The body composition and excretory burden of lean, obese, and severely obese individuals has implications for the assessment of chronic kidney disease

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Obesity could affect associations between creatinine generation, estimated body surface area, and excretory burden, with effects on chronic kidney disease assessment. We therefore examined the impact of obesity on the performances of estimated glomerular filtration rate (eGFR), the urine albumin:creatinine ratio (ACR), and excretory burden in 3611 participants of the Chronic Renal Insufficiency Cohort. Urine creatinine excretion significantly increased with body mass index (BMI) (34 and 31% greater at 40 kg/m^2 or more versus the normal of 18.5–25 kg/m^2) in men and women, respectively, such that patients with a normal BMI and an ACR of 30 mg/g had the same 24-h albuminuria as severely obese patients with ACR 23 mg/g. The bias of eGFR (referenced to body surface area-indexed iothalamate (i-)GFR) had a U-shaped relationship to obesity in men but progressively increased in women. Nevertheless, obesity-associated body surface area increases were accompanied by a greater absolute (non-indexed) iGFR for a given eGFR, particularly in men. Two men with eGFRs of 45 ml/min per 1.73 m^2, height 1.76 m, and BMI 22 or 45 kg/m^2 had absolute iGFRs of 46 and 62 ml/min, respectively. The excretory burden, assessed as urine urea nitrogen and estimated dietary phosphorus, sodium, and potassium intakes, also increased in obesity. However, obese men had lower odds of anemia, hyperkalemia, and hyperphosphatemia. Thus, for a given ACR and eGFR, obese individuals have greater albuminuria, absolute GFR, and excretory burden. This has implications for chronic kidney disease management, screening, and research.

Kidney International advance online publication, 9 April 2014; doi:10.1038/ki.2014.112

KEYWORDS: albuminuria; anemia; chronic kidney disease; glomerular filtration rate; obesity; uremia

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Received 6 November 2013; revised 17 February 2014; accepted 27 February 2014

There is an emerging global epidemic of obesity,[1] a pathology associated with increased risk for chronic kidney disease (CKD).[2–4] Severe ('morbid') obesity, defined as a body mass index (BMI) $\geqslant$40 kg/m^2, has also dramatically increased in prevalence in Western populations.[5,6] However, the implications of severe obesity for the clinical assessment of CKD with estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR) are unclear.

Fat mass increases the estimated body surface area (BSA).[7] As eGFR is expressed indexed to BSA (per 1.73 m^2), a severely obese patient is implied to have a greater absolute (i.e. non-indexed, total) glomerular filtration rate (GFR) than is a normal BMI patient of the same height and eGFR. However, eGFR equations do not take body composition into account, instead assuming a constant relationship between creatinine generation rate and BSA for a given age, gender, and race.[8,9] Consequently, if obesity-associated increases in BSA are not matched by increased creatinine generation, eGFR equations will overestimate BSA-indexed GFR in obese subjects. On the other hand, if creatinine generation rate increases with obesity, there will be implications for ACR interpretation; ACR will then underestimate 24-h albuminuria in obese patients because of greater creatininuria.

Previous studies on eGFR equation performance in obesity gave conflicting results and did not examine the severely obese category.[10–12] Thus, it is unclear whether severely obese patients have a greater absolute GFR compared with leaner subjects of the same height and eGFR. If obesity-related increases in BSA indeed indicate a greater absolute GFR for a given eGFR, the following question arises: Is obesity also accompanied by a greater excretory burden that requires a greater GFR to prevent CKD complications, or does the greater absolute GFR protect against complications?

The Chronic Renal Insufficiency Cohort (CRIC) Study targeted recruitment to establish a CKD cohort with a 50% prevalence of diabetes mellitus.[13] We utilized the resulting prevalence of obesity and severe obesity to investigate the effects of obesity on relationships between BSA, the urine creatinine excretion rate, and metabolic burden. Specifically,

Table 1 | Characteristics of the Chronic Renal Insufficiency Cohort (CRIC) study participants by BMI category

	BMI category				
	18.5 ⩽ BMI < 25 Normal	25 ⩽ BMI < 30 Overweight	30 ⩽ BMI < 35 Class I obesity	35 ⩽ BMI < 40 Class II obesity	BMI ⩾ 40 Class III obesity
Participants, *n* (%)	547 (15)	1042 (29)	951 (26)	572 (16)	499 (14)
Male, *n* (%)[a]	253 (46)	704 (68)	362 (38)	286 (50)	160 (32)
Age, years, mean (s.d.)	56 (13)	59 (11)	59 (10)	59 (10)	57 (10)
Black, %[a]	177 (32)	351 (34)	416 (44)	275 (48)	278 (56)
White, %[a]	283 (52)	493 (47)	386 (41)	228 (40)	164 (33)
Hispanic, %	45 (8)	142 (14)	127 (13)	54 (9)	52 (10)
Diabetes, %[a]	164 (30)	420 (40)	477 (50)	334 (58)	349 (70)
eGFR, ml/min per 1.73 m^2, median (IQR)	44 (23)	43 (21)	43 (20)	43 (20)	42 (21)
iGFR/BSA, ml/min per 1.73 m^2, median (IQR)	46 (27)	47 (25)	48 (29)	44 (28)	41 (22)
Albuminuria, mg/24 h, median (IQR)[a]	60 (447)	50 (437)	71 (583)	81 (565)	98 (827)
ACR, mg/g, median (IQR)	52 (442)	41 (349)	53 (459)	53 (429)	88 (755)
Moderate albuminuria (> 30 mg/24 h), *n* (%)	322 (59)	588 (56)	589 (62)	357 (62)	309 (62)
Height, cm, mean (s.d.)	168 (10)	170 (9)	170 (10)	168 (10)	166 (10)
Weight, kg, mean (s.d.)[a]	64 (9)	81 (10)	93 (11)	106 (13)	128 (22)
Fat mass, %, mean (s.d.)[a]	27 (8)	29 (8)	33 (9)	38 (9)	44 (10)
BSA, m^2, mean (s.d.)[a]	1.73 (0.17)	1.95 (0.16)	2.10 (0.18)	2.23 (0.20)	2.42 (0.26)
Hypophosphatemia, *n* (%)	57 (10)	85 (8)	89 (9)	67 (12)	64 (13)
Hyperkalemia, *n* (%)	63 (11.5)	78 (8)	86 (9)	40 (7)	39 (8)
Acidosis, *n* (%)	98 (18)	187 (18)	165 (17)	96 (17)	69 (14)
Anemia, *n* (%)	259 (47)	459 (44)	429 (45)	253 (44)	287 (58)
Hyperparathyroidism, *n* (%)[a]	193 (35)	379 (36)	375 (39)	248 (43)	260 (52)

Abbreviations: ACR, urine albumin:creatinine ratio; BMI, body mass index in kg/m^2; BSA, body surface area; eGFR, estimated glomerular filtration rate; iGFR, iothalamate-glomerular filtration rate; IQR, interquartile range.
[a]$P < 0.001$ for difference between BMI ⩾ 40 kg/m^2 and 18.5 ⩽ BMI < 25 kg/m^2.

we addressed the following clinical questions: (1) How do differences in creatinine excretion rate associated with obesity affect the bias of 24-h albuminuria estimation by ACR? (2) How does obesity affect the performance of eGFR equations at estimating BSA-indexed iothalamate (i-)GFR? (3) For a given eGFR, does a severely obese patient have a greater absolute GFR and, if so, does this protect against CKD metabolic complications?

RESULTS

Study cohort characteristics

Characteristics of the CRIC study cohort have been published previously[14] and are shown by BMI category in Table 1. Over half of the participants were obese (BMI ⩾ 30 kg/m^2) and 499 subjects (14%) were severely obese (BMI ⩾ 40 kg/m^2). The severely obese BMI category contained a greater proportion of female, diabetic, and Black participants compared with the normal BMI category and had heavier albuminuria.

Obesity, creatininuria, and ACR performance

The urinary creatinine excretion rate increased with BMI, resulting in a reciprocal underestimation bias of albuminuria assessment by ACR (Figure 1a and Table 2). However, there was some evidence of a flattening of this relationship at the highest levels of BMI, particularly in men. In regression models adjusted for age and race, geometric mean creatininuria in women was 15% (95% confidence interval (CI) 9–21%), 23% (17–31%), 29% (22–37%), and 31% (24–39%) greater, respectively, for 25 ⩽ BMI < 30, 30 ⩽ BMI < 35, 35 ⩽ BMI < 40, and ⩾ 40 kg/m^2 versus 18.5 ⩽ BMI < 25 kg/m^2 ($P < 0.001$ for all). In men, the corresponding increases were 18% (12–24%), 27% (20–34%), 34% (26–43%), and 34% (25–42%, $P < 0.001$ for all). For comparison, the creatininuria increment associated with male as against female gender (adjusted for age/race/BMI category) was 42% (38–45%, $P < 0.001$), consistent with the results from other cohorts.[15] Taking account of the ~30% greater creatininuria at BMI ⩾ 35 kg/m^2 as against normal BMI, normal BMI subjects with ACRs of 30 mg/g and 300 mg/g (threshold definitions of moderate and severe albuminuria[16]) had approximately the same 24-h albuminuria as did subjects of the same gender with BMI ⩾ 35 kg/m^2 and ACRs of 23 mg/g and 230 mg/g, respectively. Characterizing obesity by waist circumference or bioimpedance-estimated percentage fat mass gave similar findings as with BMI (Figure 1b and c).

Obesity, BSA, and eGFR performance

Although BMI is considered a measure of habitus rather than size, there was a close relationship between BMI and estimated BSA (Figure 2a). Creatinine excretion (thus generation) rate per m^2 BSA peaked at a BMI of ~30 kg/m^2 and declined at higher levels of BMI, particularly in men (Figure 2b).

The impact of obesity-related changes in creatinine generation and BSA on the bias of the Chronic Kidney Disease Epidemiology Collaboration eGFR equation, referenced to iGFR per 1.73 m^2 BSA, is shown in Figure 2c. There was a U-shaped curve of eGFR bias versus BMI in men, but a progressive increase in women. The same patterns were evident at iGFR ⩾ 45 ml/min per 1.73 m^2 and < 45 ml/min per 1.73 m^2, although the overall bias was more negative at the higher GFR (Supplementary Figure S1 online).