Obesity, hyperfiltration and early kidney damage: a new formula for the estimation of creatinine clearance

Alessio Basolo[1]*, Guido Salvetti[1] *, Domenico Giannese[2], Susanna Bechi Genzano[1], Giovanni Ceccarini[1], Riccardo Giannini[3], Gianluca Sotgia[4], Paola Fierabracci[1], Paolo Piaggi[5], Ferruccio Santini[1]

[1] *Obesity and Lipodystrophy Center, Endocrinology Unit, University Hospital of Pisa, Pisa, Italy.*
[2] *Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[3] *Department of Surgical, Medical, Molecular Pathology and Critical Area, University Hospital of Pisa, Pisa, Italy*
[4] *Consorzio Metis, University Hospital of Pisa, Pisa 56124, PI, Italy*
[5] *Department of Information Engineering, University of Pisa, Pisa, Italy*

*: these authors contributed equally to the study

E-mail addresses: alessio.basolo@unipi.it; g.salvetti@int.med.unipi.it; domenico.giannese@phd.unipi.it; susanna.bechi.dr@gmail.com; giovanni.ceccarini@unipi.it; riccardo.giannini@unipi.it; g.sotgia@consorziometis.it; pfierab2001@yahoo.it; paolo.piaggi@gmail.com; ferruccio.santini@unipi.it

Corresponding author:
Dr. Alessio Basolo
Obesity and Lipodystrophy Center
Endocrinology Unit
University Hospital of Pisa, 56124, Pisa, Italy
Telephone number: +39-050-995001
Fax number: +39-050-578772
ORCID: 0000-0001-6888-7080

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Disclosure summary

The authors declare no conflict of interest.

Abstract

Objective

Glomerular hyperfiltration may represent a direct pathogenetic link between obesity and kidney disease. The most widely used methods to estimate creatine clearance such as Cockroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) have not been validated in subjects with obesity. The performance of prediction formulas was compared to measured creatinine clearance (mCrCl) in subjects with obesity.

Methods

The study population included 342 patients with obesity (mean BMI 47.6 kg/m^2) without primary kidney disease. A urine collection was performed over 24 hours for measurement of CrCl.

Results

mCrCl increased with body weight. The CG formula showed an overestimation at high CrCl, whereas an underestimation resulted from CKD-EPI and MDRD. To improve the accuracy of estimated CrCl (eCrCl), a new CG-based formula was developed as follow:

$$53+0.7 \times (140-Age) \times Weight/(96xSCr) \times (0.85 \text{ if female})$$

A cut-off point for BMI of 32 Kg/m^2 was identified, at which the new formula may be applied to improve eCrCl.

Conclusions

In patients with obesity the glomerular filtration rate increases with body weight, and it is associated with the presence of albuminuria, suggesting an early kidney injury. We propose a

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novel formula that improves the accuracy of eCrCl to avoid missed diagnoses of hyperfiltration in patients with obesity.

1. Introduction

Obesity has become a worldwide epidemic and it is associated with various comorbidities including type 2 diabetes, cardiovascular and chronic kidney diseases (CKD) [1, 2]. A high body mass index (BMI) is one of the strongest risk factors for new-onset CKD [3]. The glomerular filtration rate (GFR) is defined as the volume of glomerular filtration per unit time and it is the gold standard for the measurement of kidney function. An increased total GFR, named glomerular hyperfiltration, is observed in a state of obesity [4] and it may represent a direct pathogenetic link between obesity and kidney disease, possibly leading to renal function loss in the long term, if left untreated [3, 5]. Several mechanisms have been proposed to explain the pathogenesis of hyperfiltration, including hemodynamic changes associated with a disequilibrium of vasoactive molecules that regulate the tone of afferent and efferent arterioles in the glomeruli, increased renal blood flow [4, 5], sodium reabsorption [6, 7], activation of renin-angiotensin-aldosterone system (RAAS) [8], secretion of hormones from the adipose tissue [9, 10], inflammation [11], and oxidative stress [12]. Hyperfiltration is considered a precursor of intraglomerular hypertension that might induce albuminuria, an early sign of kidney injury [13]. In case of delayed detection, the presence of albumin in the urine may evolve to a state of glomerulomegaly [14], glomerulosclerosis [15] and possibly to the development or progression of nephropathy in the long term [13]. In clinical practice, it is crucial to evaluate the kidney function with the aim to identify the presence of kidney damage. The most accurate and precise measurement of GFR (inulin clearance) is methodologically difficult in clinical settings (high cost, complex protocol and time consuming). Although not very accurate and/or inconvenient for

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clinicians and patients, other methods (creatinine clearance, urea, cystatin C and radioisotopic methods) have been used in clinical or research settings to estimate the renal function [16]. Thus, prediction formulas using serum creatinine levels including *Cockroft-Gault* (CG) [17], *Modification of Diet in Renal Disease (*MDRD) [18] and *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI) [19] are currently the most widely used methods in routine clinical practice as surrogates for the estimation of GFR. Yet, several studies suggest that estimated CrCl (eCrCl) using CG, CKD and MDRD formulas is not accurate when compared to the measurement of CrCl in subjects with obesity [20-22]. The lack of accuracy of eCrCl in obesity may lead to missed diagnoses of hyperfiltration/early kidney disease that requires a prompt treatment to avoid a progression to CKD and kidney failure over time. The aim of this study was to evaluate the kidney function by comparing the eCrCl using the prediction formulas (CG, CKD-EPI and MDRD) with measured CrCl (mCrCl) by 24 hours urine collection in a large population of subjects with obesity. Eventually, we elaborated a new prediction formula for eCrCl in this population at high risk for CKD.

2. Methods

2.1 Study populations

The study population included 342 patients with obesity (BMI 47.6 ± 8.9 kg/m^2 ranged from 30 to 96 kg/m^2, age 49.2 ± 12.5 years) evaluated at the Obesity and Lipodystrophy Center, Endocrinology Unit, University Hospital of Pisa, Italy. At the time of the visit, 4% had class I obesity, 13% had class II obesity and 83% had class III obesity (BMI > 40 kg/m^2). Patients with history of type 2 diabetes for more than 5 years and/or under insulin therapy and those with primary kidney disease and/or with mCrCl <60 mL/min were excluded, as well as patients with

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urine creatinine <950 mg/24 hours (suggestive of incomplete urine collection that may underestimate CrCl).

All patients underwent measurement of body weight, height, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body weight, in light clothing, was measured (to the nearest 0.1 kg) with digital electronic scale. Standing height, with no shoes, was measured (to the nearest 1 cm) using stadiometer. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Overweight and obesity were classified according to conventional definitions [23]. SBP and DBP were measured with an electronic device and the average of two measurements in the sitting position with an interval of 2 minutes with an appropriate cuff. Patients were classified as hypertensive when their blood pressure was > 140/90 mmHg or when they were on antihypertensive treatment at the time of blood pressure measurement.

Blood samples were drawn in the fasting state in the morning for the measurement of serum glucose, insulin and creatinine. A urine collection was performed over 24 hours for calculation of CrCl as follows:

Creatinine Clearence = (24 h urinary creatinine x Urinary volume)/ Serum Creatinine

eCrCl was calculated by the main formulas (**Table 1**) as previously described [17-19]. It has to be noted that CKD-EPI and MDRD formulas, at variance with CG, do not include body weight and the results are normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area. In our cohort, eCrCl was estimated by using CKD-EPI and MDRD deindexed by calculating the body surface area (BSA) of each patient (mean BSA = 2.31 m^2) (**Table 1**). BSA was calculated by the formula of Dubois and Dubois (0.0071843 × total body weight [kilograms]$^{0.425}$ × height [centimeters]$^{0.725}$) [24]. Albumin excretion in twenty-four-hour urine volume was available in 182 patients. Publication of the study was approved by the Ethical

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Committee (CEAVNO – Comitato Etico Area Vasta NordOvest) and, for policy of the University Hospital, all patients signed an informed consent to use their clinical data for scientific research.

An independent study group of 50 healthy individuals without obesity (BMI< 30 kg/m^2, mean BMI = 23.9 kg/m^2) recruited at the Nephrology Unit as donors for kidney transplantation was used for comparison.

2.2 Statistical analysis

Statistical analyses were performed using SAS software (SAS 9.3, Enterprise guide version 5.1; SAS Institute, Cary, NC). Data are expressed as mean±SD or mean with 95% confidence interval (CI). Shapiro-Wilk test was used to assess the normal distribution of the data. Albuminuria over 24 hours were log10 transformed to meet the assumptions of linear regression (i.e., homoscedasticity and normal distribution). Associations between normally distributed quantitative variables were assessed by the Pearson's correlation coefficient. Multivariate regression analysis was used to evaluate the independent determinants of CrCl and albuminuria by including age, sex, body weight, height, presence of diabetes and hypertension. Unpaired Student's *t*-test were used to evaluate differences according to gender. Paired Student's t-test was used to compare the measurement of CrCl and the estimation of creatinine clearance calculated with the different formulas with the aim to identify the under or overestimation of the renal function. A non-linear regression analysis was applied to the measured creatinine clearance data to estimate the coefficient on the denominator of the CG formula (i.e., 72 in the original CG formula) using the Levenberg-Marquardt algorithm[25, 26]. This is an optimization method for nonlinear least-squares problems, which combines the steepest descent method and the Gauss-Newton method by introducing a damping parameter to control the balance between the two

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methods. The CG formula with the new estimated coefficient (=96 by data fitting) was then modified via linear regression analysis to have a zero intercept and a unitary slope with respect to measured CrCl formula.

A cut-off point for BMI was identified at which the eCrCl calculated using the conventional CG formula was, on average, 7 mL/min higher than the mCrCl. The value of 7 mL/min corresponds to the average difference between the mCrCl and the modified CG equation.

3. Results

The anthropometric characteristics of the study population are shown in **Table 2.**

The mCrCl was positively associated with body weight (r=0.40, p=<0.0001, **Figure 1A**) and negatively related to age (r=−0.40, p=<0.0001, **Figure 1B**). In a multivariate analysis including age, gender, height, presence/absence of diabetes or hypertension, only body weight and age were independent predictors of mCrCl (β = 0.7 ml/min per 1 kg, p < 0.0001; β = -1.6 ml/min per 1 year, p=0.0001, respectively).

In 182 patients in whom 24-hour albuminuria was available, a positive correlation with the mCrCl was observed (r=0.17, p=0.02). In a multivariate analysis including age, body weight, height, gender, presence/absence of diabetes and hypertension, mCrCl (p=0.026) and diabetes (p=0.03) were both independent predictors of 24-hour albuminuria.

No significant effects could be demonstrated when systolic and diastolic blood pressure values were added to the multivariate regression analyses.

3.1 Comparison between mCrCl and eCrCl

The results of eCrCl by current formulas are reported in **Table 2**.

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The mCrCl was positively associated with eCrCl by CG ($r = 0.69$, $p < 0.01$, **Figure 2A**), deindexed CKD-EPI ($r = 0.66$, $p < 0.01$, **Figure 2B)** and deindexed MDRD ($r = 0.69$, $p < 0.01$, **Figure 2C)** prediction formulas. In our cohort, the CG formula showed a progressive overestimation at high CrCl values whereas an underestimation resulted from CKD-EPI and MDRD formulas. To further improve the precision of the eCrCl, starting from the CG formula that includes body weight in its algorithm, we generated a new coefficient (= 96 by data fitting) at the denominator (i.e., 72 in the original CG formula). The modified version of the CG formula was then adjusted via linear regression analysis to have a zero intercept and a unitary slope **(Figures 3 and 4)** with respect to the mCrCl as following:

$$\mathrm{eCrCl} = 53 + 0.7 \times \left[\frac{(140 - \mathrm{Age}) \times (\mathrm{Weight})}{\mathbf{96} \times \mathrm{SCr}} \times 0.85(\mathrm{if\ female})\right]$$

where the eCrCl is expressed in mL/min, age in years, body weight in kg, serum creatinine (SCr) in mg/dL.

To define the cut-off of BMI in terms of appropriateness of the new equation, both the conventional CG equation and our modified CG formula were applied to calculate the eCrCl in an independent study group of 50 healthy individuals without obesity (BMI< 30 kg/m^2, mean BMI = 23.9 kg/m^2). In this group, we found that our modified formula has a significant proportional bias in predicting mCrCl (slope=1.77, 95% CI: 1.12-2.43, p=0.02 vs. slope=1), whereas the conventional CG equation does not (slope=0.93, p=0.69 vs. slope=1). These results indicate that our modified CG formula is not as accurate as the conventional CG equation for calculation of eCrCl in individuals without obesity. A cut-off of BMI greater than 32 kg/m^2 (dotted line, Figure 5) was then identified as the value above which the conventional CG equation is expected to produce an overestimation of mCrCl, and the new formula may be applied to improve the estimation of CrCl in subjects with obesity.

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4. Discussion

In our population of patients with obesity without primary or overt kidney disease, mCrCl augmented with body weight, with an average increase of 0.7 mL/min per kg. This increase was associated with albumin excretion, suggesting a possible mechanism of early kidney damage. Although early renal damage may be the consequence of obesity-related comorbidities including diabetes mellitus or hypertension [27], "healthy obesity" without evidence of coexisting cardiometabolic complications is an independent risk factor for renal injury [28, 29], and glomerular hyperfiltration has been identified as a pathogenic link [5]. The mechanisms leading to increased glomerular filtration in obesity may recognize an increase in the renal plasma flow and filtration fraction [7]. The reduction of pre-glomerular vascular resistance along with a raise in post-glomerular resistance, lead to an increase in the filtering surface area thus increasing the permeability of the glomerular hydraulic barrier [5]. The hemodynamic and the tubular hypothesis have been proposed as possible explanations for this cascade of events. The hemodynamic theory hypothesizes a disequilibrium of vasoactive molecules regulating the tone of afferent and efferent arterioles. The activation of the renin-angiotensin-aldosterone system (RAAS) with increased local production of angiotensin II [8] and activation of endothelin-1 contributes to increase the resistance of efferent arterioles. Additional molecules, such as cyclooxygenase 2 (COX2)-derived prostanoids and nitric oxide, have been identified as vasodilatory mediators, leading to a reduction in the afferent arteriolar resistance. The tubular theory hypothesizes that increased sodium reabsorption in the proximal tubule leads to a deactivation of the tubuloglomerular feedback [30], causing a decrease in the afferent arteriole resistance, with consequent increase in the glomerular perfusion and filtration [5].

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Important determinants of hyperfiltration include blood pressure, sodium intake and consumption of meat protein [31]. We could not demonstrate a direct effect of blood pressure, extemporarily measured, on both CrCl and albuminuria, which may depend on the heterogeneity of the studied population and on the effect of different antihypertensive drugs. Unfortunately, due to the retrospective nature of the study, we did not have measures of 24h-urinary sodium and 24h-urinary urea reflecting sodium and protein intake, respectively. Prospective studies will be necessary to define the effect size of these determinants on hyperfiltration in subjects with obesity.

Additional mechanisms include the increase in serum leptin that may enhance the sympathetic activity that, in turn, triggers RAAS activation and sodium retention in the kidney [5]. Changes in production of adiponectin [9] and resistin [32], inflammation [11], oxidative stress [12], abnormal lipid metabolism [33], nephron mass reduction [14], insulin resistance [34], are further possible mechanisms that may affect the glomerular filtration barrier, with consequent increase in glomerular permeability. The first sign of renal damage is microalbuminuria, suggesting a potential risk of progression to renal failure and the development of premature cardiovascular events, thus worsening the prognosis in patients with obesity [35]. Our results show that the mCrCl is independently associated with albuminuria, suggesting a possible mechanism of early kidney damage in patients with obesity. To which extent hyperfiltration, per se, may represent an early sign of renal damage has not been fully clarified, yet, and the retrospective nature of our study did not allow us to demonstrate the worsening of kidney damage or a potential progression to kidney failure in our patients. The association of hyperfiltration with elevated urinary albumin excretion has been already described [5]. High prevalence of albuminuria was observed in a population of patients with obesity undergoing bariatric surgery [36]. In a cross-sectional study of

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200 subjects with overweight and obesity, the prevalence of albuminuria was positively associated with BMI [37]. Accordingly, a high prevalence of microalbuminuria (7.1%) or macroalbuminuria (2.7%) has been observed in patients with overweight without diabetes or hypertension [38]. In the NHANES 3, subjects with obesity showed higher prevalence of albuminuria in comparison with the general population [39]. A decrease in GFR [40], 24-h creatinine clearance [41], albuminuria and proteinuria [40, 42] were observed following bariatric surgery. Furthermore, adults with overweight and/or obesity, with no evidence of obesity-related comorbidities, showed increased incidence of initial sign of kidney disease [43]. It has been suggested that if hyperfiltration is not promptly treated, the initial glomerulomegaly may evolve to glomerulosclerosis [14] and eventually to renal failure [44].

Evaluation of the glomerular filtration rate in patients with obesity may therefore be important, even in the absence of overt kidney disease, to establish whether tailored strategies for weight loss and appropriate pharmacological therapies should be initiated for prevention of the renal damage [45]. Several methods including inulin clearance [46], radioisotopic methods, radiocontrast agents, urea and cystatin C [16] have been used for the evaluation of kidney function. However, these techniques show several disadvantages in the clinical practice due to potentially invasive, time-consuming and complex or expensive methods of GFR assessment. The creatinine clearance measurement by urine collection over 24 hours represents one of the most used technique, although it results inconvenient due to difficulties for urine collection [16]. To encompass these difficulties, prediction equations such as CG [17], MDRD [18] and CKD-EPI [19] have been developed for the estimation of CrCl in the general population. However, these prediction formulas show lack of accuracy in the estimation of GFR in populations without chronic kidney

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diseases compared to those with the disease [47]. Moreover, these formulas have not been validated in patients with obesity, especially when BMI is >40 kg/m^2, in whom GFR estimation is associated with important biases and inaccuracies [48]. Comorbidities such as diabetes and hypertension may also impact on CrCl estimation [49]. To minimize the impact of these biases, in our study we excluded patients with primary or overt kidney disease as well as those with measured CrCl < 60 mL/min, with the aim at identifying patients with hyperfiltration, who may need prompt specific therapeutic measures to slow down the progression of glomerular damage. In our cohort, the CG formula showed a progressive overestimation at high CrCl values, whereas an underestimation resulted from CKD-EPI and MDRD formulas. To further improve the precision of the eCrCl, starting from CG formula that includes body weight in its algorithm, we generated a new formula for the estimation of CrCl in our population of patients with obesity, with a high correlation coefficient and no deviation at high mCrCl values.

Our study has some limitations. The study population comprised patients of Caucasian ethnicity and it was predominantly composed by women. A proportion of patients were on treatment for diabetes or hypertension, and 24-h albuminuria was not measured in the whole population. Additionally, due to the retrospective nature of this study, data regarding patients' prognosis were not available. Further studies will be necessary to address this issue.

5. Conclusion

In patients with obesity without primary or overt kidney damage, the glomerular filtration rate increases with body weight, and it is associated with the presence of albuminuria, suggesting an early kidney damage. We propose a new algorithm for the estimation of CrCl that might be

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useful in clinical practice to identify a condition of hyperfiltration associated with obesity, with the aim at detecting an early glomerular damage and preventing the progression of renal disease.

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None

Author contributions

A.B. and G.S. interpreted data and wrote the manuscript. D.G., P.P., P.F. and G.C. assisted with the interpretation of the data and revised the manuscript. F.S. and G.S. designed the study protocol. All authors read, critically revised the draft and approved the final manuscript. A.B. has full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

The study was approved by the local Ethical Committee (CEAVNO – Comitato Etico Area Vasta Nord-Ovest). All procedures performed in this study were in accordance with the ethical standards of the Local Ethical Committee and with the 1964 Helsinki Declaration and its later amendments.

Data availability:

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request

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Figure legends

Figure 1. Relationship between body weight, age and mCrCl

Relationship between creatinine clearance and body weight (**A**) and age (**B**). In each panel, the Pearson's correlation coefficient (r) is reported along with its significance (p)

Figure 2. Relationship between mCrCl and the eCrCl

Relationship between measured creatinine clearance and creatinine clearance estimated by CG (**A**), CKD-EPI (**B**) and MDRD (**C**). Both CKD-EPI and MDRD were deindexed by multiplying the results for BSA/1.73. In each panel, the Pearson's correlation coefficient (r) is reported along with its significance (p).

Figure 3. Relationship between mCrCl and CrCl estimated using the new formula.

Pearson's correlation coefficient (r) is reported along with its significance (p)

Figure 4. eCrCl by using the prediction formulas and mCrCl

Panel A. Mean difference (± SD) between mCrCl and eCrCl by CG (+ 44.3 mL/min), CKD-EPI (− 29.5 mL/min), MDRD (− 34.2 mL/min) and new formula (+ 0.3 mL/min).

*: $p<0.05$ versus mCrCl as assessed by paired Student's t-test. N.S.: not significant

Panel B. Individual values of mCrCl and eCrCl by CG, CKD-EPI, MDRD and new formula.

Both CKD-EPI and MDRD formulas were deindexed by multiplying the results for BSA/1.73.

Abbreviations: CrCl: creatinine clearance; CG: Cockroft-Gault formula; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease

Figure 5. Relationship between BMI and CrCl and prediction equations in the cohort of 342 patients with obesity and 50 healthy individuals without obesity

Relationship between mCrCl and BMI in the cohort of 342 patients with obesity (black dots) and in 50 healthy individuals without obesity (red dots). A spline curve fitted to the mCrCl is shown together with the lines predicted by the conventional CG equation and by the modified CG equation. The vertical dotted line indicates a BMI cutoff above which the eCrCl calculated using the conventional CG formula was 7 mL/min higher than the mCrCl. This threshold was chosen because it corresponds to the average difference between the mCrCl measurement and the modified CG equation.

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Tables

Table 1. Summary of the formulas to measure and estimate the creatinine clearance

CrCl (mL/min)	(24 h urinary creatinine × Urinary volume)/ Serum Creatinine
CKD-EPI (mL/min *per* 1.73 m^2)	$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]
^CKD-EPI (mL/min)	$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American] × (BSA/1.73)
MDRD (mL/min *per* 1.73 m^2)	$175 \times (SCr)^{-1.154} \times (age)^{-0.203} \times 0.742$ [if female] x 1.212 [if Black]
^MDRD (mL/min)	$[175 \times (SCr)^{-1.154} \times (age)^{-0.203} \times 0.742$ [if female] × 1.212 [if Black]] × (BSA/1.73)
CG (mL/min)	[(140 - age) (weight in kg)/72 × serum creatinine] × 0.85 if female

Abbreviations: BSA: body surface area; CrCl: creatinine clearance; CG: Cockroft-Gault formula; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; MDRD: Modification of Diet in Renal Disease; SCr: serum creatinine

For the CKD-EPI formula: κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

^ : deindexed eCrCl

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Table 2. Anthropometric and clinical measures, mCrCl and eCrCl in the study population

	Men n=114	Women n= 228	Whole group n=342
Age (years)	49.0 ± 11.3	49.4 ± 13.1	49.2 ± 12.5
Body weight (kg)	148.5 ± 30.5*	122.5 ± 23.7	131.1 ± 28.8
Height (m)	1.74 ± 0.09*	1.61 ± 0.06	1.65 ± 0.09
BMI (kg/m^2)	48.7 ± 9.5	47.0 ± 8.4	47.6 ± 8.9
BSA (m^2)	2.31 ± 0.27*	2.52 ± 0.26	2.20 ± 0.21
Serum creatinine (mg/dL)	0.9 ±0.2	0.72 ± 0.16*	0.78 ± 0.19
Urine creatinine (mg/24h)	2114 ± 587	1540 ± 470*	1732 ± 579
Urine volume (mL/24h)	1769 ± 770	1642 ± 761	1680 ± 764
mCrCl (mL/min)	170 ± 60	154 ± 59*	160 ± 60
eCrCl by CKD-EPI (mL/min *per* 1.73 m^2)	97 ± 19	97 ± 20	97 ± 19
^eCrCl by CKD-EPI (mL/min)	143 ± 33	124 ± 30*	130 ± 32
eCrCl by MDRD (mL/min *per* 1.73 m^2)	96 ± 25	92 ± 27	93 ± 26
^eCrCl by MDRD (mL/min)	140 ± 40	118 ± 38*	125 ± 40
eCrCl by CG (mL/min)	221 ± 80	195 ± 78*	204 ± 79
eCrCl by new formula (mL/min)	169 ± 42	155 ± 41*	160 ± 42

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Data are presented as mean ± SD. *: $p<0.05$ between males and females as determined by unpaired Student's *t*-test.

^: deindexed eCrCl was calculated by dividing individual eCrCl by 1.73 and by multiplying the result by the BSA of each patient.

Abbreviations: BMI: body mass index; BSA: Body Surface Area; CG: Cockcroft-Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eCrCl: estimated creatinine clearance; MDRD: Modification of Diet in Renal Disease; mCrCl: measured creatinine clearance

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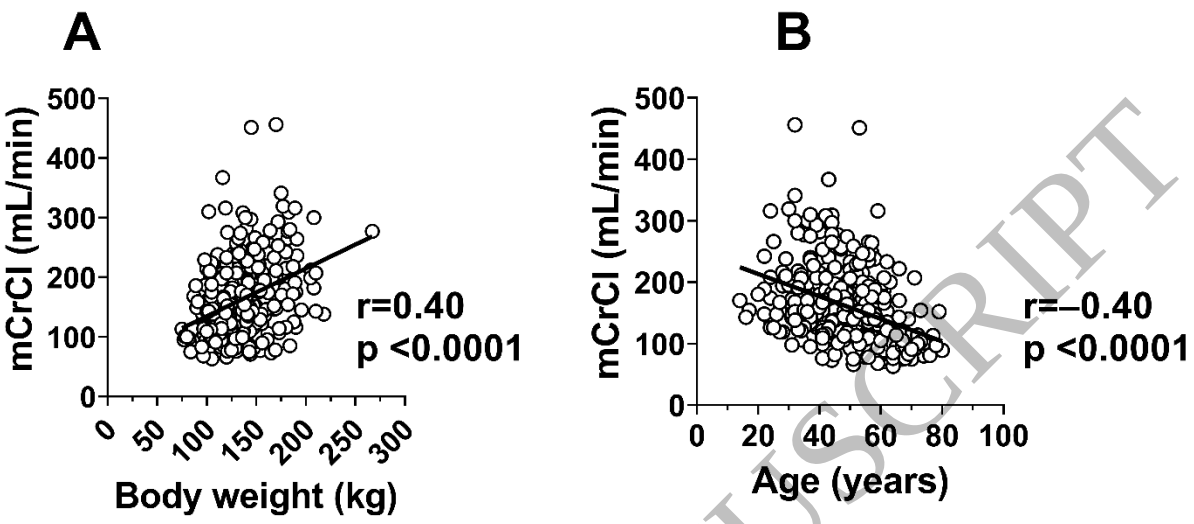

Figure 1
169x77 mm (x DPI)

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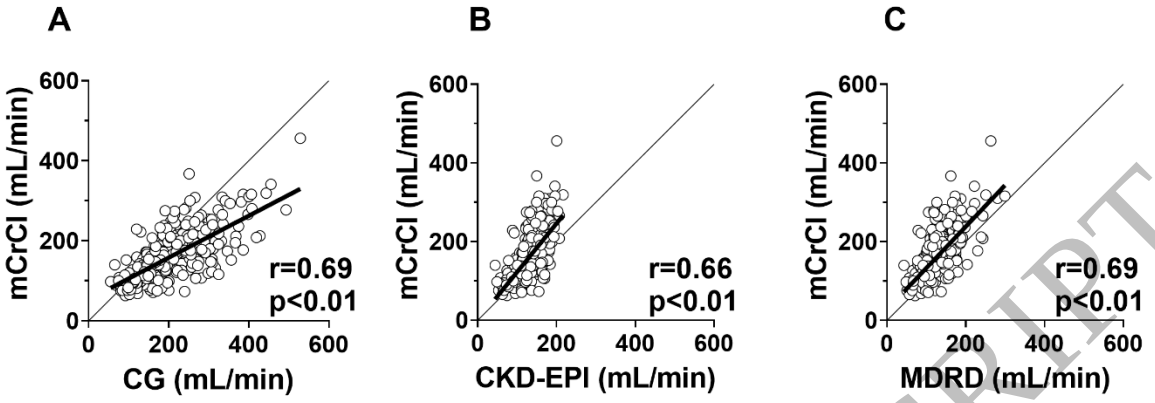

Figure 2
214x77 mm (x DPI)

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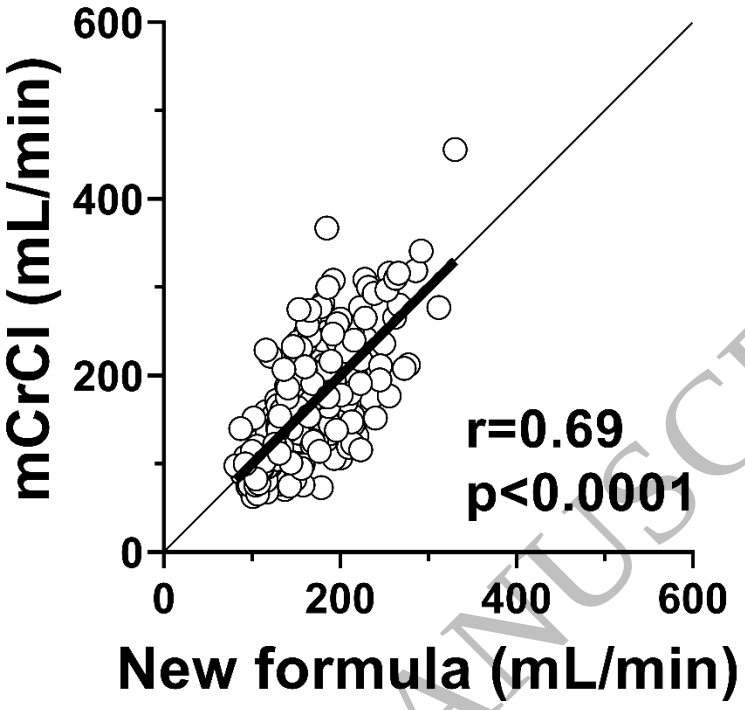

Figure 3
112x102 mm (x DPI)

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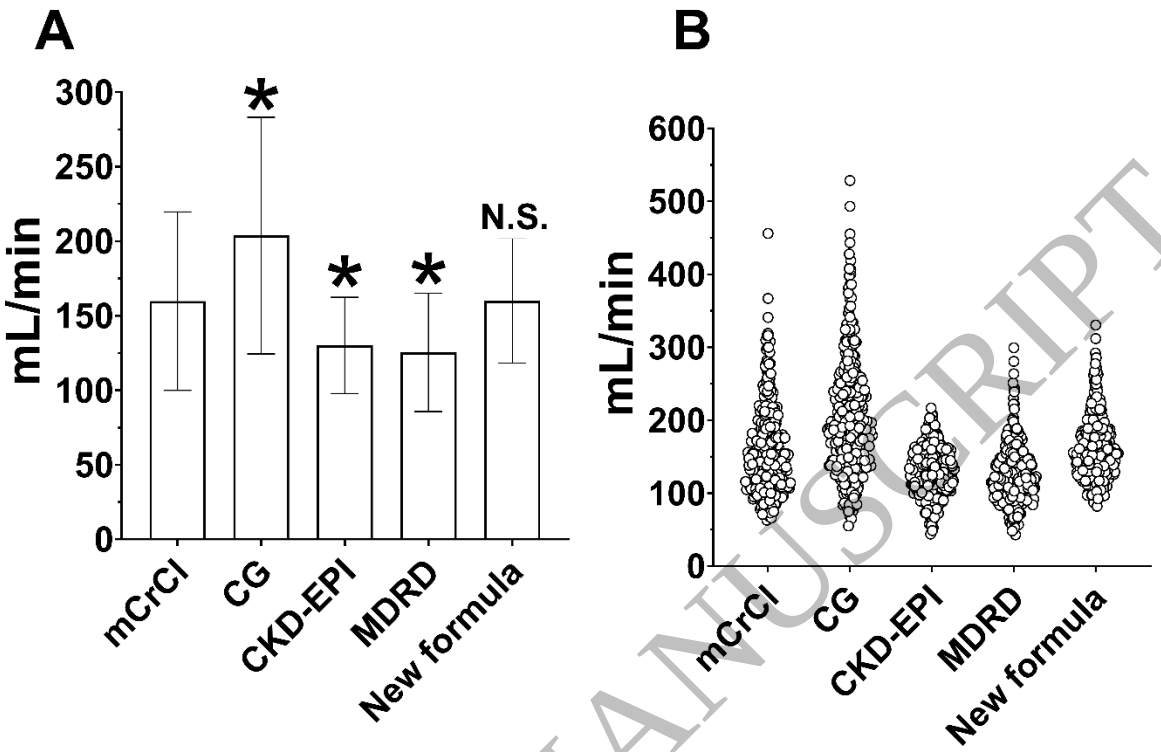

Figure 4
205x132 mm (x DPI)

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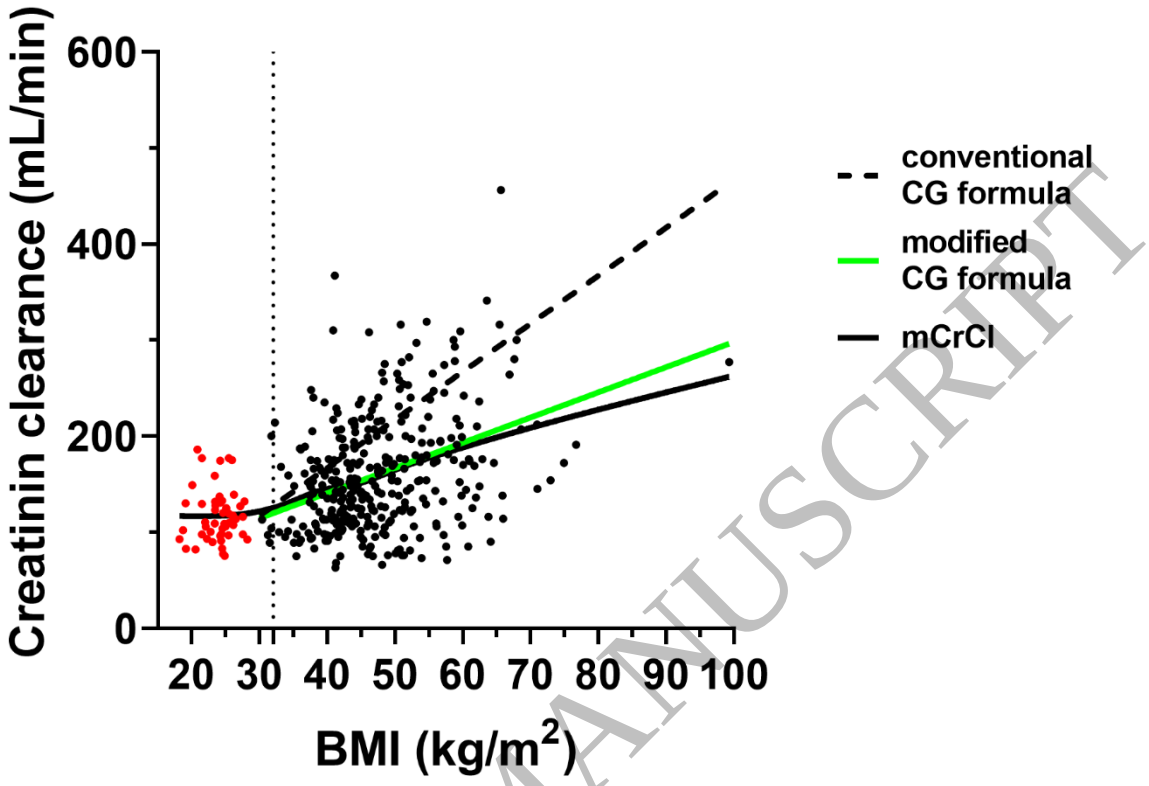

Figure 5
152x109 mm (x DPI)

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