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Subclinical atherosclerotic changes related to chronic kidney disease in asymptomatic black and white young adults: The Bogalusa Heart Study

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Abstract

Purpose—Chronic kidney disease (CKD) remains asymptomatic until its late stage, and also significantly increases the risk of cardiovascular (CV) disease morbidity and mortality. However, information is scant on the prevalence of CKD, and its association with subclinical atherosclerosis as depicted by carotid-intima media thickness (IMT) in younger adults.

Methods—This cross-sectional study included 1193 participants (43% males, 30% blacks) aged 23–43 years, residing in the semi-rural biracial (black-white) community of Bogalusa, LA. The measured variables include estimated glomerular filtration rate (eGFR) to determine functional renal changes and urine album creatinine ratio (ACR) to diagnose albuminuria, along with CV risk factor variables, and both segmental and composite carotid IMT.

Results—Ninety nine (8.5%) subjects had CKD, with blacks showing higher prevalence than whites ($p=0.01$). Subjects with albuminuria had significantly higher internal carotid IMT ($p=0.03$), common carotid IMT ($p=0.005$), and composite carotid IMT ($p=0.04$) than those without. In the multivariate logistic regression model, albuminuria was associated with black race (OR 1.92, $p=0.005$), female sex (OR 2.24, $p=0.002$), diabetes (OR 6.26, $p<0.001$), hypertension (OR 2.36, $p<0.001$), obesity (OR 1.73, $p=0.02$), and composite carotid IMT (OR 1.83, $p=0.02$), after adjusting for age. However, reduction in eGFR did not show significant independent association with carotid IMT.

Conclusions—Among asymptomatic young adults, subclinical atherosclerosis and structural renal damage depicted by albuminuria coexist, which have implications for early prevention and control.

Keywords

chronic kidney failure; glomerular filtration rate; albuminuria; carotid IMT; atherosclerosis; young adult

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Declaration of competing interests

The authors declare that they have no competing interests.

Introduction

Chronic kidney disease (CKD) is a major public health concern worldwide. The estimated prevalence of CKD in US adults was 11.7% in 2000 (1). High prevalence of CKD has also been reported internationally (2–4). Individuals with CKD remain asymptomatic until its late stage (5,6). Although simple laboratory tests can reveal early stage CKD, several studies found underdiagnosis and undertreatment (7–10). This may be due to the fact that the definition of CKD is often limited to either albuminuria or reduced estimated glomerular filtration rate (eGFR) (9,11,12). As albuminuria and glomerular filtration reflect renal damage and function, respectively, it is important to consider both in diagnosing CKD for early detection (13).

The most common risk factors for CKD include increasing age, diabetes and hypertension (5). CKD, on the other hand, significantly increases the risk of cardiovascular (CV) disease morbidity and mortality due to concurrent atherosclerosis changes (14,15). Therefore, it is important to identify CKD and related CV risk profile including subclinical atherosclerosis in asymptomatic younger individuals. The current study determines the prevalence of CKD and its correlates including CV risk factors and subclinical atherosclerosis in a bi-racial (black-white) community-based population of asymptomatic younger adults by evaluating both structural (albuminuria) and functional (reduced eGFR) changes in the kidney.

Methods

Study cohort

Individuals (N=1203) aged 23 to 43 years, residing in the biracial (65% white, 35% black) community of Bogalusa, LA, were examined as part of a long-term cohort follow-up study (16). Of these, 1193 individuals (mean age, 36.3 years, 43% males, 30% blacks) who had complete data on study variables were included in the sample. All subjects in this study gave informed consent for examination. Study protocols were approved by the Institutional Review Board of the Tulane University Medical Center.

General examination

Standardized protocols were used by trained examiners (17). Subjects were instructed to fast for 12 hours before screening, and the compliance was determined by an interview on the morning of examination. Anthropometric and blood pressure measurements were made in replicate and the mean values were used for analysis. Body mass index (BMI) calculated as weight in kilograms divided by the square of height in meters, was used as a measure of overall adiposity. Those with BMI $\geq 30\text{kg/m}^2$ were categorized as obese. Blood pressure measurements were obtained using mercury sphygmomanometers on the right arm of subjects in a relaxed, sitting position by two randomly assigned nurses (three replicates each). The first and fifth Korotkoff phases were used to determine systolic and diastolic blood pressure, respectively. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or on medication for the condition. Information on smoking status was obtained from questionnaires. Those who smoked at least one cigarette per week during the past one year were considered as current smokers.

Laboratory analyses

Serum cholesterol and triglycerides (TG) were determined enzymatically (18) on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (19). Serum glucose and creatinine were determined

by an enzymatic method, as part of multiple chemistry profile (SMA20) by the multichannel Olympus Au-5000 Analyzer (Olympus, Lake Success, NY). Urine albumin excretion was assessed using a morning spot urine sample; an enzyme-linked immunosorbent assay procedure using an albuwell kit (Exocell, Philadelphia, PA) was used to measure urinary albumin levels. The Jaffe reaction, using a commercially available kit (Sigma Chemicals, St Louis, MO), was used to determine urinary creatinine. Urinary albumin to creatinine ratio (ACR) was used to define albuminuria (ACR 30–300 mg/g plus ACR>300 mg/g). Diabetes was defined as glucose ≥ 126 mg/dl or on medication. Dyslipidemia was defined as subjects on lipid lowering medication or having one or more lipid abnormalities (HDL-C < 40 mg/dl, LDL-C ≥ 160 mg/dl, TG ≥ 200 mg/dl). Glomerular filtration rate (eGFR) was estimated as a function of age, serum creatinine, race and sex using the Chronic Kidney Disease Epidemiology collaboration formula (CKD-EPI) (20); $eGFR (ml/min/1.73m^2) = 141 \times \min(Scr/k, 1)^a \times \max(Scr/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018 [if female] \times 1.159 [if black]$, where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males; min indicates the minimum of Scr/k or 1 and max indicates the maximum of Scr/k or 1. Structural renal damage was defined by ACR ≥ 30 mg/g. CKD was defined as structural and/or functional damage of the kidney manifested by albuminuria or decreased eGFR.

Carotid ultrasonography

As part of the study protocol, carotid ultrasound measurements were done on a Toshiba Ultrasound instrument (Power Vision Toshiba SSH-380 ultrasound system, Toshiba American Medical Systems, Carrollton, TX), using a 7.5 MHz linear array transducer. Images were recorded at the common carotid, carotid bulb (bifurcation), and internal carotid arteries bilaterally according to previously developed protocols for the Atherosclerosis Risk in Communities study (21). Images were recorded on super VHS video tapes and read by certified readers from the Vascular Ultrasound Research Laboratory in Wake Forest Medical Center, North Carolina, using a semi automatic ultrasound imaging. The maximum carotid IMT readings of left and right far walls were averaged for each segment; if bilateral images could not be obtained, value of one side was used as the average. The average of carotid IMT of common, bulb, and internal segments was depicted as composite carotid IMT.

Statistical methods

All statistical analyses were performed using SPSS version 15.0 and SAS version 9.1 (SAS institute, Cary, NC). Continuous variables were tested for normality using Kolmogorov-Smirnov test. Median and interquartile range were reported for variables that were not normally distributed. General linear models were used to examine race and sex differences in risk factor variables. Differences in prevalence of albuminuria and reduced eGFR by race and sex were evaluated using chi-square test. Two subjects with kidney failure ($eGFR < 15$ ml/min/1.73m²) were excluded from further analysis. All p-values were 2-tailed and adjusted for covariates where appropriate. The level of significance for hypothesis testing was set at 5% ($\alpha = 0.05$).

Two separate models assessing the relation between albuminuria and functional renal damage ($eGFR < 60$ ml/min/1.73m²) with carotid IMT were constructed using binary logistic regression by stepwise selection (significance level: enter =0.05; stay=0.05). The independent variables included in the initial model were age, race, sex, obesity (yes/no), hypertension (yes/no), diabetes (yes/no), dyslipidemia (yes/no), smoking (yes/no) and composite carotid IMT (top quartile versus rest). Significant predictors in the stepwise model were entered in the final age adjusted model and adjusted odds ratios (OR) were determined. Wilcoxon rank sum test was used to calculate difference in carotid IMT for

subjects with and without albuminuria. Box and whisker plot was used for graphical representation of values of carotid IMT by albuminuria status.

Results

Characteristics of the study cohort by race and sex are presented in Table 1. With the exception of age, significant race and/or sex differences were observed for all risk factor variables listed. Blacks versus whites had higher BMI (females only), systolic blood pressure, diastolic blood pressure, HDL-C (males only), glucose (females only), common carotid IMT and composite carotid IMT; and lower LDL-C (females only) and triglycerides. Males versus females had higher systolic blood pressure, diastolic blood pressure, LDL-C, triglycerides, glucose (whites only), segmental and composite carotid IMT; and lower BMI (blacks only) and HDL-C. Blacks versus whites had higher prevalence of obesity (females only), hypertension, diabetes (females only) and smoking (males only); and lower prevalence of dyslipidemia. Males versus females had higher prevalence of hypertension, dyslipidemia, diabetes (whites only) and smoking (blacks only).

The mean and selected percentiles of eGFR in the study cohort by race and sex are given in Table 2. Blacks versus whites ($p=0.02$) and females versus males ($p<0.001$, blacks only) had higher values. With respect to the prevalence of albuminuria as depicted by spot urine ACR, shown in Table 3, blacks versus whites had higher prevalence ($p=0.02$).

Subjects with different stages of CKD, as defined by National Kidney Foundation (Kidney Disease Outcome Quality Initiative) guidelines (22), in the study cohort are listed in Table 4 by race and sex. Ninety nine (8.5%) subjects had CKD with blacks having higher prevalence than whites ($p=0.01$). Eighty three of those had albuminuria with normal eGFR (83.8%), 13 (13.1%) had both albuminuria and mild to severe reduction of eGFR, and only 3 (3.1%) had reduced eGFR but no albuminuria.

Figure 1 shows box and whisker plot with age, race and sex adjusted mean and interquartile range of segment-specific and composite carotid IMT in subjects with and without albuminuria. Subjects with albuminuria had significantly higher internal carotid IMT ($p=0.03$), common carotid IMT ($p=0.005$), and composite carotid IMT ($p=0.04$) than those without.

Table 5 lists age-adjusted ORs of independent factors associated with albuminuria identified by stepwise logistic regression model. Significant associations were noted for black race (OR 1.92, $p=0.005$), female sex (OR 2.24, $p=0.002$), diabetes (OR 6.26, $p<0.001$), hypertension (OR 2.36, $p<0.001$), obesity (OR 1.73, $p=0.02$), and composite carotid IMT (OR 1.83, $p=0.02$). However, reduction in eGFR in the range of functional renal damage ($<60\text{ml/min/1.73m}^2$) did not show significant independent association with carotid IMT, after adjusting for covariates. In addition, no statistically significant differences in IMT were noted in the different race-sex adjusted quartiles of eGFR.

Discussion

Consistent with National Health and Nutrition Examination Survey and Kidney Early Evaluation Program (KEEP) by National Kidney Foundation (23) the present study in community-based non-institutionalized young adults demonstrate the burden of CKD in a population largely unaware of its presence and emphasize the need for combining both albuminuria and eGFR to detect early onset renal disease. Albuminuria and reduced eGFR identify distinct but complimentary processes in CKD, because only 16.7% of those with albuminuria also had reduced eGFR; however 81.2% of those with reduced eGFR had albuminuria. However, it is also important to identify that subclinical atherosclerotic

changes in young adults with CKD is mostly driven by structural changes depicted by albuminuria, rather than functional reduction of eGFR. The role of reduction of eGFR on subclinical CV changes is controversial, and some studies with Cystatin C as a filtration marker have shown no significant independent association of IMT with eGFR even in older subjects (24,25). As our study population comprises mostly young adults with normal renal function and only few subjects with reduced eGFR, it is not possible to comment on the relation of eGFR with subclinical atherosclerosis. Nonetheless, both these tests still need to be considered for implementation in general clinical practice and follow-up as described by National Kidney Foundation KDOQI Clinical Practice Guidelines (5,6,22).

The association of albuminuria with carotid IMT highlights the importance of evaluating the progression of silent, asymptomatic systemic vascular disease in high risk groups (black race, obese subjects, diabetics and hypertensives). As carotid IMT is considered a preclinical marker for systemic atherosclerosis, it can be used to monitor CV disease progression (26). This provides additional information complementing previous studies on carotid IMT in CKD that were focused only on symptomatic population of relatively older age group (27–29). The current findings underscore the occurrence of concurrent nephrogenic and cardiovascular atherosclerosis in asymptomatic younger patients.

Although the observational and cross-sectional nature of this study can not establish causality and underlying mechanisms for the observed relationships, these findings are in accordance with previous research linking CKD with adverse CV risk factors and subclinical atherosclerosis. Several putative mechanisms link these relationships. Among others, albuminuria is associated with endothelial dysfunction, which might promote cell damage and platelet aggregation (30). This may induce systemic endothelial basement membrane leakiness especially in diabetics due to endothelial stress by high glycosylation end products (31,32). In hypertensives, increased renal damage is caused by high intraglomerular pressure resulting in albuminuria (31–33). The co-occurrence of CV risk may be attributed to dysregulation of mineral metabolism (34,35). This mechanism is of particular importance in black subjects, who have higher salt sensitivity (36) and consume high dietary sodium and low potassium (37,38) leading to hypertension. Black-white differences in healthy children noted urinary excretion of potassium to be considerably lower in blacks on equal dietary intake suggesting racial contrasts in renal tubular exchange of electrolytes (37,38). Also, studies of end-stage renal disease show a marked predilection for kidney disease in black males (39). Another interesting finding is that blacks have higher mean values of eGFR but the prevalence of kidney disease is determined by similar cut-points of reduced eGFR. The reduction in blacks is relatively higher, suggesting a greater percent reduction in eGFR. With respect to obesity, fat as a highly active endocrine organ, plays an important role in multiple areas. These include the dysregulation of hemodynamic, metabolic, and inflammatory processes through mechanisms that include activation of release of free fatty acids from the adipocytes, macrophage infiltration into the adipose tissue, hepatic lipogenesis, adipose renin-angiotensin-aldosterone system, sympathetic nervous system, inflammatory cytokines and ectopic lipid storage (40–42). These factors support the concept of multivariate and highly interrelated CV risk profile and accelerated subclinical atherosclerosis as depicted by carotid IMT in patients with CKD (43).

A few important limitations of this study merit consideration. Measurements on ACR were cross-sectional. This is important as persistent proteinuria is more reflective of renal damage than a single measurement. Recent guidelines advocate repeated measurements with confirmation of persistence of abnormal results over 3 months to diminish false positive rate of urine protein testing (5,6). It would be important to have follow-up in urine measurements, to reduce misclassification. Regardless, this should not lead to spurious association as incomplete case ascertainment is more likely to underestimate the strength of

association rather than magnifying it. Secondly, cut-off for diagnosis of albuminuria using $\text{ACR} \geq 30\text{mg/g}$ is not specific for race and sex. This is possibly the reason for female sex coming through as one of the risk factors for albuminuria. Although American Diabetes Association recommends a single cut-off, race-and sex-specific cut-offs have been proposed for accurate estimation (44). Finally, although eGFR calculated by CKD-EPI formula is the most accurate GFR estimating equation, its accuracy is decreased at high GFR estimates. A study by Stevens et al on performance of the CKD-EPI formula for estimating GFR, with pooled data from 16 studies mention that eGFR calculated by CKD-Epi formula can be used to estimate GFR above $60\text{ mL/min/1.73 m}^2$ (45). However, this equation has not been validated in younger adults. Also, this formula implies blacks and females have higher eGFR for a given value of serum creatinine which can be a potential misspecification of the equation. However, this should not lead to inaccurate case ascertainment as declined renal function is determined at lower estimates $\text{eGFR} < 60\text{ml/min/1.73m}^2$. Repeat measurements are warranted to overcome these limitations. In addition, the National Kidney Disease Education Program (NKDEP) is developing a process to standardize the serum creatinine assay to a high-quality reference standard of the National Institute of Standards and Technology (NIST) with the goal of implementing assay standardization in all laboratories (46).

The present study has several strengths. Most studies on CV risk assessment in CKD have been done on symptomatic subjects older than 40 years of age (27–29). As this study cohort includes young adults with mean age of 36.3 years, it is useful in predicting early onset renal damage as well as silent CV disease. Such studies provide additional information on subclinical concurrent atherosclerosis in asymptomatic young adults with CKD.

Conclusions

Considerable proportion (8.5%) of asymptomatic young adult population in the community have CKD, predominantly shown by albuminuria, with black race, female sex, obesity, diabetes, hypertension and subclinical atherosclerosis as depicted by carotid IMT as it's independent correlates. These findings have considerable implications for early prevention and control of CV/CKD risk.

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Selected Abbreviations and Acronyms

CKD	chronic kidney disease
CV	cardiovascular
eGFR	estimated glomerular filtration rate
IMT	intima-media thickness
ACR	urine albumin/creatinine ratio
OR	odds ratio

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Figure 1. Box and whisker plot showing age, race and sex adjusted means and interquartile range of segmental and composite carotid IMT in subjects with and without albuminuria. Note internal carotid, common carotid and composite IMT show significantly higher values in those with albuminuria.

Table 1

Characteristics of study cohort by race and sex: The Bogalusa Heart Study.

	WHITE		BLACK		p-value [†]	
	MALE	FEMALE	MALE	FEMALE	RACE	SEX
N	379	454	136	224		
Age (yr)	36.6 ± 4.3	36.3 ± 4.4	36.5 ± 4.4	35.6 ± 4.8	NS	NS
BMI (kg/m ²)	29.4 ± 5.9	28.4 ± 7.1	29.8 ± 7.4	32.0 ± 8.8	<0.001 ^f	0.006 ^b
Systolic BP (mm Hg)	118.6±11.1	111.1±11.2	128.5±16.4	119.2±15.0	<0.001	<0.001
Diastolic BP(mm Hg)	80.4 ± 8.1	75.1 ± 8.3	86.7 ± 12.2	79.9 ± 10.8	<0.001	<0.001
LDL-C (mg/dL)	129.6±34.2	124.5±32.5	125.4±43.9	116.6±32.4	0.001 ^f	0.03
HDL-C (mg/dL)	41.1 ± 11.8	50.3 ± 12.8	49.3 ± 15.7	51.6 ± 13.0	<0.001 ^m	0.05
TG (mg/dL) [‡]	125.0(108.0)	104.5(75.0)	95.0(66.5)	84.0(49.5)	<0.001	<0.001
Glucose (mg/dL)	88.7 ± 23.0	83.1 ± 17.6	90.4 ± 31.8	89.4 ± 32.6	<0.001 ^f	0.001 ^w
Obesity (BMI ≥ 30 kg/m ² ,%)	36.9	36.1	43.4	52.7	<0.001 ^f	NS
Hypertension (%)	25.7	14.3	42.6	31.3	<0.001	0.04
Dyslipidemia (%)	66.5	35.5	51.5	25.9	0.01	<0.001
Diabetes (%)	5.3	2.4	5.9	6.7	0.002 ^f	0.05 ^w
Smoking (%)	29.8	29.9	40.4	29.8	0.03 ^m	0.04 ^b
Internal carotid IMT (mm) [‡]	0.72 (0.21)	0.65 (0.20)	0.74 (0.26)	0.67 (0.18)	NS	0.004
Carotid bulb IMT (mm) [‡]	0.96 (0.29)	0.88 (0.19)	0.99 (0.26)	0.88 (0.24)	NS	0.003
Common carotid IMT (mm) [‡]	0.77 (0.18)	0.69 (0.14)	0.82 (0.18)	0.76 (0.13)	<0.001	<0.001
Composite IMT (mm) [‡]	0.82 (0.20)	0.75 (0.15)	0.87 (0.18)	0.78 (0.16)	0.03	<0.001

* All data expressed as Mean ± Standard deviation, unless mentioned otherwise.

* NS, not significant; BMI, body mass index; BP, blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; IMT, intima-media thickness;

[‡]Median (Interquartile range)

[†]Adjusted for age

^mMales only

^fFemales only

^wWhites only

^bBlacks only

Table 2 Mean ($\pm$ SD) and selected percentiles of eGFR[†] by race and sex

	Mean $\pm$ SD* (ml/min/1.73m ²)	Selected percentiles						
		5 th	10 th	25 th	50 th	75 th	90 th	95 th
White males	101.2 $\pm$ 13.7	75.4	82.7	92.9	104.3	111.9	116.9	119.0
White females	103.5 $\pm$ 15.9	78.8	80.3	92.1	108.0	114.6	120.6	125.3
Black males	104.8 $\pm$ 20.5	77.2	82.3	90.4	104.1	123.3	129.6	132.0
Black females	117.9 $\pm$ 20.6	83.5	91.9	106.1	124.5	132.6	137.9	146.8
Total sample	105.6 $\pm$ 17.9	78.8	83.0	93.5	108.0	116.3	128.2	133.9

Abbreviations same as in table 1.

[†]eGFR calculated by CKD-EPI method

* p for race difference = 0.02, blacks>whites, adjusted for age and sex

* p for sex difference <0.001, females>males among blacks, adjusted for age and race

Table 3

Prevalence of albuminuria by race and sex

Race-sex groups	ACR = 30–300 mg/g	ACR > 300 mg/g	Total
White males	14/379 (3.7%)	2/379 (0.5%)	16/379 (4.2%)
White females	30/454 (6.6%)	1/454 (0.2%)	31/454 (6.8%)
Black males	11/136 (8.1 %)	3/136 (2.2%)	14/136 (10.4%)
Black females	32/224 (14.3%)	3/224 (1.3%)	35/224 (15.6%)
Total	87/1193 (7.3%)	9/1193 (0.8%)	96/1193 (8.1%)

*
p for race difference = 0.02, blacks>whites, adjusted for age and sex

Table 4 Staging of Chronic Kidney Disease by race and sex[†]

Stage		eGFR (ml/min/1.73m ²)	WHITE		BLACK		TOTAL
			Male	Female	Male	Female	
1	Kidney damage [‡] with normal GFR	≥ 90	15	25	12	31	83
2	Kidney damage [‡] with mild ↓ GFR	60–89	1	6	1	2	10
3	Moderate ↓ GFR	30–59	1	1	1	1	4
4	Severe ↓ GFR	15–29	-	-	-	-	-
5	Renal failure	<15 or dialysis	-	-	1	1	2
Total, n (%)			17/379 (4.6%)	32/454 (7.0%)	15/136 (11.0%)	35/224 (15.6%)	99/1193 (8.5%)

[†] Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines²²[‡] Kidney damage as manifested by abnormalities noted on urine test (defined by American Diabetes Association cut-off value for spot ACR > 30mg/g)

* p for race difference = 0.01, adjusted for age and sex

Table 5

Odds ratios and 95% confidence intervals (C.I.) for having albuminuria

	Odds Ratio [‡]	95% C.I.	p-value
Black Race	1.92	1.21–3.06	0.005
Female Sex	2.24	1.36–3.70	0.002
Diabetes	6.26	3.26–12.01	<0.001
Hypertension	2.36	1.45–3.89	<0.001
Obesity	1.73	1.08–2.79	0.02
Composite carotid IMT [†]	1.83	1.10–3.04	0.02

[†]Top quartile versus rest (only composite measure was included)[‡]Adjusted for age