Hypertension-Associated Kidney Disease: Perhaps no More

Barry I. Freedman* and John R. Sedor†

*Department of Internal Medicine, Section on Nephrology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and †Departments of Medicine and Physiology and Biophysics, Case Western Reserve University School of Medicine, and Kidney Disease Research Center, Rammelkamp Center for Research and Education, MetroHealth System Campus, Cleveland, Ohio

Few kidney diseases remain as controversial as hypertensive or arteriolar nephrosclerosis, a syndrome that reportedly progresses to hypertension-associated ESRD.1–3 Nearly 30% of Americans initiating renal replacement therapy receive this nonspecific moniker each year.4 Suggesting that essential hypertension does not cause ESRD would seem laughable today, akin to suggesting that *Helicobacter pylori* infection does not underlie modern peptic ulcer disease, yet an alternative story is rapidly unfolding.

Hypertensive nephrosclerosis is a vaguely defined clinical entity, most commonly applied to African Americans with hypertension and advanced chronic kidney disease (CKD) in the absence of other causes for renal failure. Physician bias clearly contributes to ethnic differences in the frequency of diagnosis.5 In practice, this nonspecific label is applied to African American patients with CKD who do not have diabetes, lack renal biopsies and have secondarily elevated BP with resultant left ventricular hypertrophy.6 Small studies purport that proteinuria ranging from mild to nephrotic range are seen in this grouping, although a general consensus is that subnephrotic levels of urinary protein excretion are typical of hypertensive nephrosclerosis. Phenotype criteria used in the African American Study of Kidney Disease and Hypertension (AASK) required that daily protein excretion be <2.5 g.7,8 Although nephrologists agree that elevated systemic BP exacerbates all forms of CKD, speeding progression to ESRD, the epidemiologic evidence supporting mild to moderate essential hypertension as an initiator of kidney damage has always been weak. Recent molecular genetic breakthroughs now demonstrate that genetic variants within a molecular motor protein, nonmuscle myosin IIA, are associated with nondiabetic kidney disease in African Americans,9,10 suggesting it may often be kidney injury that generates the high BP and not the other way around.11

ESSENTIAL HYPERTENSION: AN UNCOMMON INITIATOR OF PROGRESSIVE RENAL FAILURE?

Cross-sectional studies revealed positive relationships between the severity of kidney dysfunction and degree of BP elevation.12 Although causation is presumably the basis for this association, severe secondary hypertension is not unexpected in those with marked kidney dysfunction. Relative to European Americans, African American residing in the southeast are at 20-fold greater risk for developing ESRD from hypertensive nephrosclerosis.13 The increased frequency and severity of high BP in African Americans does not account for the excess rate of hypertensive kidney failure,14,15 and renal transplantation from normotensive donors largely cures high BP,16 demonstrating that high BP follows the kidney in humans, as in animal models. In practice, relatively few hypertensive African Americans or European Americans with normal kidney function initially develop progressive nephropathy, with or without antihypertensive therapy.17 Most im-

ABSTRACT

Despite common wisdom, the role of essential hypertension in the etiopathogenesis of ESRD has been controversial. Two recently published studies demonstrated a strong association of genetic variants in the gene that encodes the molecular motor protein nonmuscle myosin 2a (*MYH9*) with ESRD in African American patients without diabetes. These new data demonstrate that much of the excess risk of ESRD in African American individuals is attributable to an *MYH9* risk haplotype and suggest that hypertension may cause progressive kidney disease only in genetically susceptible individuals or be the result of a primary renal disease.


Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Barry I. Freedman, Department of Internal Medicine, Section on Nephrology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1053. Phone: 336-716-6192; Fax: 336-716-4318; E-mail: bfreedma@wfubmc.edu

Copyright © 2008 by the American Society of Nephrology
portant, lowering BP to usual or low lev-
el, even with inhibitors of angiotensin II
action, does not slow progression of neph-
rophy in hypertensive African American,2,28–31
and the renal histologic changes normally associated with high
BP, arterial and arteriolar wall thickening,
do not correlate with systemic BP.22,23 Renal biopsies in patients with a
clinical diagnosis of hypertensive nep-
hrlosclerosis typically reveal segmental or
Global glomerulosclerosis with marked interstitial fibrosis and other glo-
merular diseases in the remainder.22,24

It has long been proposed that a pri-
mary renal disease could explain all of these
findings such that observed elevations in
BP would be secondary.24,25 Familial ag-
gregation of hypertensive nephrosclerosis is widely found throughout the
United States, with relatives of patients with hy-
pertensive nephrosclerosis frequently hav-
ing different kidney diseases, including un-
specified chronic glomerulonephritis,
FSGS, lupus nephritis, and HIV-associated
nephropathy (HIVAN).26

Why then has the name “hypertensive kidney disease” stuck for all these years? To
convince epidemiologists and those with
vested interest in the primacy of hyper-
tension that high BP might be a sequela of
kidney disease—that hypertensive kidney disease was an inappropriate name for this
common condition—it would be neces-
sary to identify major susceptibility genes
associated with structural renal changes in
African Americans labeled as having hy-
pertensive nephrosclerosis.

MOLECULAR GENETIC ANALYSES
IN NONDIABETIC NEPHROPATHY

As in hypertensive nephrosclerosis, Afri-
Can Americans more often develop nep-
hrlosclerosis and FSGS compared with white individu-
als.27,28 Autosomal dominant, steroid-
resistant forms of FSGS are caused by
alpha-actinin-4 and transient receptor po-
tential cation channel 6 gene polymor-
phisms, whereas autosomal recessive
glomerulosclerosis is caused by podocin
(NPHS2) and nephrin (NPHS1) poly-
morphisms.29,30 Renal biopsies in pa-
tients with clinically diagnosed hyper-
tensive nephrosclerosis often reveal
FSGS, but this entity has been relatively
overlooked as a common contributor to
hypertensive nephrosclerosis.22,24 Un-
usual variants in the podocin and Wilms’
tumor (WT1) genes make minor contribu-
tions to sporadic cases of hypertensive
nephrosclerosis and FSGS in African
Americans, but these variants are not
major causes.31,32

Polymorphisms in a candidate gene
important in sympathetic nervous sys-
tem function related to hypertension is
associated with hypertensive nephroscle-
rosis in some African American pa-
tients.33 O’Connor et al.34 evaluated the
role of chromogranin A (CHGA) in the
susceptibility to high BP in kidney dis-
ese. CHGA gene polymorphisms were
discovered in a subset of patients with CKD from hyper-
tensive nephrosclerosis.35

Associations with CHGA, WT1, and
NPHS2 make it seem likely that several
genes with relatively small effect are likely
involved in the seemingly heterogeneous
syndromes termed hypertensive nephro-
sclerosis and FSGS. In present times, there
have been few major “genetic hits” in com-
mon complex diseases. Variants of
TCF7L2 gene, for example, demonstrate the
strongest association with type 2 diabe-
tes, an effect observed in multiple ethnic
groups.35 A doubling of risk for type 2 dia-
betes is seen in those homozygous for
TCF7L2 risk alleles.36 More than 15 other
replicated genes are also involved in the
susceptibility to type 2 diabetes.

Until now, it seemed that hypertensive
nephrosclerosis would likely involve simi-
lar numbers of genes. The renal syndrome
FSGS ultimately provided the break-
through for detecting a single major gene in
what had often been mislabeled clini-
cally as hypertensive nephrosclerosis but
not until the novel analytic technique of
mapping by admixture linkage disequilib-
rium (MALD) was applied.38 MALD is
most useful in the study of inherited dis-
seases that have marked ethnic differences
in disease frequency. It uses genetic mark-
ers that are spread throughout the genome and
have large differences in allele fre-
quency between parental populations.39
African Americans are an admixed popu-
lation with a large percentage of African
and a lesser proportion of European alleles.
Because African Americans develop FSGS
and hypertensive nephrosclerosis far more
often than white individuals, the expecta-
tion would be that regions of the genome that
demonstrate an excess frequency of African
ancestry in patients with these
common kidney diseases would associate
with distinct features of a disease.

Kopp et al.3 recently detected an asso-
ciation with genetic markers on chromo-
some 22q in African Americans with bi-
opsy-proven idiopathic FSGS and
HIVAN-associated FSGS. Fine mapping
reveals that disease association centers
on multiple single nucleotide polymor-
phisms (SNP) in intron 23 of the non-
muscle myosin II A heavy chain gene
(MYH9), a gene expressed in podocytes and
implicated in several rare inherited
syndromes with glomerular involve-
ment. The most strongly associated sin-
gle SNP reveal P values in the ranges of
10−18 to 10−20 with odds ratios (OR) of 4
5, whereas a haplotype containing the
three most associated SNP had an OR of
5 (P = 4 × 10−23, recessive model). The
attributable risk for carriage of this hap-
lotype was 100% in HIVAN-associated
FSGS and 72% in sporadic FSGS. Valida-
tion was observed in European Ameri-
cans with idiopathic FSGS, with lower
frequency of susceptibility alleles in this
ethnic group (4%), and extension studies
revealed the African American risk hap-
lotype is significantly associated with
nondiabetic forms of ESRD (predomi-
nantly classified clinically as ESRD from
hypertensive nephrosclerosis) in African
Americans (OR 1.7, P = 0.003). A previ-
sous family-based study failed to detect
linkage to chromosome 22.40 demon-
strating the analytic power of MALD.

Additional information on the mag-
nitude of the MYH9 gene effect is pro-
vided by Kao et al.10 working with Afri-
can American DNA samples from the
Family Investigation in Nephropathy
and Diabetes (FIND) and Choices for
Healthy Outcomes In Caring for ESRD (CHOICE) studies, also using MALD. Initial admixture analyses of 1372 ESRD patients and 806 control subjects suggested evidence for linkage on chromosome 22. Admixture scans were then performed separately for the 669 patients with nondiabetic ESRD and the 703 with diabetic ESRD. Genome-wide significance was not detected in those with diabetic ESRD, in contrast to a highly significant log of the odds score of 5.70 in a nondiabetic ESRD cohort. The highest single point log of the odds score was 8.56 on chromosome 22 in nondiabetic ESRD cases, the associated region containing the MYH9 gene. Subsequent analysis of 14 MYH9 SNP in all patients without diabetes and with ESRD confirmed the association, with Bonferroni-corrected P values as low as 10\(^{-14}\) and an OR of 1.90. Estimating the effect of replacing African ancestry at the disease locus with European-derived ancestry would remove approximately 70% of cases of nondiabetic ESRD in the African American population. Significant association was detectable separately among cases with FSGS, hypertensive nephrosclerosis, and all nondiabetic ESRD.

The studies by Kopp et al. and Kao et al. reveal the powerful contribution of a single gene to multiple related renal syndromes with a substantial effect size for what was previously thought to be a complex disease. The markedly lower frequency of the MYH9 risk haplotype in European Americans, compared with African Americans, provides a potential reason for the observed ethnic differences in prevalence of FSGS, hypertensive nephrosclerosis, and HIVAN. These results support the concept that MYH9 is associated with clustering of disparate forms of ESRD in African American families, an unusual observation in European Americans.\(^1\)

DISPOSING OF THE TERMINOLOGY “HYPERTENSION-ASSOCIATED KIDNEY DISEASE”

Does mere genetic association of the gene encoding the nonmuscle myosin II A heavy chain with hypertension-associated ESRD exclude a primary role for high BP in disease causation? No, because hypertensive nephrosclerosis is clearly a heterogeneous disorder and hypertension may be one trigger for glomerulosclerosis in genetically susceptible individuals. Hypertensive nephrosclerosis is often misdiagnosed and likely includes cases of both FSGS and non-FSGS glomerular diseases and unrecognized malignant hypertension, renal artery stenosis, or cholesterol emboli syndrome. In addition, not all individuals affected with hypertensive nephrosclerosis will have the associated MYH9 haplotype; however, the majority of hypertensive African American patients with CKD and low-level proteinuria have segmental or global glomerulosclerosis on renal biopsy. Primary FSGS and HIVAN both are strongly associated with the MYH9 gene. Interestingly, MYH9 mutations are linked to a number of giant platelet disorders and incompletely penetrant glomerular diseases.\(^41,42\)

Myosin-IIA is a mechanoenzyme that uses the energy of ATP hydrolysis to move actin filaments and has been localized to the podocyte. Neighboring podocytes are interconnected by specialized cell–cell contacts and the slit diaphragm, and proteins that compose this structure actively regulate actin dynamics and maintain normal podocyte structure.\(^43\) Mutations affecting several podocyte proteins lead to rearrangement of the actin cytoskeleton, disruption of the filtration barrier, and subsequent renal disease. It seems likely, although not yet proved, that mutations in the gene encoding nonmuscle myosin cause podocyte injury and FSGS in the absence of hypertension by disrupting actin dynamics. The effect of immunosuppressive or steroid therapies on limiting progression of renal disease in genetically susceptible individuals remains unknown. A concerning observation is that many patients in both of the MYH9 association studies had ESRD,\(^9,10\) suggesting current therapies were inadequate. The earlier AASK study demonstrated that angiotensin-converting enzyme inhibitors slowed but did not prevent disease progression in patients with a clinical diagnosis of hypertensive nephrosclerosis, albeit without added benefit from aggressive BP lowering.\(^20\) Hopefully, studies of the mechanisms by which MYH9 gene variants cause kidney disease will result in new diagnostic tests to allow presymptomatic detection of high-risk individuals and suggest novel pathways involved in renal failure and will allow for new strategies to preserve renal function.

Important lessons from this success story include the value of a tissue diagnosis for characterizing poorly described syndromes such as hypertensive nephrosclerosis and the importance of focusing multidisciplinary research teams with expertise in clinical nephrology, molecular and statistical genetics, and cell biology on complex clinical problems. It seems time to bury the outdated term “hypertension-associated kidney disease.” Perhaps “MYH9-associated nephropathy” or “CHGA-associated nephropathy” will better serve patients in this new era of personalized medicine. Hypertensive nephrosclerosis . . . may you rest in peace.

ACKNOWLEDGMENTS

This work is support by grants DK070941, DK053591, DK57292, DK59997, and DK064719 from the National Institute of Diabetes and Digestive and Kidney Diseases; Kidney Foundation of Ohio; and the Diabetes Association of Greater Cleveland.

DISCLOSURES

None.

REFERENCES


32. Koolbeeck AD, Rader KD, de B, J, Reolta CA, Fried LF, Shilpak MG, Palms W, Stenhman-Creen C, Siscovick DS: Differences in kidney function and incident hypertension:


www.jasn.org