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Influence of body weight and Body Mass Index (BMI) on serum creatinine and creatinine clearance in apparently healthy adults

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Abstract

Serum creatinine and creatinine clearance are widely used clinically as an index of renal function to diagnose, treat and follow up renal diseases. One of the factors influencing the creatinine and its clearance is said to be body weight. To evaluate the influence of body weights on serum creatinine and creatinine clearance, a total of 160 healthy adult subjects (68 males and 92 females), within 1845 years of age were included in this study. The subjects were categorized according to body mass index (BMI): <18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal), 25-29.9 kg/m^2 (overweight) and >30 kg/m^2 (obese) consisting of 40 subjects respectively. Serum and 2hr urine samples were obtained from all subjects and analyzed using the alkaline picrate method. A statistical significant difference ($P<0.05$) was observed for both serum creatinine and creatinine clearance among the various weight categories,due to low values seen in underweight subjects and high values seen in obese subjects. Serum creatinine among males of the various weight categories were found to be significantly different ($P<0.05$), while their creatinine clearance were not significantly different ($P>0.05$). Also, serum creatinine and creatinine clearance among females of various weight were found to be significantly different ($P<0.05$). Also, values observed for males were higher than those of females. This study thus shows that body weight and BMI have significant influence on serum creatinine and creatinine clearance.

INTRODUCTION

Human body mass (weight) 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 [1,2]. Similarly, others have suggested that BMI, which by definition includes both fat and fat-free mass, estimates relative body weight but does not necessarily estimate body fat very well [3] . BMI is calculated by dividing weight (in kilograms) by square height (in meters) [4] . The WHO defines an adult who has a BMI between 25 and 29.9 as overweight - an adult who has a BMI of 30 or higher is considered obese - a BMI below 18.5 is considered underweight, and between 18.5 to 24.9 a healthy weight[5-6] .

Creatinine (MW 113 Da) is the cyclic anhydride of creatine that is produced as the final product of decomposition of phosphocreatine [7] . Creatinine is produced endogenously and released into body fluids at a constant rate and its plasma concentration is maintained within narrow limits predominantly by glomerular filtration. Consequently, both plasma creatinine concentration and its renal clearance ("creatinine clearance") have been used as markers of the glomerular filtration rate (GFR) [7] . Each day, approximately 2% of the total body creatine is dehydrated into the bye-product, creatinine. Under normal conditions the daily amount of creatinine produced is apparently quite constant and depends on body size and metabolic rates [8] .

One of the factors influencing the creatinine concentration is said to be muscle mass [9,10] . However, there is little information on the relationship between muscle mass and serum creatinine[11] . 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 [12,1] .Conversely, theoretically, serum creatinine may be falsely increased in individuals with higher muscle mass and normal renal function [13]. An alternative to this approach is the measurement of creatinine clearance [14] .

Historically, creatinine clearance has been seen as more sensitive for detection of renal dysfunction than measuring plasma creatinine [7] .The importance of creatinine clearance is in the early detection of functional impairment of kidney without overt signs and symptoms [15]. Reference ranges are for men, women and children since each has a different percentage of lean body mass (LBM). The greater the muscle mass, the greater the creatinine clearance [16] . Although obesity has been, in general, associated with glomerular hyperfiltration, visceral adiposity has been suggested to be associated with reduced glomerular filtration [17] .In nondiabetic subjects, a high waist-to-hip ratio, considered a marker of central obesity, has been associated with a lower creatinine clearance [18] .In estimating GFR from serum creatinine, body weight is included in the formula [19] or nomogram [20] to allow for variation in creatinine excretion [11] .This study is therefore aimed at evaluating the influence of body weights and BMI on serum creatinine and Creatinine clearance in apparently healthy adult subjects.

MATERIALS AND METHODS

Study Area: The study area is Ekpoma, the administrative headquarters of Esan West Local Government Area of Edo State, Nigeria. The area proper lies between latitudes 6^{0}43' and 6^{0}45' North of the Equator and longitudes 6^{0}6' and 6^{0}8' East of the Greenwich Meridian [21] , with a population of 89,628 and 127,718

at the 1991 and 2006 population census respectively [22] .

Subjects: The study population comprised a total of one hundred and sixty (160) healthy adult subjects of sixty-eight (68) males and ninety-two (92) females within the age range of 18-45 years, made up of forty (40) Underweight, Normal Weight, Overweight and Obese subjects respectively, who gave their informed consent and filled a structured questionnaire respectively..

Selection was made using a questionnaire to exclude any subject with nephrotic syndrome, diabetes, hypertension, urinary tract infection, skeletal muscle disease, or those taking nephrotoxic drugs, anabolic steroids, creatine supplement and pregnant women from this study. Subjects that are apparently healthy and fall within the weight categories were included in the study.

Anthropometric Measurement: Body weight (kg) and height (m) were measured in shoeless subjects wearing light clothing and were used to calculate BMI as weight (kilograms)/height^2 (meters). The Body weight (kg) and BMI (kg/m^2) values as obtained were used to categorise each subject into; underweight, normal weight, overweight and obese weight categories before sample collection.

Sample Collection / Preparation: Before the start of urine collection each subject was asked to empty the bladder completely as much as possible. At 00.00 hour (beginning of urine collection) each subject was given 600ml of water to increase the flow rate [15] and all urine passed within 2 hours collection period was collected into a sterile container appropriately labelled up to and the last minute of the collection period. At 1 hour into urine collection, 5ml of venous blood was collected via venepuncture using a sterile needle and syringe, into a sterile plain container appropriately labelled and allowed to clot. The volume of urine produced within the 2 hours collection period was measured (ml) and recorded. The urine was diluted 1 in 50, and an aliquot (3ml) was taken into another sterile plain container with corresponding label. Serum sample was separated from the clotted and retracted blood within five hours of collection via centrifugation at 4000 rpm for 5 minutes, into another sterile plain container with corresponding label. Samples (serum and diluted urine) were analysed after collection or stored at 4^{0}C in the refrigerator for at most 3 days and thawed at 37^{0}C for 10 minutes in a water bath before analysis.

Table 1. Mean Body Weight, BMI, Serum Creatinine, and Creatinine Clearance of various weight categories

PARAMETERS	UNDERWEIGHT (N=40)	NORMAL WEIGHT (N=40)	OVERWEIGHT(N=40)	0BESE (N=40)	F-value	P-value
Mean ± SD Body weight (kg)	49 ± 7.2^a	59 ± 6.7^b	75 ± 6.3^c	84 ± 6.3^d	225.5	P<0.05
Mean ± SD BMI (kg/m^2)	17.1 ± 1.0^a	21.3 ± 1.6^b	26.7 ± 1.1^c	32.1 ± 1.9^d	842.2	P<0.05
Mean ± SD Serum Creatinine (mg/dl)	1.0 ± 0.2^a	1.1 ± 0.2^b	1.1 ± 0.2^b	1.1 ± 0.1^b	8.95	P<0.05
Mean ± SD Creatinine Clearance (ml/min)	124 ± 31.1^a	132 ± 43.1^a	155 ± 37.3^b	140 ± 41.9	4.58	P<0.05

F_{tab}=2.60, df_1=3, df_2=156, N=number of subjects. Values in a row having different values are significantly different.

Assay: Serum and urinary creatinine levels were measured by alkaline picric acid colorimetric (Kinetic assay) method described by [23].

Statistical Analysis: Results were reported as means ± SD in suitable tables. Comparisons were performed through ANOVA (among the four groups) and Student's t-test (among two groups). A two-tailed P<0.05 was considered significant.

RESULTS

This study showed that the body weight and BMI values for all comparisons made, were significantly different (P<0.05) among the various weight categories, being lowest in underweight, increasing to be highest in obese subjects (Tables 1, 2 and 3).

The serum creatinine and creatinine clearance values were significantly different (P<0.05) among the various body weight categories. Also, serum creatinine was significantly low (P<0.05) in underweight subjects, when compared to other weight categories with same higher values, while the creatinine clearance was significantly higher (P<0.05) in overweight subjects when compared to underweight and normal weight subjects (Table 1).The serum creatinine in males of various weight categories were significantly different (P<0.05), being significantly low (P<0.05) in underweight males when compared to normal weight and overweight males with higher values respectively. However, there was no significant differences (P>0.05) in creatinine clearance observed in males of various weights categories, though low in underweight and highest in overweight males respectively (Table 2).

The serum levels of creatinine and creatinine clearance in females of various weight categories were significantly different (P<0.05). Also, the serum creatinine is significantly low (P<0.05) in underweight females, when compared to females of other weight categories with same higher values respectively, while the creatinine clearance is significantly high in overweight females in comparison with females of other weight categories respectively (Table 3). However, the mean creatinine clearance values of overweight and obese subjects in all the tables did not fall within the reference range (Tables 1, 2, 3).

DISCUSSION

The results of this study showed that serum creatinine was significantly different among the various weight categories, being significantly low in underweight subjects when compared to other weight categories. Thus, show that serum creatinine is greatly influenced by body weight, most especially underweight

Table 2. Mean Body Weight, BMI, Serum Creatinine, and Creatinine Clearance in Males of various weight categories

PARAMETERS	MALE UNDERWEIGHT (N=21)	MALE NORMAL WEIGHT (N=17)	MALE OVERWEIGHT (N=23)	MALE 0BESE (N=7)	F-value	P-value
Mean ± SD Body Weight (Kg)	53 ± 5.3^a	62 ± 6.1^b	77 ± 5.7^c	86 ± 6.0^d	100.7	P<0.05
Mean ± SD BMI (Kg/m^2)	17.4 ± 0.8^a	21.0 ± 1.4^b	26.6 ± 1.1^c	31.2 ± 0.7^d	450.3	P<0.05
Mean ± SD Serum Creatinine (mg/dl)	1.1 ± 0.1^a	1.2 ± 0.1^b	1.2 ± 0.1^b	1.1 ± 0.1	4.835	P<0.05
Mean ± SD Creatinine Clearance (ml/min)	124 ± 30.4^a	138 ± 48.7	152 ± 36.7^b	147 ± 47.7	1.972	P>0.05

F_{tab}=2.76, df_1=3, df_2=64, N=number of subjects. Values in a row having different values are significantly different

(lean body/muscle mass). This is in agreement with [10] who said that when interpreting serum creatinine, it is believed that lean body mass (LBM) should be taken into account, but disagreed with [11] who said that the contribution of LBM to variations in serum creatinine is small. The difference in serum creatinine is related to the difference in body weight/BMI most especially the muscle mass. The low values found in underweight subjects can be related to lean (low) muscle mass among this group, while high values of serum creatinine as seen in other weight categories are due to high muscle mass among these groups. This is because creatinine production is proportional to the body weight, most importantly the muscle mass. This is in accordance with [9] and Marshell, [10] who said that one of the factors influencing the creatinine concentration is muscle mass.

This study also showed that the serum creatinine values among males and females of various weight categories were significantly different respectively, with significantly low values in underweight males and females respectively. The low values observed in underweight males and females may be related to their low body weight, associated with underweight subjects respectively. This is in conformity with [11] which says that the contribution of LBM to variations in serum creatinine is small, though they worked only on female subjects. Hence, these low values are influenced by body weight, most especially underweight. The non significant low value observed in obese males can be due to low muscle mass which makes up low percentage of body mass in relation to high body fat and water composition which makes up larger percentage of the body mass, and thus account for low serum creatinine production.

In addition, it is also observed from this study that, serum creatinine in general is low in females than in males, and it is also low in females than males of the same weight categories, except in obese subjects where the values are the same for both females and males. Thus, indicating that serum creatinine is significantly influenced by body weight and sex, increasing with increase in body weight (muscle mass) and higher in males with high muscle mass. This is in accordance with, *[24] ;* who says that, the rate of creatinine production is proportional to body weight, and it decreases with age and is lower in females than in males**.** The low serum creatinine observed in females is due to low muscle mass, with high body fat and water content which decreases with age. High level of serum creatinine in male is usually due to high muscle mass and low body fat and water content. Thus the values are low in females than in males, because with low muscle mass and high body fat and water content, there is decrease in creatinine production.

Table 2. Mean Body Weight, BMI, Serum Creatinine, and Creatinine Clearance in Males of various weight categories

PARAMETERS	FEMALE UNDERWEIGHT (N=19)	FEMALE NORMAL WEIGHT (N=23)	FEMALE OVERWEIGHT (N=17)	FEMALE 0BESE (N=33)	F-value	P-value
Mean ± SD Body Weight (Kg)	44 ± 5.9^{a}	57 ± 6.5^{b}	71 ± 7.0^{c}	83 ± 3.3^{d}	193.5	P<0.05
Mean ± SD BMI (Kg/m^2)	16.8 ± 1.1^{a}	21.5 ± 1.7^{b}	26.9 ± 1.1^{c}	32.3 ± 2.0^{d}	429.2	P<0.05
Mean ± SD Serum Creatinine (Mg/dl)	0.9 ± 0.1^{a}	1.0 ± 0.1^{b}	1.1 ± 0.2^{b}	1.1 ± 0.1^{b}	10.9	P<0.05
Mean ± SD Creatinine Clearance (ml/min)	124 ± 32.6^{a}	128 ± 39.0^{a}	158 ± 39.0^{b}	138 ± 41.3^{a}	2.837	P<0.05

F_{tab}=2.60, df_1=3, df_2=156, N=number of subjects. Values in a row having different values are significantly different.

The creatinine clearance in this study is significantly different among the various weight categories, being significantly high in overweight when compared to underweight and normal weight subjects. The high clearance seen in overweight subjects can be due to their high muscle mass with associated increase in creatinine excretion and concomitant increase in clearance. This is in line with [16]; who stated that the greater the muscle mass, the greater the creatinine clearance. The low clearance seen in underweight subjects can be due to their low muscle mass with associated decrease in creatinine excretion and concomitant decrease in clearance. These findings are in perfect agreement with [13] ; who said that, serum creatinine and urine creatinine correlated significantly with body weight, but the level of correlation with lean mass was even greater.

Creatinine clearance was not significantly different among males, but significantly different among females of various weight categories, with overweight males having significantly high values when compared to underweight males, while overweight females have significantly high values when compared to females of other weight categories. These are due to high body weight in overweight subjects (muscle mass) and low body weight in underweight subjects. In addition, it is also observed that, creatinine clearance is generally low in females than in males, and more also in females than males of the same weight category, except in overweight where it is higher in females than in males. High value in males than in females can be due to the high body weight (muscle mass) in males in relation to increase in creatinine excretion. These findings are in line with, Forbes and [25] ; who said that creatinine is produced non-enzymatically in the skeletal muscle, and the amount of creatinine production, and therefore the 24 hr excretion of creatinine, is directly related to muscle mass, and also with [24] ; who said that the endogenous creatinine clearance decreases with age and is lower in females than in males. The high clearance seen in overweight females than overweight males may be due to high water and fat content which is associated with glomerular hyper-filtration.Furthermore, creatinine clearance is also observed to increase sequentially with increase in body weight, except in obese subjects where the clearance falls. This is in relation to increasing body weight (muscle mass, body fat and water) with corresponding increase in production and volume of distribution of creatinine, with concomitant glomerular hyper-filtration and subsequent increase in clearance [26] ; have shown that LBM and total plasma creatinine (plasma volume × creatinine concentration) are well correlated. More also, low creatinine clearance in obese subjects in comparison to overweight subject in this study, is in line with [18] ; who said, in nondiabetic subjects, a high waist-to-hip ratio, considered a marker of central obesity, has been associated with a lower creatinine clearance. It also agrees with [17] ; who said, although obesity has been generally associated with glomerular hyper-filtration, visceral adiposity has been suggested to be associated with reduced glomerular filtration. Hence, it can be concluded that in obese subjects, there is decrease in clearance which precedes renal failure, due to high metabolic rate and preceded hyper-filtration of the kidneys. Because nephron number does not increase with weight gain in adults, excessive weight gain raises renal plasma flow and increases single nephron perfusion, resulting in increased glomerular intracapillary pressure, hyperfiltration, and the triggering of the process that results in subsequent loss of GFR over time; [27, 28] . Obese subjects also have increased sympathetic and renin-angiotensin system activity that leads to an increment of blood pressure accelerating the progressive deterioration of renal function over time in a kidney with an already increased single nephron GFR [28-30] .

CONCLUSION

This study showed that body weight and BMI have significant influence on serum creatinine and creatinine clearance, due to low serum creatinine and creatinine clearance values in underweight subjects and high serum creatinine and creatinine clearance values in overweight subjects, with high values in males and low values in females. Hence, it is suggested that all serum creatinine and creatinine clearance results should be corrected and interpreted with consideration for body weight and BMI in respect to sex.

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