], glomerular hyperfiltration and, consequently, increased glomerular filtration rate (GFR)[1-3]. Hyperinsulinemia[4,5], hyperlipidemia[4,6], and some adipocytokines such as leptin[7] and adiponectin[8] may contribute to this state of hyperfiltration[9]. The adipose tissue contributes to the increase of angiotensin II levels, which enhances tubular sodium reabsorption and activates tubuloglomerular feedback[5,9]. These mechanisms lead to a vasodilatation of the afferent arterioles, with a consequent increase in RPF, transcapillary hydrostatic pressure gradient, and GFR[2,3].

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In clinical practice, the determination of renal function depends on rapid and accurate methods. Since measuring inulin clearance or analyzing 12- or 24-hour urine collections to determine the glomerular filtration rate (GFR) is often impractical, several methods of estimating GFR using serum creatinine concentrations (PCr) have been developed, resulting in greater clinical utility at the expense of reduced accuracy[10,11]. Although the Cockcroft-Gault (CG) equation is the most used in clinical practice[12], several other equations exist[13-25]. The accuracy of these equations is controversial in certain subgroups of patients, principally the elderly[26], those with *diabetes mellitus*[27], and the obese[28,29].

OBJECTIVE

The aim of the present study was to compare the accuracy of CG formula and the equation of diet modification in renal disease (MDRD) and another ten published equations for estimating GFR in a population of severely obese patients as well as in four subgroups of this population (glucose intolerant, *diabetes mellitus*, metabolic syndrome, and hypertension).

METHODS

Study population

One hundred and forty severely obese patients were considered eligible to participate in this study according to the inclusion criteria: body mass index (BMI) ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with two associated complications, age between 18 and 60 years, and no history of renal disease. The patients were all Brazilians and most were women (64.2%) and white (80%). The mean BMI was 46.1 ± 5.4 kg/m^2 (40.0 – 65.6 kg/m^2) and mean age was 43.2 ± 7.1 years.

Study design

The severely obese patients were categorized into one or more of four groups: glucose intolerance (fasting glucose [FG] ≥ 100 mg/dL), *diabetes mellitus* (FG ≥ 126 mg/dL and/or specific treatment), metabolic syndrome (according to IDF criteria)[27], and hypertension (patients under treatment with antihypertensive drugs). Individuals of the 140 patients could be in more than one subgroup or needed not be in any subgroup.

Study protocol and calculations

Blood samples were drawn after a minimum of 8 hours of fasting. A 24-hour urine sample also was collected from all patients. The biochemical parameters were measured using standard laboratory methods. Creatinine in serum and urine was determined by calorimetry. All the formulas used to define GFR, ideal body weight (IBW), and fat-free mass (FFM) are described in table 1. The body surface area (BSA) was not used to correct the GFR because it considerably underestimates the real value [30]. For correction, we use the patient's height in meters[31]. Glomerular hyperfiltration was defined as a GFR > 135 mL • min^{-1} • m^{-2}.

Table 1. Formulas used to predict creatinine clearance (Cl_{cr}) in severely obese subjects

Gold Standard	
GFR = Ucr x V / Pcr x 1440	FFM = Wt – FM
Equations evaluated	
Jackson, Pollock[24] Jackson et al.[25]	FM = Wt x [(1.61 x BMI) + (0.13 x Age) – (12.1 x Gender) – 13.9] / 100 (Female = 0; Male = 1)
Sobh et al.[15]	Cl_{cr} = [(140 – Age) / Pcr] x Wt$^{0.54}$ x Ht$^{0.40}$ x 0.014
Jelliffe [17]	Cl_{cr} (men) = [(100 / Pcr) – 12] x (BSA / 1.73) Cl_{cr} (women) =[(80 / Pcr) – 7] x (BSA / 1.73)
Jelliffe [18]	Cl_{cr} = [98 – 0.8(Age – 20) / Pcr] x (BSA / 1.73) (x 0.9 if women)
Mawer et al.[19]	Cl_{cr} (men) = Wt[29.3 – (0.203 x Age)] x [1 – (0.03 x Pcr)] / (14.4 x Pcr) x (70 / Wt) Cl_{cr} (women) = Wt[25.3 – (0.175 x Age)] x [1 – (0.03 x Pcr)] / (14.4 x Pcr) x (70 / Wt)
Gates[20]	Cl_{cr} (men) = (89.4 x Pcr$^{-1.2}$) + (55 – Age) x (0.447 x Pcr$^{-1.1}$) x (BSA / 1.73) Cl_{cr} (women) = (60 x Pcr$^{-1.1}$) + (56 – Age) x (0.3 x Pcr$^{-1.1}$) x (BSA / 1.73)
Bjornsson[22]	Cl_{cr} (men) = [27 – (0.173 – Age)] x (Wt x 0.07) / Pcr Cl_{cr} (women) = [25 – (0.175 – Age)] x (Wt x 0.07) / Pcr
Davis,Chandler[23]	Cl_{cr} = (140 – Age) / Pcr (x 0.85 if women)
Hull et al.[21]	Cl_{cr} = [((145 – Age) / Pcr) – 3] x (Wt / 70) (x 0.85 if women)
MDRD complete[14]	Cl_{cr} = 170 x Pcr$^{-0.999}$ x Age$^{-0.176}$ x BUN$^{-0.170}$ x Albumin$^{0.318}$ (x 0.762 if women)
Cockcroft, Gault[12]	Cl_{cr} = (140 – Age) x Wt / 72 x Pcr (x 0.85 if women)
CG-FFM[12]	Cl_{cr} = (140 – Age) x FFM / 72 x Pcr (x 0.85 if women)
Salazar, Corcoran[13] (Ht in meters)	Cl_{cr} (men) = [137 – Age] x [(0.285 x Wt) + (12.1 x Ht^2)] / Pcr x 51 Cl_{cr} (women) = [146 – Age] x [(0.287 x Wt) + (9.74 x Ht^2)] / Pcr x 60

GFR: glomerular filtration rate; Ucr: urinary creatinine (mg); V: urinary volume (mL in 24 h); Cl_{cr}: creatinine clearence (mL/min); Pcr: plasma creatinine (mg/dL); Wt: weight (kg); Ht: height (cm); albumin in g/dL; BUN: blood urea nitrogen (mg/dL); FFM: free fat mass (kg); BMI: body mass index (kg/m^2); BSA: body surface area
Correction used for all formulas: Cl_{cr} (mL/min/m) = Formula / Ht (in meters)

BMI is defined as the individual's body weight divided by the square of his/her height. To define MS, we used the IDF criteria: waist circumference ≥ 94 cm in men, ≥ 80 cm in women or BMI ≥ 30 kg/m^2; triglyceride levels ≥ 150 mg/dL (1.7 mmol/L) and/or specific treatment; HDL-C levels < 40 mg/dL (1 mmol/L) in men, < 50 mg/dL (1.3 mmol/L) in women and/or specific treatment; fasting glucose ≥ 100 mg/dL (5.6 mmol/L) and/or DM2 patient; systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg and/or specific treatment. The individual must present at least three of the five risk factors to be diagnosed with MS [27].

Statistical analyses

Variables with normal distribution were expressed as mean ± standard deviation (SD). Results of the MDRD equation and the Cockcroft-Gault formula were compared with the measured GFR by correlation, paired two-tailed *t*-test, and Bland-Altman procedures[32]. The sensitivity and specificity of both formulas for the diagnosis of glomerular hyperfiltration in severely obese patients were assessed from nonparametric receiver operating characteristic curves (ROC) generated by plotting sensitivity *versus* 1 – specificity, attributing to the ideal test a sensitivity = 1 and a specificity = 1. Areas under the curves (AUCs) were calculated according to the procedure of Hanley and McNeil[33] and compared by a fully paired univariate z-score test of the difference between the areas under two ROC curves (area test). The AUC is commonly > 0.5 with values ranging from 1 (ideal perfect separation of the tested values) to 0.5 (no apparent distribution difference between the tested groups).

Three methods were used to compare the accuracy of each equation. The first method assessed precision and bias as described by Sheiner and Beal[34], and the second was ANOVA of the bias and precision between prediction methods followed by a post-hoc Duncan test. The mean prediction error (MPE = $1 / n \times \Sigma [Y_i - Y]$, where Y_i is the predicted value and Y the measured value) was defined as the bias. A method is biased if the 95%CI of the MPE does not include zero and therefore differs from zero. A method is unbiased if the 95%CI of the mean's actual difference includes zero. The precision of each equation was measured by root mean square error ($RMSE = [1 / n \times \Sigma (Y_i - Y)^2]^{1/2}$). The third method used correlation coefficients obtained using simple linear regression and correlation of measured versus estimated GFR. The 95%CIs were constructed around the bias and precision using the *t*-statistic to assess significance of the first two methods. The accuracy of each equation (% Error), or how well it represents the true renal function, was assessed by comparing its results with those of the standard method. This was performed by using the following equation: (predicted value – true value [GFR]) x 100 / true value. Stepwise linear regression using the backward stepwise method was performed on serum creatinine levels (P_{cr}), serum albumin levels (P_{al}), serum BUN (P_{BUN}), and demographic variables of age, height, and body weight for the entire database to develop an equation for predicting GFR for severely obese patients.

All statistical analyses were made with the statistical software package SPSS (v15.0; SPSS, Chicago, IL), MedCalc software, and ROCKIT 0.9B (Department of Radiology from The University of Chicago). Statistical significance was considered at $p < 0.05$.

RESULTS

CG formula *versus* MDRD Equation

The mean measured GFR was 91.7 ± 23.2 mL • min^{-1} • m^{-2}. The mean MDRD equation underestimated GFR (62.9 ± 14.4 mL • min^{-1} • m^{-2}; $p < 0.05$ *versus* measured GFR) while the mean Cockcroft-Gault formula overestimated GFR (125.3 ± 33.3 mL • min^{-1} • m^{-2}; $p < 0.0001$ *vs*. measured GFR). As shown in Figure 1A, both estimations were poorly correlated to measured GFR (CG formula r = 0.052, p = 0.538; MDRD equation r = 0.032, p = 0.590 between r values). The Bland-Altman procedure (Figure 1B) revealed a bias for the MDRD equation as the estimation minus GFR (mean -28.8 mL • min^{-1} • m^{-2}, 2 SDs 53.0) was negatively correlated to the mean (r = -0.44, $p < 0.0001$), which was not the case for the CG formula (mean +33.5 mL • min^{-1} • m^{-2}, 2 SDs 78.8, r = 0.37, $p < 0.0001$). The ROC curve analysis (Figure 1C) showed that the maximum diagnostic accuracy of the MDRD equation for the diagnosis of glomerular hyperfiltration was similar to the CG formula (CG formula AUC 0.639, cutoff limit 106.6; MDRD equation AUC 0.643, cutoff limit 55.4; p = 0.915). This was mainly due to a similar sensitivity and specificity of both formulas (CG formula sensitivity 60.8% and specificity 66.6%; MDRD equation sensitivity 63.5% and specificity 68.1%).

Predicted performance of 12 equations

Bias assessments using the method of Sheiner and Beal are listed in table 2. Inspection of the table reveals that the mean bias of most equations was generally high (> 10 mL/min/m). For the entire population, the Salazar-Corcoran and the Sobh equations were the only ones that were unbiased and the Jelliffe 1971 was

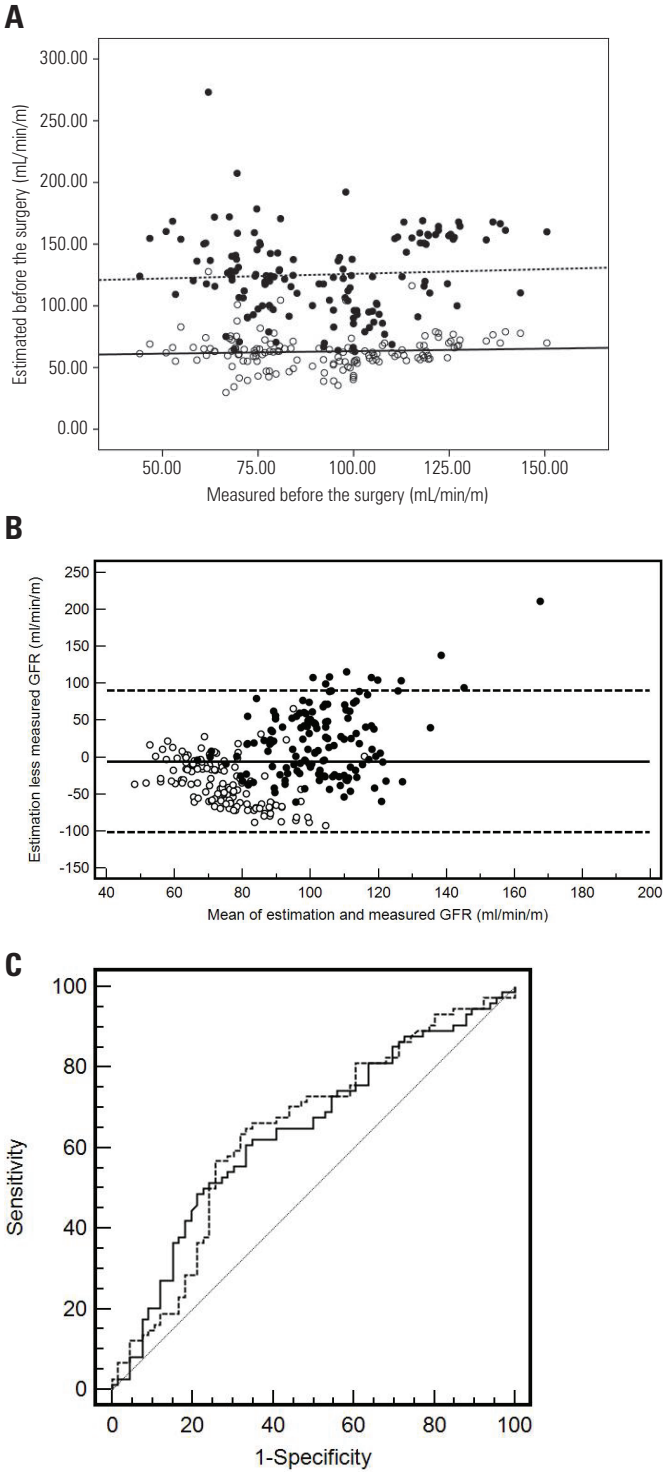

Figure 1. A: Estimated GFR as a function of its urinary measurement (milliliters per minute per meters) in 140 severely obese patients before RYGBP. B: Bland-Altman plots of differences between estimated and measured GFR as a function of average GFR by both methods in 140 severely obese subjects before RYGBP. C: ROC curves comparing AUCs of the Cockcroft-Gault formula and the MDRD equation for the diagnosis of glomerular hyperfiltration (GFR > 90 mL • min-1 • m-2) before RYGBP. ● Cockcroft-Gault formula (—); ○ MDRD equation (---). Glomerular hyperfiltration was defined as a GFR > 135 ml • min-1 • m-2.
GFR = Glomerular filtration rate
RYGBP = Roux-en-Y gastric bypass
MDRD = Equation of diet modification in renal disease

the most precise (Table 3). ANOVA performed on bias assessments showed the Sobh and Salazar-Corcoran equations to be of similar bias ($p = 0.540$). The Sobh equation was significantly less biased than the other equations ($p < 0.05$) and the Salazar-Corcoran equation did not differ significantly from the equations of Jelliffe 1971, Jelliffe 1973, and Davis-Chandler ($p > 0.05$).

For the population with impaired glucose tolerance the only equation that was unbiased was the Hull method. The Bjornsson equation was the most precise. ANOVA demonstrated that the Hull method did not differ significantly from the equation of Bjornsson ($p = 0.820$), and was significantly less biased than all the other equations ($p < 0.05$). The only equation that was unbiased for the severely obese patients with *diabetes mellitus* was the Sobh formula, and was also the most precise of all equation studied. ANOVA revealed different biases among all equations ($p < 0.0001$). The Sobh equation differs significantly only from the equations of Mawer, Gates, and the CG-FFM ($p < 0.05$).

In severely obese patients with metabolic syndrome, the Bjornsson equation was the only unbiased one, and the Sobh equation was the most precise. The Bjornsson equation was the least biased of all equations ($p < 0.0001$), except those of Cockcroft-Gault, Sobh, and Hull ($p > 0.05$). Finally, in hypertensive severely obese subjects, Sobh was the only unbiased equation. The bias of the Sobh method did not differ between the equations of Jelliffe 1971, Jelliffe 1973, Salazar-Corcoran, and Bjornsson ($p > 0.05$). The Salazar-Corcoran equation showed the best accuracy (% Error = 2.72 ± 5.08%), followed by Jelliffe 1973 (% Error = -5.85 ± 40.13%) (Figure 2). ANOVA revealed different accuracies among all equations ($p < 0.0001$). The Salazar-Corcoran equation was the most accurate of all equations ($p < 0.0001$), except for Sobh, Jelliffe 1971, Jelliffe 1973, and Davis-Chandler ($p > 0.05$).

Linear regression

In the entire population, correlation coefficients ranged from 0.05 to 0.28 and were fairly consistent from subgroup to subgroup. The impaired glucose tolerance group had the poorest correlation of any subgroup, with correlation coefficients ranging from 0.01 to 0.56. In the metabolic syndrome we found the best correlation, with correlation coefficients ranging from 0.09 to 0.56. Within the entire population and each subgroup, the Hull equation had the lowest correlation coefficients (range 0.01 to 0.55) and the CG-FFM and the CG

Table 2. Bias, as assessed by mean prediction error, of the 12 equations used to predict creatinine clearance

	ALL (n = 140)	IGT (n = 43)	DM (n = 24)	MS (n = 76)	HYP (n = 66)
	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
MDRD[14]	-28.83 (-33.27, -24.39)	-52.14 (-56.13, -48.16)	-37.63 (-46.85, -28.40)	-48.17 (-51.26, -45.09)	-32.17 (-39.13, -25.22)
Cockcroft, Gault[12]	33.52 (26.89, 40.15)	22.62 (15.97, 29.28)	25.33 (7.67, 42.99)	12.31 (5.99, 18.64)	33.72 (23.15, 44.30)
Sobh et al.[15]	6.20 (-0.30, 12.70)[a]	-30.35 (-37.92, -22.79)	-5.37 (-22.00, 11.24)[a]	-13.13 (-21.20, -5.07)	-3.55 (-12.55, 5.45)[a]
Salazar, Corcoran[13]	-5.21 (-11.44, 1.02)[a]	-40.46 (-48.10, -32.33)	-16.23 (-31.73, -0.72)	-24.18 (-31.87, -16.50)	-13.93 (-22.70, -5.16)
Jelliffe[17]	-12,37 (-18.06, -6.68)	-45.57 (-51.98, -39.16)	-17.88 (-34.47, -1.30)	-31.41 (-37.93, -24.89)	-17.57 (-25.88, -9.26)
Jelliffe[18]	-12,27 (-18.07, -6.48)	-47.05 (-53.41, -40.69)	-22.38 (-37.19, -7.57)	-31.43 (-38.27, -24.54)	-20.82 (-28.94, -12.71)
Mawer et al.[19]	109.68 (95.57, 123.80)	62.27 (39.86, 84.69)	95.06 (62.86, 127.25)	88.42 (69.09, 107.75)	95.23 (76.60, 113.86)
Gates[20]	-53.81 (-59.96, -47.66)	-87.18 (-94.11, -80.25)	-60.15 (-77.15, -43.15)	-72.50 (-80.31, -64.69)	-60.65 (-69.48, -51.82)
Hull et al.[21]	31.47 (23.57, 39.37)	0.47 (-10.96, 11.91)[a]	19.10 (0.26, 38.46)	10.44 (0.88, 20.01)	24.56 (13.98, 35.14)
Bjornsson[22]	27.41 (20.03, 34.80)	-11.60 (-20.58, -2.62)	15.42 (3.10, 33.96)	7.64 (-1.70, 16.98)[a]	16.95 (7.08, 26.82)
Davis, Chandler[23]	-21.65 (-27.06, -16.24)	-55.16 (-60.53, -49.78)	-31.28 (-45.84, -16.72)	-40.38 (-46.66, -34.10)	-29.74 (-37.58, -21.90)
CG FFM[12]	-45.87 (-51.26, -40.47)	-76.07 (-83.67, -68.47)	-55.33 (-67.88, -42.78)	-64.67 (-71.11, -58.22)	-54.71 (-62.71, -46.71)

IGT: impaired glucose tolerance; DM: *diabetes mellitus*; MS: metabolic syndrome; HYP: hypertension; CI: confidence interval; CG FFM: Cockcroft-Gault using free-fat mass; MDRD: modification of diet in renal disease.
[a]0.00 included in 95% CI (Unbiased).

Table 3. Precision, as assessed by root mean square error, and correlation coefficients of the 12 equations used to predict creatinine clearanc

	ALL (n = 140)	IGT (n = 43)	DM (n = 24)	MS (n = 76)	HYP (n = 66)
	Mean (95%CI) (r)	Mean (95%CI) (r)	Mean (95%CI) (r)	Mean (95%CI) (r)	Mean (95%CI) (r)
MDRD[14]	33.40 (-29.98, -36.83) (0.06)[a]	52.19 (48.27, 56.11) (0.48)[a]	39.49 (31.85, 47.13) (0.23)	48.37 (45.46, 51.28) (0.52)[a]	37.27 (32.10, 42.43) (0.05)
Cockcroft, Gault[12]	40.95 (35.62, 46.27) (0.05)[a]	27.87 (23.57, 32.18) (0.44)[a]	37.34 (24.23, 50.45) (0.05)	25.64 (22.01, 29.28) (0.56)[a]	40.69 (31.75, 49.63) (0.03)
Sobh et al. [15]	31.04 (27.00, 35.08) (0.25)[a]	33.08 (26.72, 39.44) (0.23)	32.64 (23.50, 41.78) (0.35)	29.57 (24.29, 34.85) (0.39)[a]	29.13 (23.67, 34.59) (0.18)
Salazar, Corcoran[13]	30.31 (26.61, 34.02) (0.26)[a]	42.21 (35.56, 48.86) (0.33)[a]	33.02 (23.71, 42.33) (0.35)	34.41 (29.18, 39.64) (0.42)[a]	31.72 (26.52, 36.92) (0.18)
Jelliffe[17]	29.12 (25.54, 32.70) (0.22)[a]	45.57 (39.16, 51.98) (0.08)	35.24 (25.06, 45.41) (0.44)[a]	36.14 (31.08, 41.20) (0.32)[a]	30.83 (25.38, 36.27) (0.15)
Jelliffe1973[18]	29.77 (26.18, 33.36) (0.24)[a]	47.38 (41.27, 53.50) (0.13)	34.25 (24.54, 43.96) (0.34)	37.03 (31.88, 42.18) (0.35)[a]	32.42 (27.14, 37.70) (0.15)
Mawer et al. [19]	111.45 (97.73, 125.17) (0.26)[a]	68.01 (47.28, 88.75) (0.43)[a]	100.02 (70.75, 129.29) (0.33)	91.67 (73.15, 110.18) (0.45)[a]	97.46 (79.55, 115.37) (0.17)
Gates[20]	58.01 (53.05, 62.97) (0.24)[a]	87.18 (80.25, 94.11) (0.46)[a]	66.40 (54.49, 78.31) (0.42)[a]	76.05 (70.30, 81.80) (0.42)[a]	64.12 (56.95, 71.29) (0.27)[a]
Hull et al.[21]	43.77 (37.73, 49.80) (0.13)[a]	30.73 (24.46, 36.99) (0.01)	35.64 (21.27, 50.01) (0.55)[a]	32.33 (25.86, 38.80) (0.09)	38.00 (30.23, 45.77) (0.03)
Bjornsson[22]	39.92 (34.36, 45.47) (0.25)[a]	25.30 (19.68, 30.92) (0.22)	36.87 (25.26, 48.48) (0.38)	29.89 (23.32, 36.45) (0.39)[a]	32.14 (24.95, 39.32) (0.16)
Davis, Chandler[23]	32.06 (28.38, 35.74) (0.18)[a]	55.16 (49.78, 60.53) (0.06)	40.70 (31.56, 49.98) (0.31)	44.28 (39.60, 48.97) (0.27)[a]	36.84 (31.13, 42.54) (0.14)
CG FFM[12]	48.00 (43.15, 52.85) (0.28)[a]	76.07 (68.47, 83.67) (0.56)[a]	56.07 (44.14, 68.00) (0.22)	65.72 (59.87, 71.58) (0.45)[a]	55.62 (48.02, 63.22) (0.27)[a]

IGT: impaired glucose tolerance; DM: diabetes mellitus; MS: metabolic syndrome; HYP: hypertension; CI: confidence interval; CG FFM: Cockcroft-Gault using free-fat mass; MDRD: modification of diet in renal disease. [a] $p < 0.05$.

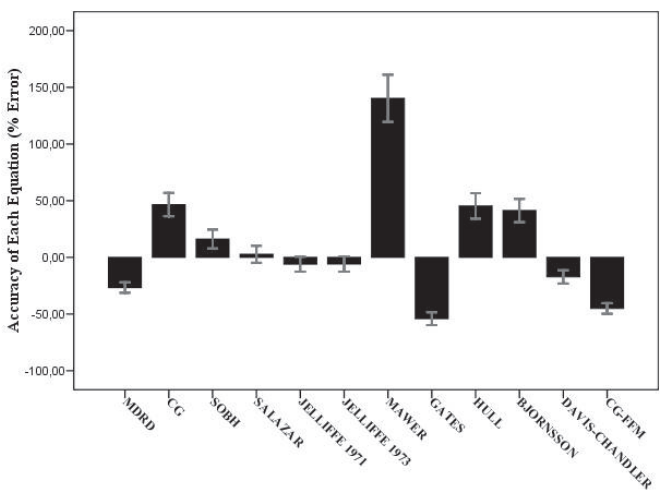

Figure 2. Accuracy, as assessed by %Error, of the 12 equations used to predict creatinine clearance. The Salazar-Corcoran method was the most accurate with no significant difference with Sobh, Jelliffe 1971, Jelliffe 1973 and Davis-Chandler equations ($p > 0.05$)

had the highest (range 0.22 to 0.56 and 0.03 to 0.56, respectively).

Stepwise linear regression performed on the entire group using GFR as the dependent variable with height and creatinine as independent variable produced the followed equation:

GFR (mL/min/m) = 253.263 + 73.112 (Creatinine in mg/dL) – 101.683 (Height in m)

This equation had a correlation coefficient of 0.57 (SE = 29.12) and was unbiased (Bias = -0.25 mL/min/m; 95%CI = -5.33, 5.32) and precise (Precision = 26.72; 95% CI = 23.84, 29.60) for the entire population. The accuracy of this equation was 4.94 ± 23.78%, and the correlation coefficient between the measured and estimated GFR with this equation was 0.427 ($p < 0.0001$). The variables age, weight, serum albumin, and BUN concentration were not shown to significantly improve correlation.

DISCUSSION

CG formula *versus* MDRD equation

The CG formula is a simple, widely used and recommended means of assessing renal function, but the estimation by CG formula, in this study, is poorly correlated with the GFR determined by urine samples (r = 0.052). Prior studies found the main problem with the Cockcroft-Gault formula to be overestimation of the GFR[35,36]; even so, it is low, which we also found to be true. Our results suggest that this overestimation alters the sensitivity of the CG formula for the diagnosis of glomerular hyperfiltration.

The presence of weight in this formula is probably the main cause of error, especially in patients with severe obesity. GFR is proportional to body weight in the CG formula. However, most of the excessive body weight in obesity is fat, which does not produce creatinine. According to a proportional relationship, an obese subject who loses 10% of his body weight would lose 10% of the GFR. In contrast, Solerte et al. found that a 20% diet-induced weight loss was associated with a 20% increase in GFR[37].

The MDRD equation is derived from the results of 1,070 renal-insufficient patients, validated in 558 other patients. It was clearly more accurate than the CG formula in this population and it does not require body weight[14]. However, the MDRD equation has not been validated in individuals without renal disease[14]. We show that it underestimates GFR at high levels, as has already been reported by others studies[37,38].

Our work shows similar results of CG and the MDRD formula for severely obese subjects. In summary, both equations are imprecise for severely obese patients. The National Kidney Foundation Practice Guideline for Chronic Kidney Disease recommends measuring GFR by using clearance methods in obesity[39].

Predicted performance of 12 equations

Since the early 1970s, several equations and nomograms have been published for estimating GFR from plasma creatinine but selecting which equation is the best for approximating renal function for a given patient continues a topic of debate. There have been few studies conducted investigating the predictive performance of these equations and nomograms in specific patient groups, like the severely obese. Many of these studies only analyzed predictive performance from a few selected equations, and not all assessed precision, bias, and accuracy, with some of the earlier studies comparing equations based on linear regression only. Recently, some researchers have studied the predictive performance of many equations in subgroups of patients[10], but the accuracy of these equations in severe obesity have remained unknown.

The CG equation may be considered the gold standard equation of GFR prediction, being used as a benchmark by many for comparing the accuracy of various other equations. In this study, the CG method was biased in all subgroups of obesity patients as was the MDRD equation, another gold standard procedure. For the entire obese population, only the Salazar-Corcoran equation, which was developed specifically for use in obese patients[13], and the Sobh formula were unbiased. In addition, the finding that the Salazar-Corcoran equation has the lowest bias is also consistent with previous research[10,29].

The subgroup of diabetic patients had the lowest overall bias and the second highest overall precision of all subgroups analyzed in this study. While in comparison with the other subgroups the bias was low overall for each equation, the only equation that was unbiased was Sobh's. Looking at all 12 equations, there are an evident trends to underpredicting the GFR, with eight equations tending to underpredict and 4 tending to overpredict GFR. While the CG formula was shown to perform well in normal weight patients with diabetic nephropathy[27,40], in our study the CG formula overpredicted the GFR by 33.52 mL/min/m in severely obese diabetic patients, similar to other studies[41].

When examining the impaired glucose tolerance subgroup, the bias is the highest and the precision is the lowest of all subgroups studied. All equations were biased with the exception of the Hull equation, which had the lowest bias of all equations in the study. The MDRD equation, which was the best method for screening for kidney function in normal weight patients with impaired glucose tolerance[42], was biased and imprecise in obese subjects.

A direct correlation has been suggested between obesity-associated hypertension and hyperfiltration[2,43]. While all equations except the Sobh method were biased in the severely obese hypertensive patients, this subgroup had the highest overall precision and had the second lowest overall bias. Finally, in the metabolic syndrome subgroup, all equations were biased, except for the Bjornsson formula.

Trends seen across the entire group and each of the four subgroups were that the Sobh equation performed the best overall, being unbiased and precise in the entire group as well as in two of the subgroups. With the exception of the Salazar-Corcoran equation in the entire group, Hull in the impaired glucose tolerance subgroup and Bjornsson in the metabolic syndrome group, all others equations had the highest bias and the lowest precision. The gold standards CG formula and MDRD equation had high mean errors and low mean precisions.

Overall, if a method whose bias varied less than ±10% from the mean measured GFR is considered clinically acceptable, then the Sobh and Salazar-Corcoran equations are accepted in the entire population. In the subgroups, we can accept Sobh for the diabetes and hypertension groups (conditions frequently associated with obesity), Hull for impaired glucose tolerance, and Bjornsson for metabolic syndrome.

With the exception of nephrotoxic drugs, which were not administered to our patients, our study is limited by the lack of control of various drugs that can affect either GFR or the creatinine assay, the small number of patients, and the fact that dietary influences were not controlled. Many patients also had more than one comorbidity, making confounding likely. Also, we used the 24-hour urine sample to measure GFR and not the infusion of external substances such as ^{99}Tc-diethylenetriaminepentaacetate, iothamalate, inulin, iohexol, and ^{51}Cr-EDTA, which are gold standard procedures. Creatinine estimates of GFR have their limitations. All of the estimating equations depend on a prediction of the 24-hour creatinine excretion rate, which is a function of muscle mass. Also, creatinine clearance is no longer widely performed due to the difficulty in assuring a complete urine collection.

The lack of consensus in results of previous studies evaluating the accuracy of equations for estimating glomerular filtration rate could be due, in part, to heterogeneity in patient condition or disease status. This study used a medium database and evaluated the predictive performance of 12 different equations, unlike earlier studies that looked at fewer equations.

CONCLUSIONS

The findings and the results of the present study suggest that the MDRD and CG equations are imprecise in obese patients. Overestimation and the influence of weight reduce the sensitivity and the accuracy of the CG formula. The MDRD equation is more difficult to calculate in clinical practice and underestimates GFR levels.

This study demonstrates that the Salazar-Corcoran equation is often an unbiased estimate of GFR for many patients, regardless of the underlying comorbidity. In addition, the Sobh equation or the regression equation presented here may be the preferred method for estimating GFR in severely obese patients, who are often diabetic and hypertensive, when ease of application is not a high priority. However, like the recommendation of the National Kidney Foundation Practice Guideline for Chronic Kidney Disease, we believe that the 24-urine sample is the method of choice when assessing the glomerular filtration rate in severely obese patients.

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