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The association between body composition and cystatin C in South Asians: Results from the MASALA study

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Summary

While South Asians have high rates of obesity and kidney disease, little is known about the effect of regional body composition on kidney function. We investigated the association between body composition measures and cystatin C-based estimated glomerular filtration rate ($eGFR_{cysC}$) in 150 immigrant South Asians. The inverse association between overall adiposity and $eGFR_{cysC}$ was attenuated by C-reactive protein (CRP), while the association of ectopic fat was completely attenuated by metabolic covariates and CRP. In immigrant South Asians, the associations between overall adiposity and ectopic fat with decreased kidney function are largely explained by metabolic alterations and inflammation.

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Keywords

Body composition; Ectopic fat; Cystatin C; South Asian

Chronic kidney disease (CKD) is of great concern in South Asians (SAs), a population with a high prevalence of diabetes, hypertension and kidney disease progression [1,2]. Obesity is a risk factor for CKD, but less is known about the role of regional body composition [3]. This is of interest in SAs where body mass index (BMI) underestimates visceral fat [4]. SAs are prone to falsely normal values of creatinine (Cr) in early CKD given their lower lean mass [5]. Therefore, cystatin C (cysC) may be useful in improving detection of CKD [6]. The effect of higher levels of adiposity on kidney function in SAs remains unknown. We hypothesized that in immigrant SAs, higher overall and regional adiposity is associated with worse kidney function, measured by cystatin C-based estimated glomerular filtration rate ($eGFR_{cysC}$).

Using data from the Metabolic Syndrome and Atherosclerosis in South Asians Living in America (MASALA) study, we performed a cross-sectional analysis of 150 immigrant SAs recruited from the San Francisco Bay Area. Sampling strategy, recruitment procedures, and detailed study methods have been previously described [7]. Eligible participants were: ages 45-84, self-identified as Asian Indian, and had no clinical cardiovascular disease.

Details on data collection, clinical diagnoses, and laboratory measurements including glucose, lipids, Cr, and urine microalbumin have been described [7]. GFR was estimated using the CKD-EPI equation (*female*- $Cr \leq 0.7$: $144 \times (Cr/0.7)^{-0.329} \times 0.993^{age}$; $Cr>0.7$: $144 \times (Cr/0.7)^{-1.209} \times 0.993^{age}$; *male* - $Cr \leq 0.9$: $141 \times (Cr/0.9)^{-0.411} \times 0.993^{age}$; $Cr>0.9$: $141 \times (Cr/0.9)^{-1209} \times 0.993^{age}$) [8]. C-reactive protein (CRP) was measured using a particle enhanced immunonepholometric assay (Dade Behring/Siemens). CysC was measured using the N Latex cysC kit (Dade-Behring/Siemens) on a BN II Nephelometer at the University of Vermont. To achieve harmonisation across reagent lots, measured cysC values were adjusted upwards by 17%. The CKD-EPI cysC equation ($Cr \leq 0.8$: $133 \times (\text{cystatin C}/0.8)^{-0.499} \times 0.996^{age}$ (×0.932 if female); $Cr>0.8$: $133 \times (\text{cystatin C}/0.8)^{-1.328} \times 0.996^{age}$ (×0.932 if female)) was used to calculate $eGFR_{cysC}$ [8]. Details on body composition measurements (BMI, waist circumference, total fat mass, subcutaneous and visceral fat area, and hepatic fat) have been described [7].

Baseline characteristics were compared across tertiles of $eGFR_{cysC}$ using the chi-squared test, ANOVA or Kruskall–Wallis. Based on biologic plausibility, multivariate models were specified to assess the relationship between body composition and $eGFR_{cysC}$. Using linear regression, we sequentially adjusted for covariates, and STATA (version 13.1, College Station, TX) was used.

CysC measurements were available in 149 participants. Table 1 shows baseline characteristics of participants by tertile of $eGFR_{cysC}$. Age, systolic blood pressure, diabetes prevalence, CRP and BMI were inversely associated with $eGFR_{cysC}$. Cr-based eGFR was associated with $eGFR_{cysC}$.

Next, we conducted multivariate analyses with stepwise adjustments to investigate the association between body composition and $eGFR_{cysC}$ (Fig. 1). Inverse associations of BMI and subcutaneous fat with $eGFR_{cysC}$ were attenuated by CRP. Associations of waist circumference, visceral fat, and hepatic fat with decreased kidney function were attenuated by metabolic covariates and CRP.

These findings add to the literature on adiposity and cystatin C. The Framingham Offspring Study found that visceral and subcutaneous fat are independently associated with cysC, while the Cardiovascular Health Study did not find such an association [3,9]. Furthermore, cysC is secreted by adipose tissue and is elevated in obese individuals, including SAs, independent of eGFR [10,11]. Therefore, the adiposity and cysC story is complex.

The roles of various body composition measures in kidney disease remain unclear. Visceral fat is metabolically active and therefore distinct from subcutaneous fat. Metabolic dysregulation and inflammation play a role in kidney disease [3]. One study found that in Caucasians and African Americans, the association between overall adiposity and central obesity with eGFR was attenuated by hypertension, diabetes, and CRP [3]. Studies that did not adjust for inflammation found a significant association between visceral and subcutaneous fat and kidney function [9,12]. Our data are consistent with these findings. However, findings from another study suggest that subcutaneous fat does not contribute to the inflammation [13]. And a study in SAs found a significant association between central obesity and albuminuria, even after adjusting for CRP [14].

This is the first study in immigrant SAs to investigate the association of several ectopic fat measures with kidney function using $eGFR_{cysC}$. However, our small sample size and relatively homogeneous population limit the generalizability of this study. In conclusion, the association between overall and visceral adiposity with kidney function is largely mediated by metabolic dysregulation and inflammation in immigrant SAs. Ongoing larger prospective cohort studies will better evaluate the effect of body composition on kidney function in SAs compared to other ethnicities [15].

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Abbreviations

MASALA	Metabolic Syndrome and Atherosclerosis in South Asians Living in America
eGFR	estimated glomerular filtration rate
LDL	low-density lipoprotein
HDL	high-density lipoprotein
Cr	creatinine
HU	Hounsfield unit
cysC	cystatin C
CRP	C-reactive protein

CKD	chronic kidney disease
SAs	South Asians
BMI	body mass index

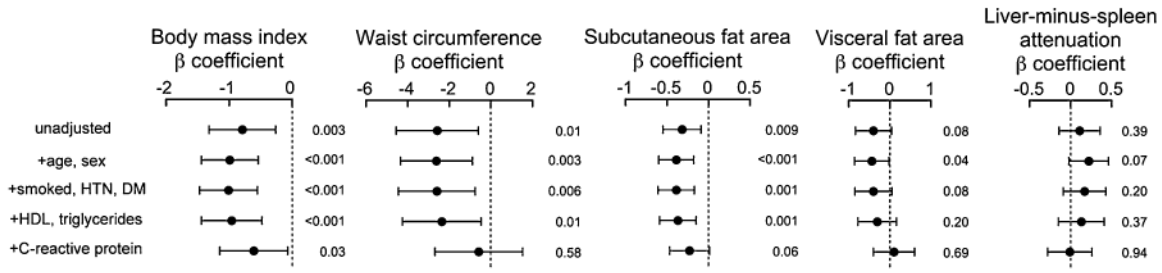

Figure 1.

Forest plot of sequentially adjusted associations between body composition measures and cystatin C-based eGFR. Model 1 is unadjusted; model 2 is adjusted for age and sex; model 3 is adjusted for age, sex, history of ever smoking, hypertension and diabetes; model 4 is adjusted for age, sex, history of ever smoking, hypertension, diabetes, HDL and log triglycerides; and model 5 is adjusted for age, sex, history of ever smoking, hypertension, diabetes, HDL, log triglycerides and log CRP. The β-coefficient and 95% confidence interval for sequentially adjusted associations between body composition measures and cystatin C-based eGFR are represented here as a forest plot.

Table 1

Baseline characteristics[a] of MASALA study participants by tertile of cystatin C-based estimated GFR, 2006–2007.

Characteristic	Tertile of cystatin C-based estimated GFR			
	Tertile 1, *n* = 50 (41.65–87.97 ml/min/1.73m^2)	Tertile 2, *n* = 50 (88.34–101.14ml/min/1.73m^2)	Tertile 3, *n* = 49 (101.53–131.43 ml/min/1.73m^2)	*P*-value
Age (years)	62 ± 9	57 ± 7	53 ± 6	<0.001
Male sex	26 (52)	23 (46)	26 (53)	0.75
Alcohol (≥1 drink/week)	19 (38)	27 (54)	28 (57)	0.12
Ever smoker	11 (22)	6 (12)	8 (16)	0.41
Physical activity (METS/week)	1339 (525, 2760)	1501 (683, 3150)	1155 (683, 2250)	0.23
Systolic blood pressure (mmHg)	129 ± 16	124 ± 17	120 ± 17	0.04
Diastolic blood pressure (mmHg)	72 ± 10	73 ± 12	73 ± 12	0.88
Hypertension	25 (50)	22 (44)	16 (33)	0.21
Fasting glucose (mg/dL)	97.6 (87.1, 115)	94 (86.4, 102)	92.5 (86.4, 111)	0.81
2-h post-challenge glucose (mg/dL)	163 (137, 227)	133 (104, 174)	140 (108, 204)	0.03
Diabetes	14 (29)	11 (22)	15 (31)	0.05
Total cholesterol (mg/dL)	184 ± 38	194 ± 34	187 ± 28	0.30
LDL-cholesterol (mg/dL)	108 ± 33	117 ± 31	112 ± 25	0.27
HDL-cholesterol (mg/dL)	48 ± 13	50 ± 14	49 ± 14	0.72
Triglycerides (mg/dL)	122 (87, 178)	121 (89, 159)	109 (91, 156)	0.78
C-reactive protein (μg/ml)	1.90 (0.87, 4.45)	1.24 (0.75, 2.6)	1.04 (0.47, 1.61)	0.005
Measures of renal function				
Creatinine–estimated GFR (ml/min/1.73m^2)	75 ± 14	79 ± 12	93 ± 15	<0.001
Spot urine albumin to Cr ratio (μg/mg)	8.0 (4.6, 17.4)	6.3 (4, 9.9)	5.1 (4.0, 8.6)	0.07
Body composition				
Body mass index (kg/m^2)	27.6 ± 5.1	25.4 ± 5.1	25.5 ± 3.2	0.03
Waist circumference (cm)	99.0 ± 13.5	95.4 ± 13.4	94.3 ± 9.7	0.14
Waist-hip ratio	0.95 ± 0.07	0.94 ± 0.07	0.95 ± 0.07	0.62
Total fat (kg)	26.6 ± 9.5	24.3 ± 8.7	22.9 ± 5.0	0.07
Subcutaneous fat area (cm^2)	249 (202, 353)	233 (170, 290)	220 (172, 262)	0.11
Visceral fat area (cm^2)	146 ± 63	124 ± 57	131 ± 46	0.14
Liver-minus-spleen (HU)	11 (5.5, 16.5)	13 (5, 17.8)	13.5 (6, 19)	0.57
Liver-to-spleen attenuation ratio	1.21 ± 0.21	1.21 ± 0.27	1.24 ± 0.22	0.73
Fatty liver	7 (15)	11 (23)	6 (14)	0.49

[a] Values represent *n*(%) for chi-square analyses, mean ± SD for analysis of variance (ANOVA) and median (25th percentile, 75th percentile) for Kruskall–Wallis test. *P*-values resulted using the chi-square test, ANOVA or Kruskall–Wallis test as appropriate.