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Reappraisal of the Impact of Race on Survival in Patients on Dialysis

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Abstract

Racial differences in the etiology, natural history and effects of chronic kidney disease have long been the subject of investigation. Dialysis-dependent kidney failure occurs nearly four times more often in African Americans than European Americans. Despite this observation, studies repeatedly demonstrate that African Americans have a significant survival advantage after initiating dialysis. Although this phenomenon has been attributed to environmental and socioeconomic factors, recent studies demonstrate that inherited factors strongly influence racial differences in development of diverse kidney diseases and may impact the risk for nephropathy-associated cardiovascular disease. Herein we review relevant studies and propose the hypothesis that inherited factors leading to organ-limited kidney diseases and a lower burden of systemic atherosclerosis contribute, in part, to the improved survival rates seen in African American patients on dialysis.

Keywords

African Americans; chronic kidney disease; dialysis; race; European Americans; genetics; survival

Prevalence of Kidney Failure

Racial Differences

All studies agree that the prevalence of kidney failure is higher in African Americans than European Americans by a factor of at least two [1,2]. Postulated causes include increased prevalence of early stage chronic kidney disease (CKD), higher CKD progression rates, and lower mortality rates (survival advantage) in the earlier stages of CKD in African Americans.

Using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation for estimating glomerular filtration rate (GFR) in the NHANES III (Third National Health and Nutrition Examination Survey) study population, the overall 13% adult prevalence of CKD is concentrated in the early stages (Stage I-III), with a prevalence of only 0.35% in advanced (Stage IV) CKD[3]. Using the that same formula in four populations, early stages of CKD were less prevalent in African Americans compared to European Americans 4–8 (Table 1). This racial difference tends to reverse in the more advanced stage of CKD 6,[8]. Although increased

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CKD risk was found using the Cockroft-Gault formula for estimating GFR in both NHANES II and REGARDS (Reasons for Geographic and Racial Differences in Stroke) study populations [4,6], this is likely due to higher serum creatinine values in African Americans causing underestimation of GFR9. Increased relative risk for African Americans versus European Americans was also found in the Medicare population where identification of CKD depends on provider coding2,[10]. If racial differences in early stage CKD prevalence exist, it would imply differences in mechanisms of initiation of kidney disease. This important question will probably not be resolved until more refined techniques for identifying early stage CKD become available.

The sharply lower prevalence of Stage IV CKD indicates that few patients with moderately reduced kidney function progress to kidney failure. Death before development of kidney failure (competing risk) contributes to this phenomenon [8,11,12]. The greater relative risk for advanced CKD in African Americans versus European Americans, compared to earlier stages, implies higher progression rates of CKD in African Americans 6[–8,13]. This implication is supported by direct measurements of progression rates [8,13–16]. Racial differences in prevalence of kidney failure are partially explained by differences in incidence and severity of hypertension and diabetes, access to healthcare or socioeconomic status 2,17,18; and an effect of environmental factors on progression of CKD is suggested by the similar progression rates seen in African American and European American Veterans Administration (VA) patients with equivalent access to care 12. However, higher progression rates in African Americans were found in the MDRD trial in which care was standardized 15, and in a large VA population where access to care was similar 8; in the latter study, no correction for differences in blood pressure control was possible. In the AASK (African American Study of Kidney Disease and Hypertension) trial, African Americans with CKD reportedly due to hypertensive nephrosclerosis progressed despite excellent hypertension control and use of angiotensin converting enzyme (ACE) inhibitors 19. Interestingly, African Americans in AASK were much more likely to progress to kidney failure than to die of cardiovascular causes, the opposite result from that observed in general, racially mixed populations 7,8,11,[20]. Further studies are needed to characterize racial differences in kidney disease progression rates and the extent to which they contribute to the increased incidence of kidney failure in African Americans; unfortunately AASK lacked a European American group for comparison.

A higher mortality in European Americans compared to African Americans in the early stages of CKD could contribute to an increased prevalence of kidney failure in African Americans versus European Americans. However, most studies show just the opposite [8,21], a phenomenon that may contribute to the lower mortality rates in African Americans with advanced CKD and kidney failure.

Heredity and Racial Differences

African Americans have incidence rates of kidney failure attributed to type 2 diabetes mellitus, “hypertension-associated” nephropathy, and organ-limited (focal segmental glomerulosclerosis [FSGS]) and systemic (human immunodeficiency virus-associated nephropathy [HIVAN]) glomerular diseases far exceeding those in European Americans [22]. Relative to European Americans, African Americans in the southeast and central eastern seaboard have a 4–20 fold higher risk for developing “hypertensive nephropathy” 23,24. Collapsing FSGS from HIV infection nearly always occurs in African Americans 25. Major roles for inherited factors underlying racial differences in disease causation are supported by familial clustering of kidney failure and *MYH9* (non-muscle myosin heavy chain 9) gene associations.

Familial aggregation of CKD and kidney failure has been observed for nephropathy associated with diabetes [26–28], hypertension 29,30, HIV infection [31] and systemic lupus erythematosus

(SLE) [32]. Among nearly 26,000 incident dialysis patients, African American race was an independent risk factor for familial aggregation 30. Familial clustering of kidney failure due to multiple etiologies within single families suggested the existence of generalized kidney disease "susceptibility genes" 28,29,[33,34].

This prediction held true with demonstration of the strong association between *MYH9* and CKD in African Americans [35–38]. Significant association was detectable in idiopathic FSGS, HIVAN, and kidney disease attributed to hypertension and type 2 diabetes (Table 2). The *MYH9* gene accounts for approximately 70% of non-diabetes associated kidney failure and 16% of diabetes-associated kidney failure in African Americans, approximately 43% of all kidney failure in this racial group. Strong association between *MYH9* and FSGS is present in European Americans, but the attributable risk is far lower due to a 4% frequency of risk alleles compared to 60% in African Americans [35,39,40]. *MYH9* gene–environment and/or gene-gene interactions appear necessary to initiate nephropathy, since not all genetically susceptible individuals will develop nephropathy [37].

Survival in Kidney Failure

Racial Differences

National and regional studies reveal consistent and clinically significant survival advantages in African Americans on dialysis, relative to European Americans [1,41–44]. The survival advantage remains after adjustment for age, co-morbidity, socioeconomic disparities and differences in rates of kidney transplant and dialysis withdrawal. One study reported that racial differences in kidney failure survival could be eliminated by the combined effects of case mix and treatment variables [42]; however, the persistence of survival differences in a randomized clinical trial with tightly controlled treatment parameters supports additional, unidentified factors [45]. African Americans have higher serum creatinine concentrations than European Americans at dialysis initiation [41,42] and higher serum creatinine levels are independent predictors of reduced mortality 46–48. This finding could affect the time of starting dialysis and hence outcomes on dialysis [49], but the mechanism(s) of the higher serum creatinine levels in African Americans and its associated survival advantage has not been elucidated. [48]

The lower mortality rates in African Americans with kidney failure stand in stark contrast to their higher mortality rates in the general population [50–52] and in those with the earlier stages of CKD [7,8,53,54]. Mortality rates in African Americans may be affected by differences in access to care and other socioeconomic factors, as two VA studies providing equal access to care reveal lower mortality rates in African Americans with CKD 12 and diabetes 55. Survival of a "healthier" population of African Americans who develop kidney failure may contribute to the lower mortality. 42,[54] Since nearly 50% of deaths in dialysis patients are due to cardiovascular disease (CVD) [22], particularly sudden cardiac death 56,57, the surprising finding of a reduced prevalence of CVD in African Americans initiating dialysis (Table 3)[41, 48,58–61] likely contributes to their survival advantage. While survival bias may be a factor, we propose that the lower prevalence of CVD in African Americans has two biologic causes: the clustering of *MYH9*–associated nephropathy and a genetic mechanism that reduces atherosclerosis.

Association with MYH9

The disease historically labeled "hypertensive nephrosclerosis" reportedly causes 35% of kidney failure in African Americans and 25% in European Americans[22]; but has different pathologic mechanisms and clinical associations between racial groups (Table 4). African Americans have more severe nephropathy with greater numbers of solidified glomeruli (focal global glomerulosclerosis) and interstitial fibrosis, vascular changes (arteriolar

nephrosclerosis) that do not correlate with level of blood pressure [62,63], and a strong association with *MYH9* polymorphisms [38]. European Americans labeled with hypertensive nephrosclerosis are typically older, more often have arteriolar nephrosclerosis, and a stronger association with generalized atherosclerosis involving the coronary and carotid arteries [64,65]. We believe that African Americans with *MYH9*–associated nephropathies are more likely to have organ-limited kidney diseases (e.g., FSGS and focal global glomerulosclerosis) with less extra-renal atherosclerosis. This results in lower CVD rates on starting renal replacement therapy, compared to older European Americans with diffuse large vessel atherosclerosis. Hypertensive kidney failure in African Americans appears to be a misnomer unrelated to high blood pressure [19] and is strongly associated with *MYH9* in AASK participants.[66] This likely explains why strict blood pressure control and use of ACE inhibitors failed to halt kidney disease progression in AASK and other studies [37,67].

Potential Differences in Extra-renal Cardiovascular Disease

In addition to the *MYH9* nephropathy phenotype, there are growing indications that other hereditary factors contribute to a phenotype with reduced CVD in African Americans.

Two large studies in patients with diabetes (without advanced nephropathy) having equal access to medical care at the VA and Kaiser Permanente revealed 50% lower rates of myocardial infarction in African Americans, relative to European Americans. This surprising result was seen despite poorer glycemic and blood pressure control in African Americans [68, 69]. These results appear relevant to the issue of dialysis survival, since nearly 50% of incident dialysis patients have diabetes. The pre-dialysis course of CVD in diabetic patients could contribute to racial variation in survival.

Computed tomography-derived coronary artery calcified atherosclerotic plaque, a marker of atherosclerosis and strong predictor of future CVD events 70, is markedly lower in diabetic and non-diabetic African Americans, relative to European Americans 71–75. The lower rates of myocardial infarction in African Americans with diabetes, present well before advanced nephropathy develops, are likely associated with this phenomenon. Extra-cranial carotid artery atherosclerosis also demonstrates racial differences in the general population that appear biologically mediated. Carotid artery atherosclerosis is more often present (and severe) in European Americans, whereas African Americans with stroke more commonly have intracranial small vessel cerebrovascular disease [76–78].

We demonstrated that the burden of calcified atherosclerotic plaque in the carotid, coronary and aorta of patients with type 2 diabetes correlated with albuminuria in European Americans, but not African Americans[73,79]. As diabetes-associated CKD progresses with increasing albuminuria, atherosclerosis would appear more likely to develop in European Americans. In CKD and dialysis patients, coronary artery calcified atherosclerotic plaque is increased relative to individuals without CKD or known coronary artery disease.[80,81] We are unaware of reports evaluating racial differences in coronary artery calcified atherosclerotic plaque in large numbers of incident dialysis patients. A report in prevalent dialysis patients (81 African Americans and 61 European Americans) did not reveal racial differences in coronary artery calcified atherosclerotic plaque [82]. However, these patients had been on dialysis for 4 years and likely had vascular disease relating to factors such as longstanding hyperphosphatemia, vitamin D deficiency, and use of calcium-containing phosphate binders. These environmental exposures would be likely to overwhelm inherited predisposition to atherosclerotic CVD; thus, incident dialysis patients and those not yet on dialysis should be evaluated for racial differences in coronary artery calcified atherosclerotic plaque.

Familial clustering of coronary and carotid artery disease appears to be stronger in European American families, relative to African American 83–85. This suggests the existence of

susceptibility genes underlying arterial calcification occurring more frequently in European Americans. Relative to European Americans, African Americans with diabetes develop less calcified atherosclerotic plaque in response to smoking and receive greater protection from high-density lipoprotein cholesterol.[86] Reduced levels of arterial calcified atherosclerotic plaque in African Americans may be associated with enhanced bone mineralization (lower rates of osteoporosis), despite ingestion of less dietary calcium. Osteoporosis and atherosclerosis appear to be linked disease processes [87] and blood vessels acquire calcified atherosclerotic plaque as vascular cells assume osteoblastic phenotypes 88. It is clear that conventional CVD risk factors must have differential effects on development of atherosclerosis between races[86,89] and it is unlikely that these effects relate solely to environmental exposures. It may prove difficult to demonstrate differential genetic susceptibility in the context of overwhelming environmental risk factors.

The favorable biologic factors leading to reduced CVD rates in African Americans on dialysis (relative to European Americans), may be attenuated by environmental factors such as poor access to healthcare. Lower socioeconomic status likely increases CVD rates in the general African American population. The net result of these competing factors appears to yield a lower burden of CVD in African Americans, despite higher burdens of kidney failure. The combined effects of reduced susceptibility to atherosclerosis and the greater prevalence of *MYH9*-associated organ-limited kidney diseases at dialysis initiation likely contribute to subsequent survival advantages in African Americans.

Conclusions

The key to understanding African American–European American differences in survival on dialysis likely involves the markedly lower prevalence of CVD in African Americans at initiation of renal replacement therapy [55,61]. Since nearly 50% of deaths in dialysis patients are due to CVD, the lower prevalence of CVD in African Americans starting dialysis would be expected to translate into improved survival. Although survival bias due to socioeconomic factors and unequal access to care in the predialysis stages of CKD likely contribute to observed racial differences in dialysis survival, we propose biological explanations based on inherited susceptibility to organ-limited forms of kidney failure, coupled with inherited protection from atherosclerosis in African Americans.

There is a growing realization that differential frequencies of risk alleles in disease genes exist between racial groups. Although we all share >99% of our genome, small differences in genetic make-up have the potential to produce major differences in phenotype. Methods exploiting racial differences in allele frequency are being used to identify genomic regions underlying complex diseases that are more common in certain racial groups [90,91]. African Americans have higher frequencies of the *MYH9*-associated kidney failure gene leading to organ-limited diseases in the spectrum of FSGS. Individuals with *MYH9*-associated nephropathy, predominantly African Americans, would appear less likely to develop extra-renal vascular disease at dialysis initiation. In addition, marked racial differences exist in susceptibility to development of atherosclerosis and calcified atherosclerotic plaque. In contrast to kidney disease, familial clustering of CVD traits is stronger in European Americans, a racial group more susceptible to risk factors producing systemic atherosclerosis with small vessel arteriolar nephrosclerosis and progressive CKD. Therefore, European Americans may be more likely to develop CVD complications, including death, in the setting of kidney failure. Ongoing genomic analyses in complex human diseases are clarifying these effects. We conclude that environmental factors alone are insufficient to fully explain the striking and consistent survival advantage that is observed in African American patients on dialysis.

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Table 1

Racial differences in the prevalence of early stage CKD

Study; Population	eGFR (ml/min/1.73 m^2)[a]	Prevalence		Statistic
		EA	AA	
Coresh et al (2003)[4]; NHANES III (1988–94)				
	60–89	35.2	17.4	0.37 (0.32–0.42)[§]
	30–59	4.8	3.1	0.56 (0.44–0.71)[§]
Coresh et al (2005)[5]; NHANES 1999–2000				
	60–89	42.0	18.1	NR
	30–59	4.1	3.2	NR
McClellan et al (2006)[6]; REGARDS				
	50–59	31.1	18.9	0.42 (0.40–0.46)[§]
	40–49	13.0	8.5	0.37 (0.33–0.41)[§]
	30–39	4.5	3.5	0.38 (0.32–0.45)[§]
Newsome et al (2007)[7]; Medicare[*]				
	45–59	27.9	21.3	P < 0.001[†]
	30–44	19.3	16.3	P < 0.001[†]
Choi et al (2009)[8]; VA[**]				
	60–89	56.3	42.5	P < 0.001[††]
	45–59	15.2	8.2	P < 0.001[††]
	30–44	5.5	3.3	P < 0.001[††]

Abbreviations: NR, Not Reported; AA, African American; EA, European American; CKD, chronic kidney disease; NHANES, National Health and Nutrition Examination Survey; REGARDS, Reasons for Geographic and Racial Differences in Stroke; eGFR, estimated glomerular filtration rate.

[*] Cooperative Cardiovascular Project. Randomly selected Medicare inpatients with discharge diagnosis of acute myocardial infarction.

[**] All veterans with one or more outpatient serum creatinine measurements between October 2000 and September 2001

[§] Odds Ratio African American vs European American (95% confidence interval)

[†] Cumulative logit model

[††] Chi square

Note: GFR estimated by IDMS-traceable 4-variable MDRD Study equation; factor for conversion from ml/min/1.73 m^2 to ml/s/1.73 m^2, ×0.01667.

Table 2

Genetic association results in *MYH9*-associated nephropathy studies

Condition (cohort)	Reference	Race	Marker	OR (95% CI)	P value
FSGS (NIDDK)					
	35	AA	E1 haplotype	4.65 (3.11–7.02)	9×10^{-16}
	35	EA	E1 haplotype	7.66 (0.75–380.0)	0.05
HIVAN (NIDDK)	35	AA	E1 haplotype	5.92 (2.89–12.85)	7×10^{-8}
Non-diabetic ESRD (FIND)	36	AA	rs16996674	3.10 (2.15–4.47)	1.5×10^{-9}
Diabetic ESRD (FIND)	36	AA	rs16996674	1.51 (1.01–2.27)	0.04
Non-diabetic ESRD (Wake Forest)	37	AA	E1 haplotype	2.23 (1.78–2.80)	4.5×10^{-12}
Diabetic ESRD (Wake Forest)	38	AA	E1 haplotype	1.27 (1.04–1.56)	0.02
Serum creatinine (Eurospan)	39	European	rs11089788	N/A	0.0089
Urine ACR (HyperGEN)					
	40	AA	E1 haplotype	N/A	0.01
	40	EA	E1 haplotype	N/A	0.49
Hypertensive CKD	66	AA	rs4821481	2.69 (1.30–5.58)	0.008

Abbreviations: AA, African American; EA, European American; OR, odds ratio; CI, confidence interval; ACR, albumin-creatinine ratio; N/A, not applicable; FSGS, focal segmental glomerulosclerosis; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; ESRD, end-stage renal disease; FIND, Family Investigation of Nephropathy and Diabetes; CKD, chronic kidney disease; AASK, African American Study of Kidney Disease and Hypertension; HIVAN, human immunodeficiency virus–associated nephropathy; rs, reference single-nucleotide polymorphism identification number.

Table 3

Racial differences in prevalence of coronary artery disease in incident dialysis patients

Study	Population	Prevalence (%)		Statistic
		AA	EA	
Mesler et al (1999)[41]	USRDS[a]	33	39	P < 0.001[§]
Cheung et al (2000)[58]	HEMO Study	NR	NR	OR, 0.64 (P = 0.017)[†]
Stack et al (2001)[59]	USRDS[b]	37	43	OR, 0.54 (95% CI, 0.41–0.72)[††]
Volkova et al (2006)[60]	Medicare/Medicaid[c]	15.7	31.2	OR, 0.41 (95% CI, 0.40–0.43)[‡]
Trivedi et al (2009)[48]	USRDS[d]	16.9	32.7	NR

Abbreviations: EA, European American; AA, African American; NR, Not reported; USRDS, US Renal Data System; OR, odds ratio.

[a] Case mix severity study. Randomly selected national sample age 20 or older.

[b] Dialysis Morbidity and Mortality Study Wave 2. Sample of incident dialysis patients 1996/1997.

[c] Incident dialysis patients Network 6 1995–2006

[d] Incident dialysis patients 1997–2001.

[§] Chi square

[†] Adjusted odds ratio black vs white

[††] non-white vs white, P<0.01, reported in Trespalacios et al (2002)[61]

[‡] Unadjusted odds ratio black vs white

Table 4

Discordant phenotypes in hypertension-associated nephropathy, by race

Renal phenotype	European Americans	African Americans
Glomerulosclerosis type	Obsolescent; collagen-rich	Solidified, focal global
Presence of segmental glomerulosclerosis	Less common	More common
Microvascular lesions	Moderate	Severe
Systemic BP correlation with microvascular lesions	No	No
Interstitial fibrosis	Moderate	Severe
GFR stabilization with blood pressure lowering	Often effective	Ineffective
MYH9 gene association	Unknown	Strong, suggesting disease is in the FSGS spectrum
Survive to initiate dialysis	Minority	Majority

Abbreviations: FSGS, focal segmental glomerulosclerosis; BP, blood pressure; GFR, glomerular filtration rate.