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The effects of weight change on glomerular filtration rate

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ABSTRACT

Background. Little is known about the effect of weight loss/gain on kidney function. Analyses are complicated by uncertainty about optimal body surface indexing strategies for measured glomerular filtration rate (mGFR).

Methods. Using data from the African-American Study of Kidney Disease and Hypertension (AASK), we determined the association of change in weight with three different estimates of change in kidney function: (i) unindexed mGFR estimated by renal clearance of iodine-125-iothalamate, (ii) mGFR indexed to concurrently measured BSA and (iii) GFR estimated from serum creatinine (eGFR). All models were adjusted for baseline weight, time, randomization group and time-varying diuretic use. We also examined whether these relationships were consistent across a number of subgroups, including tertiles of baseline 24-h urine sodium excretion.

Results. In 1094 participants followed over an average of 3.6 years, a 5-kg weight gain was associated with a 1.10 mL/min/1.73 m^2 (95% CI: 0.87 to 1.33; $P < 0.001$) increase in unindexed mGFR. There was no association between weight change and mGFR indexed for concurrent BSA (per 5 kg weight gain, 0.21; 95% CI: −0.02 to 0.44; $P = 0.1$) or between weight change and eGFR (−0.09; 95% CI: −0.32 to 0.14; $P = 0.4$). The effect of weight change on unindexed mGFR was less pronounced in individuals with higher baseline sodium excretion ($P = 0.08$ for interaction).

Conclusion. The association between weight change and kidney function varies depending on the method of assessment. Future clinical trials should examine the effect of intentional weight change on measured GFR or filtration markers robust to changes in muscle mass.

Keywords: body surface area, glomerular filtration rate, indexing, obesity, weight

INTRODUCTION

Over the last few decades, the prevalence of obesity has increased dramatically, now affecting approximately one in three adults in the USA and one in five adults in the developed world [1]. Obesity increases the risk for a number of health conditions including hypertension, diabetes and chronic kidney disease (CKD) [2–5]. Obese persons have a markedly higher risk of end-stage renal disease (ESRD) [6]. Obesity-related glomerulopathy characterized by proteinuria, glomerulomegaly and foot process effacement has been well described [7]. Although weight loss has been shown to reduce proteinuria [8–13], the effects of weight loss or gain on glomerular filtration rate (GFR) have been less studied [13–15]. Accurate assessment of GFR is important, both to evaluate the effect of weight loss or gain on kidney function as well as to inform drug dosing and patient counseling. However, optimal methods of measuring kidney function in the setting of obesity [16] or longitudinally in the setting of weight change are uncertain.

In the direct assessment of kidney function, it is standard practice [and recommended in the current Kidney Disease Improving Global Outcomes (KDIGO) CKD evaluation guidelines] to index measured glomerular filtration rate (mGFR) to BSA [17]. The rationale for BSA indexing arises from the

observation that kidney function across mammalian species is directly proportional to body size [18]. Thus, indexing of GFR by BSA allows for comparable estimates of GFR across different body sizes in a population. However, controversy exists about the appropriateness of BSA indexing in persons at the extremes of body size, and in longitudinal analyses, where indexing for concurrently measured BSA might introduce bias since BSA changes as weight changes [19].

Few studies have examined the longitudinal association between kidney function and weight change using multiple methods of kidney function assessment, particularly in patients with CKD. Thus, we evaluated this association among participants from the African-American Study of Kidney Disease and Hypertension (AASK), assessing kidney function by three different methods: (i) 'unindexed mGFR', where change in mGFR assessed by renal clearance of iodine-125-iothalamate was presented as the raw change from initial mGFR, (ii) mGFR indexed to concurrently measured BSA, and (iii) eGFR estimated from serum creatinine using the AASK equation [20].

MATERIALS AND METHODS

Study population

The AASK study was a multicenter randomized clinical trial of 1094 African-American adults with mGFR of 20–65 mL/min/1.73 m^2 [21]. Participants were randomly assigned to one of two BP goals: a usual mean arterial pressure (MAP) goal of 102 to 107 mmHg or to a lower MAP goal of <92 mmHg, and to treatment with one of three anti-hypertensive drugs (metoprolol, ramipril or amlodipine). Participants were self-identified African-American adults with hypertension and no other identified causes of renal insufficiency. Exclusion criteria were diastolic BP <95 mmHg, known history of diabetes, urinary protein/creatinine ratio >2.5 g/g, accelerated or malignant hypertension within 6 months, secondary hypertension, evidence of non-BP-related causes of renal disease, serious systemic disease, clinical congestive heart failure or specific indication or contraindication to a study drug or procedure. Participant enrollment began in February 1995 and ended in September 1998.

Assessment of anthropomorphic data and kidney function

Body surface area was calculated using the DuBois formula [22]: $\text{BSA}\,(m^2) = 0.20247 \times \text{height}\,(m)^{0.725} \times \text{weight}\,(kg)^{0.425}$, and body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared [23]. Measurement of height was recorded at baseline; mGFR, serum creatinine, and weight were obtained at baseline, follow-up months 3 and 6 and then every 6 months during the trial. GFR was directly measured by renal clearance of iodine-125-iothalamate (mGFR). In brief, participants were instructed to ingest ~5 mL/kg of body weight of water prior to arrival, and another 10 mL/kg after arrival to the clinic. Next, participants ingested two drops of supersaturated potassium iodide to block thyroidal uptake of ^{125}I-iothalamate, and then received a subcutaneous injection of 35 uCi of ^{125}I-iothalamate in the subdeltoid area. Four 30-min urine collections were performed with blood samples taken at the end of each period. GFR for each 30-min period was calculated using the logarithmic mean of the plasma ^{125}I-iothalamate counts compared with urine counts during each period. The mean of four periods was used to calculate GFR in the vast majority of participants. For the present study, change in mGFR was represented two ways: 'unindexed GFR', where change in mGFR was presented as the raw change from initial mGFR (scaled to baseline BSA for comparability to change in indexed mGFR and eGFR), and GFR indexed by concurrently measured BSA. Serum creatinine was measured using a kinetic alkaline picrate assay (Jaffe method). Estimated GFR (eGFR) was calculated using the AASK equation: $\text{eGFR} = 329 \times \text{SCr}^{-1.096} \times \text{age}^{-0.294} \times (0.736 \text{ if female})$ [20]. Units for both measured GFR and eGFR are expressed as mL/min/1.73 m^2.

Statistical analysis

For comparison of baseline characteristics, annual slope of weight change was determined for each individual using ordinary least squares regression with the first 2 years of weight data so as to minimize the effect of survival on category of weight change. Means and proportions of baseline characteristics were compared across quintiles of weight change using analysis of variance without adjustment for other baseline variables. For analyses of change in kidney function as a function of change in weight, data from all participants during the full follow-up period was used. Mixed-effects models were adjusted for time, baseline weight, time-varying diuretic use (yes/no), randomization group and an interaction term for randomization group with time (before and after 3 months), allowing the rate of eGFR decline to vary by baseline weight, using a robust covariance structure. An interaction of time and change in weight with change in GFR was tested but not statistically significant. Since the relationship between change in weight and change in GFR did not differ by time, the relationship between weight change and change in GFR was modeled by aggregating data from all time-points during the AASK trial. Weight change was modeled continuously and also categorically, comparing quintiles of weight change to the middle quintile. Continuous analyses were repeated using log-transformed mGFR and eGFR to express change in GFR on a percentage basis. Analyses were performed for each method of kidney function assessment: (i) unindexed mGFR (scaled by baseline BSA); (ii) mGFR indexed for concurrent BSA and (iii) eGFR using the AASK equation. By scaling the unindexed mGFR to baseline BSA, each of the three measures of kidney function will be expressed in the same units, mL/min/1.73 m^2. Such an approach will facilitate direct comparisons of results across the three measures.

We conducted subgroup analyses by baseline BMI categories (<25 kg/m^2, 25–29.99, 30–34.99, ≥35), and body shape categories. No measures of central obesity were collected; thus, body shape categories were categorized as heavier/taller (above median weight/above median height), heavier/shorter (above median weight/below median height), lighter/taller (below median weight/above median height) and lighter/shorter (below median weight/below median height). Because changes in weight could be due to changes in total body water, subgroup analyses

were done by history of heart disease (yes/no), tertiles of baseline 24-h urine sodium excretion, and in a subgroup of patients who reported no diuretic use throughout the trial. Importantly, AASK excluded patients with clinical congestive heart failure, so the stratification by baseline heart disease does not contain participants with prevalent heart failure. Additional subgroup analyses were done by gender, proteinuria status [protein/creatinine ratio (PCR) >1.0, 0.5–1.0 and <0.5 g/d] and baseline GFR (≥45 mL/min/1.73 m^2 versus <45 mL/min/1.73 m^2). Each subgroup was also formally tested for an interaction with change in weight by adding relevant product terms to the mixed models.

For the analyses evaluating the relationship between weight change and GFR, we performed the following sensitivity analyses: (i) adjusting for time-varying 24-h urine urea nitrogen excretion to account for protein intake as a confounder; (ii) using unindexed mGFR, not scaled to baseline BSA and (iii) adjusting analyses with eGFR as the dependent variable for time-varying 24-h urine creatinine to examine whether changes in muscle mass could account for observed differences between eGFR and mGFR trajectories with weight change.

Finally, to understand the magnitude by which findings could differ depending on method of kidney function assessment, we evaluated the difference between each pair of GFR estimates [(mGFR/concurrent BSA − unindexed mGFR), (eGFR − unindexed mGFR) and (eGFR − mGFR/concurrent BSA)] with change in weight using the same model as described above.

All analyses were performed using Stata version 13.0 (College Station, TX). P-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics by weight change trajectory over initial 2 years

Follow-up weight measurements within the first 2 years were available in 1045 of the 1094 participants. Median weight change over the first 2 years was +0.9 kg/year (IQR −1.4 to 3.2 kg/year). There was substantial variation in the degree of weight change over the first 2 years as median weight change in the highest quintile was +6.4 kg/year compared with −3.4 kg/year in the lowest quintile (Table 1). Figure 1 shows the weight trajectories for 50 randomly selected individuals. There were significant differences in baseline age, weight, BMI, BSA, diastolic blood pressure, mGFR and prevalence of proteinuria between quintiles of weight change ($P < 0.05$ for all analysis of variance comparisons). Individuals with the largest weight gain and largest weight loss tended to have higher baseline weight, BMI, diastolic blood pressure and prevalence of proteinuria than the more stable weight change groups. Individuals with the largest weight gains tended to be younger and have higher BSA, whereas individuals with the largest weight loss tended to have lower baseline mGFR and eGFR. There were no significant differences in randomization group, baseline diuretic use or history of heart disease among the different weight change categories.

Association between change in weight and mGFR

Over a median follow-up time of 3.6 years, a direct, linear association was observed between change in weight and change in unindexed mGFR. Every 5 kg increase in weight was

Table 1. Baseline characteristics by weight change slope over initial 2 years

N	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P value[a]
	209	209	209	209	209	
Weight change slope over first 2 years (kg/year)	−3.4 (−4.9 to −2.5)	−0.9 (−1.4 to −0.3)	0.9 (0.6 to 1.3)	2.8 (2.2 to 3.2)	6.4 (5.0 to 8.8)	
Total weight change over entire study	−4.5 (−8.2 to −1.8)	−0.5 (−2.3 to 2.3)	0.9 (−1.8 to 3.6)	3.6 (0.9 to 7.3)	9.1 (3.2 to 14.5)	
Total study follow-up time	3.2 (2.1 to 4.6)	4.0 (3.0 to 5.0)	4.0 (3.1 to 5.0)	3.7 (3.0 to 5.0)	4.1 (2.7 to 5.0)	0.002
Age (years)	55.4 (10.5)	55.4 (10.8)	56.7 (10.2)	53.6 (10.8)	51.7 (10.6)	<0.001
Female (%)	41.6	35.9	39.2	40.2	37.3	0.8
<High school education (%)	40.2	48.8	40.2	36.8	38.8	0.1
Current smoker (%)	31.1	31.6	30.6	23.4	31.1	0.3
History of heart disease (%)	53.1	49.3	54.1	46.9	54.5	0.4
Height (cm)	170.4 (10.2)	171.5 (9.9)	170.2 (9.5)	170.5 (10.0)	172.5 (10.7)	0.1
Weight (kg)	90.9 (22.4)	87.6 (19.0)	85.1 (18.5)	88.7 (18.9)	94.7 (22.7)	<0.001
BMI (kg/m^2)	31.3 (7.1)	29.8 (6.3)	29.4 (6.1)	30.6 (6.4)	31.7 (6.6)	0.001
BSA (m^2)	2.01 (0.26)	1.99 (0.23)	1.96 (0.22)	2.00 (0.23)	2.08 (0.27)	<0.001
SBP (mmHg)	152.6 (24.5)	150.7 (22.8)	148.4 (23.4)	148.5 (23.5)	149.8 (23.1)	0.3
DBP (mmHg)	96.8 (14.5)	94.6 (13.9)	93.3 (13.6)	95.1 (13.8)	97.3 (14.6)	0.02
mGFR (mL/min/1.73 m^2)	44.2 (14.3)	46.8 (14.2)	47.8 (13.1)	47.9 (13.4)	46.2 (12.6)	0.04
Protein/creatinine ratio >0.22 (%)	40.7	33.0	20.6	27.3	37.8	<0.001
Randomized to low BP goal (%)	48.3	47.8	55.0	50.2	48.8	0.6
Randomized drug (%)						
Ramipril	43.5	40.7	42.6	36.4	34.5	0.7
Metoprolol	34.5	38.8	39.7	43.5	47.4	
Amlodipine	22.0	20.6	17.7	20.1	18.2	
Baseline diuretic use (%)	66.5	61.7	62.9	64.9	64.7	0.9

Annual slope of weight change was determined for each individual using ordinary least squares regression with first 2 years of weight data to minimize the effect of survival on category of weight change. Weight change slope, total weight change and total study follow-up time are reported as median (IQR). Otherwise, results are presented as mean (SD) or percentages.
[a]Means and proportions of baseline characteristics compared using ANOVA.

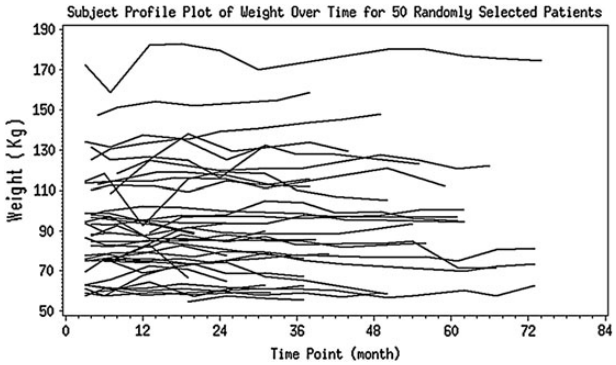

FIGURE 1: Weight trajectories of 50 randomly selected patients.

Table 2. Relationship of change in GFR measures with change in weight (per 5 kg)

GFR measure	Mean (95% CI) change in GFR per 5 kg change in weight (mL/min/1.73 m^2)	P value
Unindexed mGFR (scaled to baseline BSA: mL/min/1.73 m^2)	1.10 (0.87 to 1.33)	<0.001
mGFR/concurrent BSA (mL/min/1.73 m^2)	0.21 (−0.02 to 0.44)	0.1
eGFR (mL/min/1.73 m^2)	−0.09 (−0.32 to 0.14)	0.4

Because the relationship between change in weight and change in GFR did not differ by time, data from all time-points were aggregated in mixed-effects models adjusted for time, baseline weight, time-varying diuretic use, randomization group and an interaction term for randomization group with time (before and after 3 months).

associated with a 1.10 mL/min/1.73 m^2 (95% CI: 0.87 to 1.33; P < 0.001) increase in unindexed mGFR (Table 2). In contrast, the association was greatly attenuated and no longer significant between weight change and mGFR indexed for concurrent BSA (0.21 mL/min1.73 m^2; 95% CI: −0.02 to 0.44; P = 0.1).

Figure 2 shows the relationship between quintiles of weight change and change in GFR measures. Ranges of weight change in the lowest (Q1) to highest quintile (Q5) were ≤ −1.8 kg, −1.8 to 0 kg, 0 to +2.3 kg, +2.3 to +5.9 g and ≥ +5.9 kg. Compared with Q3, Q1 was associated with a decrease in unindexed mGFR of −1.03 (95% CI: −1.70 to −0.37; P = 0.002), and Q2 was not significantly different (0.22, 95% CI: −0.40 to 0.84, P = 0.5). Q4 and Q5 were associated with increases of 1.43 (95% CI: 0.82 to 2.03; P < 0.001) and 1.90 (95% CI: 1.14 to 2.66; P < 0.001) (Figure 2, left panel). These estimates were attenuated when mGFR was indexed for concurrent BSA (Figure 2, middle panel).

Similarly, when evaluated using log-transformed mGFR as the outcome, a 5 kg increase in weight was associated with a 3.23% (95% CI: 2.60 to 3.86%, P < 0.001) increase in unindexed mGFR. This association was attenuated though significant when mGFR was indexed to concurrent BSA (per 5 kg weight gain, 1.08% (95% CI: 0.46 to 1.70%, P = 0.001).

Association between change in weight and eGFR

There was no significant association between change in weight and change in eGFR in continuous models (per 5 kg weight gain, −0.09 mL/min/1.73 m^2, 95% CI: −0.32 to 0.14; P = 0.4) (Table 2), or in categorical analyses (Figure 2, right panel). Likewise, when using log-transformed eGFR as the outcome, there was no significant association between weight change and eGFR [per 5 kg weight gain, 0.29% (95% CI: −0.31 to 0.89%, P = 0.3)].

Subgroup and sensitivity analyses

In subgroup analyses, results were similar across groups stratified by gender, baseline BMI, body shape, urine PCR and history of heart disease (Table 3). For baseline 24-h urine sodium excretion, a significant interaction was detected; weight gain was associated with a more negative change in unindexed mGFR and eGFR in those with higher baseline 24-h urine sodium excretion (P = 0.08 for interaction on mGFR and 0.09 for interaction on eGFR). For instance, individuals in the lowest tertile of baseline 24-h urine sodium excretion had a 1.37 mL/min/1.73 m^2 (95% CI: 0.96 to 1.77; P < 0.001) increase in unindexed mGFR whereas individuals in the highest tertile of baseline 24-h urine sodium excretion had a 0.87 (95% CI: 0.49 to 1.25; P < 0.001) increase in unindexed mGFR. In individuals in the highest tertile of baseline 24-h urine sodium excretion, a 5-kg weight gain was associated with a −0.38 (95% CI: −0.73 to −0.02; P = 0.04) change in eGFR. When stratified by diuretic use (ever versus never), no significant interaction was detected. However, in participants who never used diuretics (n = 93), a 5-kg weight change was associated with a −0.92 (95% CI: −1.83 to −0.01; P = 0.05) change in eGFR (Table 3). In sensitivity analyses, additional adjustment for time-varying 24-h urine urea nitrogen to assess for protein intake as a confounder had little effect on the mGFR or eGFR analyses [per 5 kg weight gain, 1.05 mL/min/1.73 m^2 (0.82 to 1.29, P < 0.001) change in unindexed mGFR, 0.16 (−0.07 to 0.39, P = 0.2) change in mGFR indexed to concurrent BSA and −0.11 (−0.33 to 0.12, P = 0.3) change in eGFR]. Adjusting for time-varying 24-h urine creatinine as a surrogate for muscle mass had little effect on eGFR analyses (per 5 kg weight gain, −0.09 (−0.31 to 0.14, P = 0.4).

Differences between the three methods of GFR assessment in evaluating the relationship between weight change and kidney function

Using unindexed mGFR as the reference, mGFR/concurrent BSA underestimated the association between weight change and kidney function (per 5 kg weight gain, −0.89 mL/min/1.73 m^2, 95% CI: −0.94 to −0.83, P < 0.001). Analyses using eGFR underestimated the association between weight change and kidney function whether using unindexed mGFR (scaled to baseline BSA) as the reference (per 5 kg weight gain, −1.12 mL/min/1.73 m^2, 95% CI: −1.33 to −0.91, P < 0.001), or using mGFR adjusted for concurrent BSA as the reference (per 5 kg weight gain, −0.26 mL/min/1.73 m^2, 95% CI: −0.46 to −0.05; P = 0.02) (Table 4).

DISCUSSION

In this study of African-Americans with CKD attributed to hypertension, measured GFR increased with weight gain,

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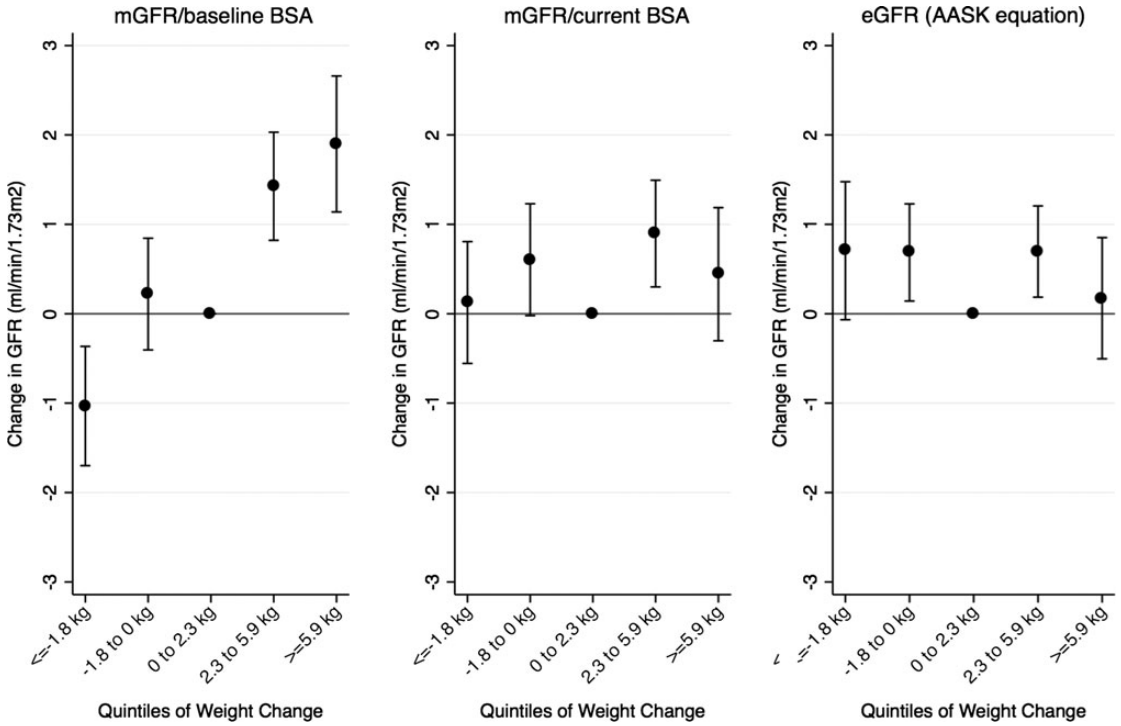

FIGURE 2: Association between categories of weight change and GFR measures. Because the relationship between change in weight and change in GFR did not differ by time, data from all time-points were aggregated in mixed-effects models adjusted for time, baseline weight, time-varying diuretic use, randomization group, and an interaction term for randomization group with time (before and after 3 months). Quintiles of weight gain/loss were compared with the middle quintile (0–2.3 kg).

although this relationship was attenuated and not statistically significant when GFR was indexed for concurrent BSA. Whether compared with unindexed mGFR or mGFR indexed to concurrent BSA, eGFR had a significantly smaller association with weight change. Furthermore, the direction of the association was reversed in some of the subgroup analyses demonstrating how analyses using eGFR can differ significantly from mGFR in the setting of weight fluctuation. This implies that studies evaluating the impact of weight loss on kidney function should use either directly measured GFR or other markers of filtration that are unrelated to muscle mass.

The attenuation of the longitudinal relationship between weight change and mGFR after adjustment for concurrent BSA is consistent with observations in cross-sectional studies [19, 24–26]. These findings should not be surprising since BSA increases as weight increases, resulting in lower indexed mGFR than unindexed mGFR values. For example, in a study of 301 non-diabetic participants of East African descent, individuals who were overweight and obese had higher unindexed mGFR, filtration fraction, and higher prevalence of glomerular hyperfiltration (defined as GFR ≥140 mL/min in this study) than normal-weight individuals [24]. These differences were attenuated and no longer significant when mGFR was indexed for BSA. Similar findings were observed in a study of 315 healthy individuals in the Netherlands [26], where higher BMI was associated with higher filtration fraction and higher unindexed mGFR. Again, indexing for BSA attenuated the association between BMI and mGFR to non-significance.

Although our study focused on persons with CKD, the direction of association between increased weight and increased mGFR may support the concept of 'obesity-associated glomerular hyperfiltration.' No universal definition for hyperfiltration exists, and the mechanisms behind this relationship are unknown [27]. Although usually described in the setting of normal kidney function, hyperfiltration can theoretically occur in the setting of globally decreased kidney function as well. In patients with CKD who may have experienced significant nephron loss, hyperfiltration may occur at the single nephron level. Experimental studies suggest that compensatory glomerular hyperfiltration leads to increased glomerular capillary pressure and subsequent injury [28]. This relationship between body mass and unindexed mGFR is also supported by studies of patients undergoing bariatric surgery. Unindexed mGFR has been shown to decrease after bariatric surgery whereas mGFR/concurrent BSA does not change 1 year after bariatric surgery in patients with baseline normal or supranormal kidney function [13, 29]. Others have reported cases of nephrotic-range proteinuria resolving after bariatric surgery [30, 31]. Few studies have examined the effects of intentional weight loss in patients with CKD and have been limited by small sample size or use of creatinine-based eGFR [32, 33].

Although we show that indexing for BSA affects the interpretation of the relationships between weight and mGFR, it remains unclear whether using indexed mGFR is more appropriate than using unindexed mGFR. In general, the impact of indexing is likely small for most individuals. However, there may be some situations where exact knowledge of kidney function may be important, particularly when renally cleared

Table 3. Subgroup analyses examining relationship between change in weight (per 5 kg) with changes in GFR measures

Subgroups[a]	Unindexed mGFR (scaled to baseline BSA)		mGFR/concurrent BSA		eGFR	
	Estimate (95% CI) (mL/min/1.73 m^2)	P value	Estimate (95% CI) (mL/min/1.73 m^2)	P value	Estimate (95% CI) (mL/min/1.73 m^2)	P value
Gender						
Male (n = 669)	1.01 (0.70 to 1.31)	<0.001	0.15 (−0.15 to 0.45)	0.3	−0.18 (−0.46 to 0.10)	0.2
Female (n = 425)	1.27 (0.93 to 1.62)	<0.001	0.31 (−0.04 to 0.66)	0.08	0.08 (−0.31 to 0.47)	0.9
Baseline BMI groups						
BMI <25 (n = 222)	1.01 (0.31 to 1.71)	0.01	−0.16 (−0.85 to 0.53)	0.7	−0.34 (−1.08 to 0.39)	0.4
BMI 25–29.99 (n = 362)	1.22 (0.72 to 1.72)	<0.001	0.16 (−0.36 to 0.68)	0.6	0.05 (−0.41 to 0.51)	0.8
BMI 30–34.99 (n = 266)	1.06 (0.62 to 1.50)	<0.001	0.12 (−0.32 to 0.56)	0.6	−0.33 (−0.79 to 0.13)	0.2
BMI ≥35 kg/m^2 (n = 244)	1.05 (0.69 to 1.40)	<0.001	0.36 (0.01 to 0.72)	0.05	0.02 (−0.30 to 0.34)	0.9
Baseline body shape groups						
Wt ≤87.1 kg, ht ≤1.72 m (n = 359)	1.28 (0.81 to 1.975)	<0.001	0.06 (−0.42 to 0.54)	0.8	−0.01 (−0.59 to 0.56)	1.0
Wt ≤87.1 kg, ht >1.72 m (n = 201)	0.96 (0.29 to 1.63)	0.01	−0.04 (−0.73 to 0.64)	0.9	−0.46 (−1.07 to 0.16)	0.1
Wt >87.1 kg, ht ≤1.72 m (n = 207)	1.16 (0.74 to 1.58)	<0.001	0.31 (−0.10 to 0.72)	0.1	−0.01 (−0.38 to 0.37)	1.0
Wt >87.1 kg, ht >1.72 m (n = 327)	1.00 (0.55 to 1.45)	<0.001	0.24 (−0.16 to 0.63)	0.2	−0.14 (−0.50 to 0.22)	0.4
Urine protein/creatinine ratio (PCR)						
PCR <0.5 (n = 866)	1.05 (0.78 to 1.33)	<0.001	0.08 (−0.19 to 0.35)	0.5	−0.15 (−0.41 to 0.11)	0.3
PCR 0.5–0.99 (n = 97)	1.13 (0.58 to 1.67)	<0.001	0.48 (−0.06 to 1.02)	0.08	0.12 (−0.47 to 0.72)	0.7
PCR ≥1.0 (n = 127)	0.96 (0.46 to 1.46)	<0.001	0.37 (−0.14 to 0.88)	0.2	−0.68 (−1.14 to −0.22)	0.004
History of heart disease						
No (n = 530)	1.09 (0.78 to 1.40)	<0.001	0.23 (−0.07 to 0.54)	0.1	−0.04 (−0.32 to 0.25)	0.8
Yes (n = 564)	1.11 (0.77 to 1.46)	<0.001	0.18 (−0.17 to 0.53)	0.3	−0.08 (−0.43 to 0.26)	0.6
Baseline 24-h urine Na excretion[a]						
<2.74 g/day (n = 377)	1.37 (0.96 to 1.77)	<0.001	0.45 (0.06 to 0.84)	0.02	0.19 (−0.23 to 0.62)	0.4
2.74–4.24 g/day (n = 362)	1.17 (0.73 to 1.61)	<0.001	0.25 (−0.21 to 0.70)	0.3	0.05 (−0.35 to 0.45)	0.8
≥4.24 g/day (n = 354)	0.87 (0.49 to 1.25)	<0.001	0.02 (−0.36 to 0.41)	0.9	−0.38 (−0.73 to −0.02)	0.04
Diuretic use throughout trial						
Never (n = 93)	0.89 (−0.25 to 2.03)	0.1	−0.30 (−1.48 to 0.88)	0.6	−0.92 (−1.83 to −0.01)	0.05
Ever (n = 999)	1.09 (0.85 to 1.32)	<0.001	0.21 (−0.29 to 0.44)	0.09	−0.07 (−0.30 to 0.16)	0.6
Baseline GFR						
<45 mL/min/1.73 m^2 (n = 475)	1.01 (0.69 to 1.34)	<0.001	0.33 (0.02 to 0.64)	0.04	−0.05 (−0.35 to 0.26)	0.8
≥45 mL/min/1.73 m^2 (n = 619)	1.14 (0.82 to 1.47)	<0.001	0.10 (−0.23 to 0.43)	0.5	−0.18 (−0.48 to 0.12)	0.2

Because the relationship between change in weight and change in GFR did not differ by time, data from all time-points were aggregated in mixed-effects models adjusted for time, baseline weight, time-varying diuretic use, randomization group and an interaction term for randomization group with time (before and after 3 months).

[a]Association between weight change and unindexed mGFR and eGFR differed by baseline 24-h urine sodium excretion (P = 0.08 for interaction on mGFR and P = 0.09 for interaction on eGFR).

Table 4. Differences between the three methods of GFR assessment in evaluating the relationship between weight change and kidney function

	Difference in estimate (95% CI) (mL/min/1.73 m^2)	P value
mGFR/concurrent BSA − unindexed mGFR (scaled to baseline BSA)	−0.89 (−0.94 to −0.83)	<0.001
eGFR − unindexed mGFR (scaled to baseline BSA)	−1.12 (−1.33 to −0.91)	<0.001
eGFR − mGFR/concurrent BSA	−0.26 (−0.46 to −0.05)	0.02

To understand the magnitude by which findings could differ depending on method for kidney function assessment, we evaluated the difference between each pair of GFR with change in weight in mixed-effects models adjusted for time, baseline weight, time-varying diuretic use, randomization group and an interaction term for randomization group with time (before and after 3 months).

medications with narrow therapeutic windows are prescribed (e.g. cisplatin). One approach to examine the optimal strategy for indexing could be to compare the longitudinal relationship between metabolic burden (i.e. urea nitrogen, phosphate) with GFR (unindexed and indexed for BSA) [34]. More research on the implications of BSA indexing is needed, particularly in patients at the extremes of body mass or in the setting of massive weight change.

This study has several strengths, including a large cohort of over 1000 individuals followed for nearly 4 years with both directly measured and estimated GFR assessed at several time-points. Our study also has limitations. The analysis is observational; as such, cause-and-effect cannot be determined. Secondly, the reasons for weight change are unknown, and we are unable to determine whether changes in weight reflect changes in fat mass, fat-free mass or total body water. Indeed, the effect of weight change on unindexed mGFR varied by baseline 24-h urine sodium excretion, suggesting that some of the observed association may be driven by changes in total body water. Weight loss/gain could have been intentional or unintentional, and weight loss may occur due to progression of CKD. Thirdly, other factors may confound the relationship between weight and kidney function, driving both changes in weight and GFR simultaneously. For example, decreased protein intake could result in decreased weight and acutely decreased GFR though results were unchanged after adjusting for 24-h urine urea nitrogen. The AASK study did not collect measures of central obesity, which may promote renal injury more strongly

than general obesity [26]. Other novel filtration markers such as cystatin C, beta-trace protein or b2-microglobulin may be less influenced by factors associated with weight loss/gain than creatinine but were unavailable in follow-up visits and thus not examined.

In conclusion, we demonstrate that weight gain is associated with increased unindexed mGFR, but no change in mGFR adjusted for concurrently measured BSA or eGFR. Future clinical trials should carefully assess anthropometrics, and examine the effect of intentional weight loss using directly measured GFR or alternative filtration markers not affected by muscle mass.

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CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Hyperfiltration in Indigenous Australians with and without diabetes

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ORIGINAL ARTICLE

ABSTRACT

Background. Hyperfiltration (HF) has been linked to the development of diabetic kidney disease (DKD), but the causative or predictive role of HF in the pathogenesis of DKD still remains unclear. To date, there have been no studies of HF in Indigenous Australians, a population with high rates of both diabetes and end-stage kidney disease. We aimed to compare the characteristics and frequency of HF in Indigenous Australians with and without type 2 diabetes.

Methods. Indigenous Australian participants, recruited across five pre-defined strata of health, diabetes status and kidney function, had a reference glomerular filtration rate (GFR) measured using plasma disappearance of iohexol [measured GFR (mGFR)] over 4 h. HF was defined in various ways: (i) mGFR > 144 mL/min/1.73 m^2, which is mGFR > 1.96 × SD above the mean of the mGFR in non-diabetic participants with normal albuminuria and normal renal function (mGFR > 90 mL/min/1.73 m^2); (ii) age-corrected mGFR (>144 mL/min/1.73 m^2) to account for the effect of ageing on GFR in subjects over 40 years of age with cut-off 1 mL/min/1.73 m^2 lower for every year; (iii) mGFR > 144 mL/min, without correction for body surface area or age, as well as (iv) mGFR > 125 mL/min/1.73 m^2, without adjustment for age.

Results. A total of 383 Indigenous participants, 125 with and 258 without diabetes, with mGFR > 90 mL/min/1.73 m^2 were studied. The proportion of participants with HF was 7% using mGFR > 144 mL/min/1.73 m^2, 11% using the age-adjusted definition, 19% using mGFR > 144 mL/min and 27% using mGFR > 125 mL/min/1.73 m^2. Diabetes was more common in participants with HF (40–74%) compared with normofiltering participants (28–31%), regardless of the definition of HF.

Conclusions. HF exists in Indigenous Australians with and without diabetes. A greater proportion of participants had diabetes in HF group compared with normofiltration group. Long-term follow-up of this cohort is necessary to determine if HF plays a role in the development of DKD and non-DKD.

Keywords: CKD-EPI equation, diabetic kidney disease, ethnicity, glomerular filtration rate, hyperfiltration

INTRODUCTION

Controversy exists regarding whether or not hyperfiltration (HF) is a maladaptive response that may contribute to the development of diabetic kidney disease (DKD) [1, 2]. Early studies in people with type 1 diabetes have suggested that marked glomerular HF may contribute to late glomerular