Influence of Muscle Mass and Physical Activity on Serum and Urinary Creatinine and Serum Cystatin C

Alessandra Calábria Baxmann,* Marion Souza Ahmed,† Natália Cristina Marques,*
Viviane Barcellos Menon,* Aparecido Bernardo Pereira,† Gianna Mastroianni Kirsztajn,†
and Ita Pfeferman Heilberg†

*Nutrition Program, Universidade Federal de São Paulo, and †Nephrology Division, Universidade Federal de São Paulo,
São Paulo, Brazil

Background and objectives: For addressing the influence of muscle mass on serum and urinary creatinine and serum cystatin C, body composition was assessed by skinfold thickness measurement and bioelectrical impedance analyses.

Design, setting, participants, & measurements: A total of 170 healthy individuals (92 women, 78 men) were classified as sedentary or with mild or moderate/intense physical activity. Blood, 24-h urine samples, and 24-h food recall were obtained from all individuals.

Results: Serum and urinary creatinine correlated significantly with body weight, but the level of correlation with lean mass was even greater. There was no significant correlation between body weight and lean mass with cystatin C. Individuals with moderate/intense physical activity presented significantly lower mean body mass index (23.1 ± 2.5 versus 25.7 ± 3.9 kg/m^2) and higher lean mass (55.3 ± 10.0 versus $48.5 \pm 10.4\%$), serum creatinine (1.04 ± 0.12 versus 0.95 ± 0.17 mg/dl), urinary creatinine (1437 ± 471 versus 1231 ± 430 mg/24 h), protein intake (1.4 ± 0.6 versus 1.1 ± 0.6 g/kg per d), and meat intake (0.7 ± 0.3 versus 0.5 ± 0.4 g/kg per d) than the sedentary individuals. Conversely, mean serum cystatin did not differ between these two groups. A multivariate analysis of covariance showed that lean mass was significantly related to serum and urinary creatinine but not with cystatin, even after adjustment for protein/meat intake and physical activity.

Conclusions: Cystatin C may represent a more adequate alternative to assess renal function in individuals with higher muscle mass when mild kidney impairment is suspected.

Accurate renal function measurements are important in the diagnosis and treatment of kidney diseases, adjustment of drug dosages, and decision-making regarding when to initiate renal replacement therapy. Serum creatinine is the most commonly used indicator of renal function, but its measurement suffers from a variety of analytical interferences and significant standardization problems (1,2).

Serum creatinine can be affected by age, gender, ethnicity, dietary protein intake, and lean mass and may remain within the reference range despite marked renal impairment in patients with low muscle mass. Consequently, the sensitivity of serum creatinine for the early detection of kidney disease is poor and not a good predictor when analyzing the elderly (3,4). Conversely, theoretically, serum creatinine may be falsely increased in individuals with higher muscle mass and normal renal function.

The GFR represents the best overall assessment of kidney function, but the gold standard techniques for the measurement of GFR, such as inulin clearance, [^{125}I]iothalamate, ^{51}Cr-EDTA,

^{99m}Tc-diethylenetriaminepentaacetic acid, and iohexol are too labor-intensive and costly for routine clinical use (5,6), so creatinine clearance is used instead.

To rid the need of 24-h urine collections, several serum creatinine–based prediction formulas have been proposed to predict GFR (7–16). The equations of Cockcroft and Gault (7,8) and the one derived from the Modification of Diet in Renal Disease (MDRD) study (10) are the most widely accepted; however, the competence of such formulas to predict GFR in patients with normal values of serum creatinine is debated.

Despite the important influence of muscle mass on serum creatinine, the different equations used to predict GFR do not include parameters of body composition such as lean mass. Human body mass can be partitioned into two main compartments: Fat and lean (fat-free) mass. The latter comprises body cell mass (BCM), bone mass, and extracellular water. The gold standard techniques for the measurement of body composition include hydrodensitometry, computed tomography, magnetic resonance imaging, dual-photon absorptiometry, neutron activation analysis, total body potassium counting, and isotope dilution (17,18). Nevertheless, in clinical practice, the indirect, low-cost, noninvasive methods of determining human body composition, such as bioelectrical impedance and skinfold thickness, are used instead (17). Muscle mass is extremely

variable among elderly individuals and in children (4,19–22) and can be substantially modified by physical exercise (23).

Cystatin C, a low molecular weight basic protein (13 kD) that is freely filtered and metabolized after tubular reabsorption with only small amounts excreted in the urine, is an endogenous filtration marker that is being considered as a potential replacement for serum creatinine. Unlike serum creatinine, the serum concentration of cystatin remains constant up to 50 yr of age. It is commonly accepted that cystatin is produced at a constant rate in virtually all nucleated cells and that it is unaltered by inflammatory conditions. The advantages of using cystatin C as a filtration marker are less influence by age, gender, weight, and muscle mass than serum creatinine (24–31). An overall meta-analysis based on 46 studies performed on adults and children demonstrated, by means of receiver operating characteristic analysis, that cystatin C is superior to serum creatinine as a marker of kidney function (32). To address the influence of muscle mass on serum and urinary creatinine determination and serum cystatin C, we evaluated the body composition through bioelectrical impedance and skinfold thickness in healthy individuals with distinct levels of physical activity.

Concise Methods

A total of 206 healthy volunteers were recruited from the hospital staff and gymnastics schools. Selections were made using a questionnaire to exclude any carriers of kidney disease; those with relevant morbid conditions; or those taking anabolic steroids, creatine, vitamins, or any sort of dietary supplements. Spot urine samples were obtained, and screening tests using urine dipsticks were performed to exclude those who had positive protein, glucose, erythrocytes, nitrites, or leukocyte esterase tests. A total of 170 healthy adults (92 women and 78 men) were eligible to be enrolled in this study. A written consent was obtained from all participants, and the local ethics committee of the Universidade Federal de São Paulo approved the study.

All participants were subjected to an anthropometric evaluation and body composition assessment through skinfold thickness and bioelectrical impedance. They were then given collection containers and instructions for 24-h urine collection for creatinine and microalbuminuria determination. On the morning they completed the 24-h urine collection, a blood sample was drawn, and an additional fasting morning urine sample was collected at the laboratory for urinalysis and determination of retinol-binding protein (RBP). They were then asked to complete a 24-h food recall questionnaire to assess their food intake.

Biochemical Parameters

Serum creatinine, cystatin C, urea, and albumin were determined in serum samples. Creatinine was determined according to a modified Jaffé reaction (33) in Hitachi 912 (Roche Diagnostic System, Basel, Switzerland), by an isotope dilution mass spectrometry traceable method. Estimates of GFR were obtained using the Cockcroft-Gault (7,8) and re-expressed four-variable MDRD equations (10,34). Cystatin C was measured using a fully automated particle-enhanced immune turbidimetric method (DAKO Cystatin C Pet kit, Copenhagen, Denmark). Inter- and intra-assay variation, calculated from the control samples with assigned values of 0.97 and 3.36 mg/L, was 3.2 and 1.4%, respectively. Microalbuminuria was determined by ELISA and RBP by the immunoenzymometric method (35).

Measurements and Assessments

A 24-h food recall to assess daily energy intake and macronutrients (protein, lipids and carbohydrate) was undertaken by each participant. The amount of striated muscle intake (meat intake) was also assessed. Nutrient intakes were calculated with a computerized program developed in our department. The food table used in the program was from the US Department of Agriculture.

Anthropometric parameters included body weight, height, waist circumference, and body mass index (BMI). BMI was calculated as weight (kg)/height (m²). Body composition was assessed by two indirect methods: Skinfold thickness and bioelectrical impedance analysis (BIA). Skinfold measurements were performed by the same nutritionist in the nondominant arm at four sites—biceps, triceps, subscapular, and suprailiac—using a Lange skinfold caliper (Cambridge Instrument, Cambridge, MA). Three sets of measurements were averaged for each site. Body fat was calculated according to Siri's equation (36). BIA was performed with a portable device model BIA 101 Quantum, RJL Systems (Detroit, MI), and the software provided by the manufacturer calculated total body water, fat-free mass, BCM, and fat mass. BCM was defined as fat-free mass without bone mineral mass and extracellular water.

Physical Activity

The Baecke questionnaire (37), validated in a Brazilian population survey (38), was used to calculate the level of physical activity.

Statistical Analyses

Results were reported as means ± SD. Comparisons were performed through ANOVA (among the three groups). The Pearson correlation coefficient was used to determine the correlation between parameters. A multivariate analysis of covariance was performed to determine the effect of body weight, fat-free mass, and BCM (independent variables) on serum and urinary creatinine and cystatin C (dependent variables), adjusting for physical activity, protein intake, and meat intake (covariates). For the purpose of this analysis, the variables without normal distribution were converted in logarithmic (log10) scale. The level of significance was defined as $P < 0.05$.

Results

A total of 170 healthy individuals (78 men and 92 women; 36.6 ± 13.6 yr of age (range 18 to 75 yr old) participated in the study. None of the participants presented altered urinalysis, microalbuminuria, or increased urinary RBP.

Correlations between fat-free mass, BCM, and body weight and serum and urinary creatinine are shown in Figure 1. Serum and urinary creatinine levels significantly correlated with body weight ($r = 0.512$ [95% confidence interval (CI) 0.391 to 0.615] and $r = 0.539$ [95% CI 0.422 to 0.638]; $P = 0.0001$), but the level of correlation was greater with fat-free mass ($r = 0.734$ [95% CI 0.656 to 0.797] and $r = 0.706$ [95% CI 0.620; 0.774]; $P = 0.0001$). There was no overlap between both CI.

Correlations between fat-free mass, BCM, and body weight and serum cystatin C are shown in Figure 2. There was no significant correlation between body weight, fat-free mass, or BCM and serum cystatin C.

Mean daily energy intake of individuals according to their level of physical activity (sedentary or mild or moderate/intense activity) was shown to be significantly higher among the group with moderate/intense *versus* mild physical activity and
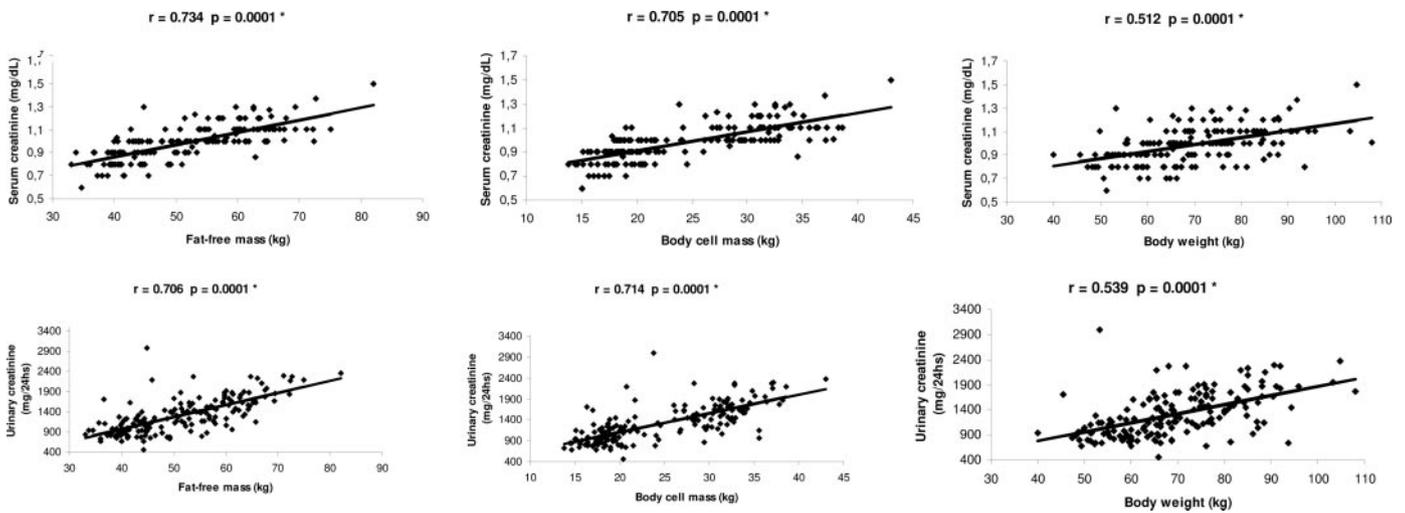
Figure 1. Correlation between fat-free mass, BCM, and body weight and urinary and serum creatinine.

versus sedentary individuals (36 ± 14 *versus* 28 ± 9 and *versus* 26 ± 10 kcal/kg per d; data not shown). Distribution of macronutrients (protein, lipids, and carbohydrates) was shown to be significantly higher as well: 1.4 ± 0.6 *versus* 1.2 ± 0.5 and *versus* 1.1 ± 0.6 and g/kg per d, 81 ± 42 *versus* 68 ± 32 and *versus* 63 ± 27 g/d, and 342 ± 173 *versus* 261 ± 106 and *versus* 218 ± 74 g/d, respectively. Meat intake was also significantly higher in individuals with moderate/intense physical activity *versus* mild and *versus* sedentary: 0.7 ± 0.3 *versus* 0.6 ± 0.4 and *versus* 0.5 ± 0.4 g/kg per d.

Table 1 shows the mean anthropometric, body composition, and renal function parameters according to the level of physical activity. Individuals with moderate/intense physical activity presented with a trend for lower body weight and a significantly lower BMI, higher muscle mass, and lower body fat content than the sedentary individuals or those with mild physical activity. Waist circumference was also significantly lower in individuals with moderate/intense activity when compared with sedentary individuals.

Individuals with moderate/intense physical activity presented a significantly higher serum creatinine and albumin compared with the other two groups and a significantly higher urinary creatinine than the sedentary individuals. There were no differences in serum cystatin or urea, microalbuminuria, and measured creatinine clearance among these groups. Individuals with moderate/intense physical activity presented with a

trend for lower estimated creatinine clearance and GFR (Cockcroft-Gault and MDRD equation) than sedentary individuals.

Table 2 shows the results of the multivariate analysis of covariance showing that body weight, fat-free mass, and BCM were significantly related with serum creatinine ($R^2 = 0.37$ and $R^2 = 0.54$ and $R^2 = 0.56$, $P < 0.001$) and with urinary creatinine ($R^2 = 0.34$ and $R^2 = 0.48$ and $R^2 = 0.51$, $P < 0.001$, respectively), even after adjustment for physical activity and protein and meat intake. Conversely, there was no significant association between body weight, fat-free mass, or BCM and serum cystatin C in this model.

Discussion

Serum creatinine is influenced by gender, age, and the amount of muscle mass; however, formulas that predict GFR take into account gender, age and weight but not muscle mass (7–16). To date, no study has evaluated the influence of muscle mass on serum and urinary creatinine and serum cystatin C in healthy individuals with distinct levels of physical activity.

In this study, although serum and urinary creatinine were significantly correlated with body weight, the level of correlation with lean (fat-free) mass and BCM was even greater. Conversely, there was no significant correlation between body weight, fat-free mass, or BCM and serum cystatin C.

The group with moderate/intense physical activity presented a significantly higher mean serum creatinine compared
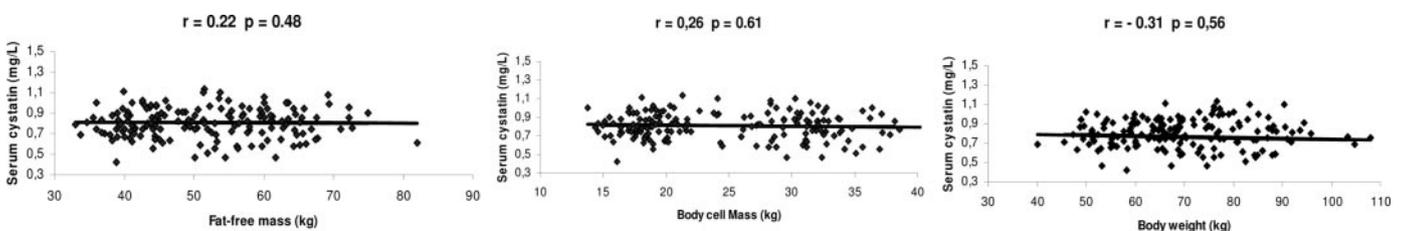

Figure 2. Correlation between fat-free mass, BCM, and body weight and serum cystatin.

Table 1. Anthropometric, body composition, and renal function parameters according to the level of physical activity[a]

Parameter	Sedentary (n = 57)	Mild (n = 61)	Moderate/Intense (n = 52)	P
Age (yr)	37.2 ± 14.0	39.5 ± 14.6	32.5 ± 10.9[b]	0.0200
Weight (kg)	69.3 ± 14.2	70.5 ± 12.9	67.8 ± 11.5	0.5400
BMI (kg/m^2)	25.7 ± 3.9	25.6 ± 4.1	23.1 ± 2.5[b,c]	0.0001
Waist circumference (cm)	82.1 ± 10.3	80.6 ± 14.7	75.7 ± 10.9[c]	0.0300
Body fat (skinfold thickness; %)	31.4 ± 8.4	30.7 ± 8.9	20.7 ± 8.8[b,c]	0.0001
Body fat				
%	29.6 ± 7.4	27.7 ± 6.7	18.4 ± 6.2[b,c]	0.0001
kg	20.7 ± 7.7	19.7 ± 6.9	12.5 ± 4.7[b,c]	0.0001
Fat-free mass				
%	70.4 ± 7.4	72.3 ± 6.7	80.0 ± 11.9[b,c]	0.0001
kg	48.5 ± 10.4	50.8 ± 9.6	55.3 ± 10.0[b,c]	0.0002
BCM (kg)	22.8 ± 7.2	23.9 ± 6.7	27.4 ± 6.3[b,c]	0.0020
Serum cystatin (mg/L)	0.82 ± 0.14	0.80 ± 0.14	0.79 ± 0.14	0.6000
Serum urea (mg/dl)	29.2 ± 8.1	29.1 ± 8.2	30.6 ± 8.2	0.5900
Serum albumin (g/dl)	4.46 ± 0.26	4.56 ± 0.26	4.70 ± 0.32[b,c]	0.0001
Serum creatinine (mg/dl)	0.95 ± 0.17	0.96 ± 0.13	1.04 ± 0.12[b,c]	0.0020
Urinary creatinine (mg/24 h)	1231 ± 430	1283 ± 400	1437 ± 471[c]	0.0400
Urinary RBP (mg/L)	0.05 ± 0.03	0.06 ± 0.05	0.08 ± 0.05[c]	0.0300
Microalbuminuria (μg/min)	6.7 ± 18.3	6.6 ± 10.8	7.2 ± 7.9	0.9600
CrCl (ml/min per 1.73 m^2)	88.3 ± 17.3	87.5 ± 18.3	91.2 ± 22.2	0.5600
CG (ml/min per 1.73 m^2)	93.0 ± 17.4	87.6 ± 15.0	89.0 ± 14.2	0.1500
MDRD (ml/min per 1.73 m^2)	84.5 ± 17.7	79.6 ± 12.2	81.8 ± 13.2	0.1900

[a]Data are means ± SD. BCM, body cell mass; BMI, body mass index; CG, Cockcroft-Gault; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease
[b]$P < 0.05$ *versus* mild.
[c]$P < 0.05$ *versus* sedentary.

Table 2. Multivariate analysis of covariance adjusted for physical activity, total protein, and meat intake

Dependent Variables	Independent Variables[a]	R^2	P
Serum creatinine[a]	Body weight	0.37	0.001
	Fat-free mass	0.54	0.001
	BCM	0.55	0.001
Urinary creatinine[a]	Body weight	0.34	0.001
	Fat-free mass	0.48	0.001
	BCM	0.51	0.001
Serum cystatin	Body weight	0.01	0.904
	Fat-free mass	0.01	0.803
	BCM	0.01	0.892

[a]Variables converted in logarithmic (log10) scale.

with the group with mild activity or the sedentary group and higher urinary creatinine than the latter. Mean values of measured creatinine clearance did not differ between these groups. Nevertheless, individuals with moderate/intense physical activity presented with a trend for lower estimated creatinine clearance (Cockcroft-Gault) and GFR (MDRD equation) than sedentary individuals, although not reaching statistical significance. Individuals with higher physical activity presented lower body weight, BMI, waist circumference, and body fat

content and higher muscle mass than the sedentary or those with mild physical activity. These results were expected because intense physical activity directly influences body composition, reducing the body fat and increasing the fat-free mass (23). Conversely, serum cystatin did not differ between groups. These findings further corroborate that cystatin C is not influenced by muscle mass (24–31).

Whether the capacity of cystatin C to predict GFR in healthy individuals is influenced by body composition has been con-

troversial (39), with some investigators advocating some association (40,41) and others finding no association of cystatin C and lean body mass (24–31). As pointed out recently by Shlipack (39), although the findings of MacDonald *et al.* (41) indicated a potential influence of lean body mass on cystatin C, adjustment for body surface area could possibly have eliminated such influence. In addition, dual-energy x-ray absorptiometry–determined lean body mass also may not reflect BCM well in patients with chronic kidney disease because of changes in hydration.

In this series, urinary creatinine was also significantly higher in the individuals with moderate/intense physical activity than the sedentary. Indeed, creatinine excretion is also influenced by muscle mass, because creatinine formation occurs almost exclusively in the muscle; therefore, theoretically, the urinary excretion is the most specific index to define muscle mass (42,43). Healthy men and women excrete approximately 1.5 and 1.2 g/d creatinine, respectively; however, these values can be modified according to the amount of muscle mass and diet. Food contributes with three distinct components that can alter the urinary excretion of creatinine: (*1*) Proteins that have arginine and glycine, precursors of creatine and guanidoacetate production; (*2*) creatine itself, which leads to a direct increase of the muscular creatine "pool," thereby raising the urinary excretion of creatinine; and (*3*) dietary creatinine, which is excreted readily as soon as absorbed (43–45). In this study, individuals with moderate/intense physical activity presented higher urinary creatinine, probably as a result of the larger muscle mass and the higher mean protein and meat intake consumed by these individuals. Not only was the protein intake higher, but also the lipid and carbohydrate intake were higher when compared with sedentary individuals. It is noteworthy that, despite consuming more energy, individuals with moderate/intense physical activity tended to exhibit lighter weight and lower BMI, and the percentage of fat mass was significantly lower than that in the sedentary individuals. This might have been attributed to their higher fat-free mass, which requires and expends more energy (46).

The Cockcroft-Gault formula was developed from 249 men with a range of creatinine clearance between 30 and 130 ml/min to estimate creatinine clearance on the basis of serum creatinine, age, gender, and body weight (7). The Cockcroft-Gault equation systematically overestimates GFR, because it was developed to estimate creatinine clearance and not GFR. Furthermore, because of the inclusion of weight in the numerator, the equation overestimates creatinine clearance in patients who are edematous or overweight (16,47) or in individuals with low creatinine production (malnourished patients). Conversely, it may underestimate creatinine clearance in individuals with high creatinine production as a result of higher muscle mass. In this study, the lower weight and the higher serum creatinine of individuals with moderate/intense physical activity might have contributed to the slightly lower mean value of the Cockcroft-Gault formula, although not achieving statistical significance, when compared with the sedentary individuals. Lim *et al.* (48) compared the acuity of some formulas used to estimate the GFR in healthy individuals with and without the adjust-

ment for lean or fat-free mass and concluded that when the Cockcroft-Gault equation was corrected per fat-free mass, there was a significant increase in its acuity; however, in their study, muscle mass was not measured by BIA or skinfold thickness but roughly estimated through a formula.

The re-expressed four-variable MDRD equation (34) estimates GFR adjusted for body surface area on the basis of serum creatinine, age, gender, and race. As for the Cockcroft-Gault formula, the muscle mass is not considered. The overestimation of GFR by the MDRD formula in older populations (49) may reflect a relatively lower serum creatinine concentration, as a result of reduced muscle mass, compared with the middle-aged population in which the MDRD formula was derived. Conversely, the tendency of the formula to underestimate the GFR in the majority of the studies carried out in healthy individuals can be explained by their higher muscle mass contrasting with that of patients with chronic renal failure as a result of anorexia, chronic inflammation, and metabolic acidosis leading to muscle breakdown (50). In individuals with high creatinine production and higher muscle mass, underestimation of MDRD is expected. In this series, the higher serum creatinine of individuals with moderate/intense physical activity might have contributed to the slightly (although not significantly) lower mean value of MDRD compared with the sedentary individuals.

Finally, to separate the potential influence of protein and meat intake from the influence of fat-free mass itself, on serum/urinary creatinine, a multivariate analysis of covariance was performed in this study. Such analysis disclosed that fat-free (lean) mass remained significantly related to serum and urinary creatinine, even after adjustments for protein/meat intake and physical activity. Conversely, a significant association between fat-free mass with serum cystatin C was not depicted.

Conclusions

This study showed that muscle mass affects serum and urinary creatinine but not cystatin C; therefore, the use of cystatin may represent a more adequate alternative to assess renal function in healthy individuals with higher muscle mass and potential mild kidney impairment.

Acknowledgments

Disclosures
None.

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