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Rethinking hypertensive kidney disease: arterionephrosclerosis as a genetic, metabolic, and inflammatory disorder

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Abstract

Purpose of review—Hypertension is the attributed cause of approximately 30% of end-stage kidney disease cases in the United States, but there has been controversy as to whether benign hypertension is a cause of chronic kidney disease.

Recent findings—The histology of chronic kidney disease attributed to nonmalignant hypertension is arterionephrosclerosis, with pathology in the terminal branches of the interlobular arteries, together with global glomerulosclerosis. The identification of coding region variants in *APOL1*, encoding apolipoprotein L1, has opened a new perspective on this debate. These variants are restricted to populations of recent African descent and are strongly associated with clinically diagnosed arterionephrosclerosis, particularly when there is moderate-grade or high-grade proteinuria or progression to more advanced levels of kidney dysfunction. Nevertheless, not all African Americans with hypertension who progress to end-stage kidney disease have two *APOL1* risk variants, and individuals of European and Asian descent also manifest arterionephrosclerosis. Further, we do not understand the mechanisms by which *APOL1* initiates pathology in the renal microcirculation.

Summary—*APOL1* nephropathy comprises a disease spectrum (perhaps with distinct endophenotypes), including focal segmental glomerulosclerosis, collapsing glomerulopathy, and arterionephrosclerosis. The terms hypertensive kidney disease and hypertensive nephrosclerosis have outlived their usefulness. It may be time to use the established, etiologically neutral term, arterionephrosclerosis, to consider whether this is a disease rather than a pathologic description, and to determine the causal role of various clinical correlates including aging, obesity, hyperlipidemia, smoking, chronic inflammation, and oxidative stress.

Keywords

apolipoprotein L1; arterionephrosclerosis; hypertensive kidney disease

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INTRODUCTION

The US Renal Data System tabulates the cause of end-stage kidney disease (ESKD), generally defined as the need for chronic dialysis or kidney transplant, based on data submitted by the clinician who completes the Medical Evidence Form (HCFA-2728). For the year 2012, 111 728 patients developed ESKD and of these cases 32 345 (29%) were attributed to hypertension [1]. Thus, hypertension-attributed ESKD is the second leading cause of ESKD in the United States, after diabetes mellitus (44%). Among 557 263 prevalent ESKD cases, the pattern of attributed causes is similar, with the underlying kidney disease given as diabetes in 38% and hypertension as 25%. The lower fractions of hypertension-attributed ESKD in the prevalent ESKD population, compared with the incidence population, are largely because of increased mortality in patients with kidney disease attributed to diabetes and hypertension compared with other etiologies, rather than temporal trends. Furthermore, NHANES data from 1996–2006, involving 12 240 adults drawn from the general US population, show an interaction between hypertension and albuminuria in the prevalence of chronic kidney disease (CKD), defined as estimated glomerular filtration rate less than 60 ml/min/1.73 m^2. Among subjects with urine albumin/creatinine ratio more than 30 mg/g, the prevalence of CKD increased with blood pressure category, as follows (with 95% confidence intervals): normotension, 1.4% (1.3–1.6%); prehypertension, 3.4% (3.2–3.7%); undiagnosed hypertension, 11.0% (10.3–11.7%); and diagnosed hypertension, 11.7% (11.1–12.4%); $P < 0.0001$ [2]. Thus, there is no doubt that hypertension is associated with CKD – but does hypertension cause CKD or follow CKD, or some of both? As has long been recognized, individuals of African descent have a strong predisposition to hypertension-attributed CKD and ESKD, as shown in Table 1. This incidence is most striking in individuals reaching ESKD between the ages of 30 and 59, a point that will be further developed later.

THESIS: HYPERTENSION CAUSES CHRONIC KIDNEY DISEASE

The view that untreated or inadequately treated, but nonmalignant, hypertension causes the renal pathology that has been termed hypertensive nephrosclerosis has been advocated by many authors, including Luke [3], Ruilope and Bakris [4], and Jamerson and Townsend [5]. These last-mentioned authors quote the seminal work by Perara, reporting in 1955 from Columbia University on 500 individuals (one-third African Americans) with untreated hypertension followed for an average of 20 years, until death, which occurred at an average age of 52 [6]. Radiographic evidence of cardiac hypertrophy was present in 67%, myocardial infarction in 8%, and stroke in 12%. Eighteen percent of individuals had elevation of nitrogenous substances including elevation of these substances occurring as a terminal event, and 10% died with uremia. Although we do not know the threshold for determining elevation of urea, it is striking that the rate of renal disease was relatively low, and that at least some of this renal dysfunction might be attributed to congestive heart failure (present in 50%) or embolic events of the renal arteries. One can argue that if untreated chronic hypertension causes kidney disease, then it might be expected to do so more often. This report, like so many others, is not able to exclude the possibility that some or many of these patients with hypertension and CKD in fact had underlying renal disease that caused the hypertension. Jamerson and Townsend note the mechanisms by which hypertension is

linked to CKD remain controversial, suggesting that primary kidney disease due to *APOL1* variants might contribute or alternatively that systemic blood pressure might be transmitted to the glomerulus via a failure of autoregulation at the level of the glomerular vasculature. This is a nuanced view of the relationship between hypertension and CKD.

ANTITHESIS: MOST CHRONIC KIDNEY DISEASE AT PRESENT ATTRIBUTED TO HYPERTENSION LIKELY HAS OTHER CAUSES

There is convincing evidence that malignant hypertension is associated with kidney injury that frequently evolves into progressive CKD [7]. On the other hand, numerous authors have previously suggested that nonmalignant hypertension may not be the cause of much of what is labeled hypertensive nephrosclerosis (and pathologically described as arterionephrosclerosis), or more provocatively have proposed that nonmalignant hypertension does not ever cause CKD. Proponents of the various versions of this skeptical position have included Weisstuch and Dworkin [8], Luft [9], Meyrier and Simon [10], Hsu [11], Skorecki and Wasser [12], and in particular Freedman and colleagues [13–15,16▪▪].

Hsu, writing in 2002 for this journal, laid out several lines of evidence that nonmalignant hypertension does not cause CKD, or at least is not a common cause of CKD [11]. First, if hypertension causes CKD, then more effective treatment of hypertension would be expected to reduce the appearance of CKD. A meta-analysis by Hsu of 10 randomized controlled hypertension treatment trials published between 1966 and 1997 and involving 25 000 patients and 114 000 treatment-years, which reflects a sufficiently long duration to see an effect of blood pressure control on renal outcomes, demonstrated that lowering blood pressure has no effect on the development of renal dysfunction [17]. More recently, the data from the African American Study of Kidney Disease and Hypertension (AASK) showed that even with excellent blood pressure control and the use of a renin–angiotensin system inhibitor, progression of underlying CKD is relentless [18]. Second, the diagnosis of hypertension-attributed CKD is often erroneous [19] and even when great care has been taken in the clinical definition, as was the case in the AASK study, it is quite possible that many cases have underlying primary kidney disease due to genetic variants, as will be discussed below. Third, the apparent link between hypertension and CKD may be confounded by the effect of hypertension to accelerate underlying CKD of any origin, including primary glomerular disease and renal artery stenosis.

HYPERTENSION AND NEPHROSCLEROSIS

Churg and Sobin [20] defined arterionephrosclerosis, or nephrosclerosis, as including arterial intimal thickening, medial hypertrophy, and duplication of the internal elastic lamina, together with glomerulosclerosis and tubular atrophy. Arteriosclerosis particularly affects the terminal branches of the interlobular renal arteries (particularly those with a diameter <150 μm). Arteriolar hyalinosis may also be present, but this appears to correlate more closely with age than with hypertension (two variables that correlate with each other, at least in industrialized societies) and may be associated with loss of vasoregulatory responses in the glomerular arteriole [21]. Clearly people of all ancestries (African, European, and Asian) develop nephrosclerosis in the setting of hypertension, as shown for

example in a German series of 1177 unselected cases obtained from individuals with hypertension [22]; the issue is whether and how frequently hypertension is indeed the primary cause. Kasiske [23] studied nephrosclerosis in 57 autopsies obtained from individuals with mild atherosclerosis and 57 autopsies obtained from individuals with moderate–severe atherosclerosis. In a multivariable model, he found that age and intra-renal vascular disease were most closely correlated with glomerulosclerosis, and concluded that the nephrosclerosis of aging is more closely related to atherosclerosis than to hypertension.

In nephrosclerosis, the glomeruli manifest three morphologic patterns. First is the obsolescent glomerulus, which may be a partially or wholly collapsed glomerular tuft, with accumulation of extracellular material in Bowman space. Second is solidified global glomerulosclerosis, in which the glomerular tuft remains expanded but is entirely replaced by collagen and possibly other matrix material. In the setting of arteriosclerosis, this form is more common among African Americans compared with others, for reasons that are unknown [24]. Third is segmental glomerulosclerosis, which could represent part of the spectrum of focal segmental glomerulosclerosis (FSGS; including primary, genetic, and adaptive forms) or could represent the consequences of glomerular hyperfiltration occurring in remnant nephrons in the setting of another disease process.

In the AASK study, the study population was of African descent and the entry criteria were carefully defined, with an iothalamate glomerular filtration rate of 20–65 ml/min/1.73 m^2 and urine protein/creatinine ratio less than 2.5 g/g; this yielded a study group with a mean urine protein/creatinine ratio of 0.2 g/g. With these criteria, the AASK pilot biopsy study of 39 patients showed 37 patients with arterionephrosclerosis and/or arteriolonephrosclerosis (five subjects had at least one segmentally scarred glomerulus, which arguably would support a diagnosis of FSGS or alternatively could represent hyperfiltration injury in remnant nephrons) and 2 patients with other glomerular diseases (diabetic nephropathy and mesangiopathic glomerulonephritis) [25]. This demonstrates that when African-American subjects are carefully selected for features of hypertension-attributed CKD, most do indeed have arterionephrosclerosis on kidney biopsy and lack other specific glomerular diseases, with the possible exception of FSGS.

HYPERTENSIVE INJURY VIA VASCULAR DYSREGULATION

Animal models, particularly the remarkable work of Griffin and Bidani [26] over a period of many years, have convincingly demonstrated that in rats, the transmission of elevated arterial pressures to the glomerular microcirculation, due to a failure of autoregulation in the renal myogenic response, is associated with glomerular injury and glomerulosclerosis. Further, these investigators have demonstrated that the threshold for autoregulatory vasoconstrictive responses is increased in certain rat disease models, including diabetes and renal mass reduction, so that even modestly elevated systemic blood pressure levels may be associated with glomerular injury. Vavrinec *et al*. [27▪▪] have shown that in 5/6 nephrectomized rats, proteinuria correlates inversely with in-vitro measured myogenic constriction of small renal arteries in response to exogenous angiotensin II, that is, more vasoconstriction correlates with less proteinuria.

Several lines of evidence from human studies support the concept that hypertension can be associated with vasoregulatory dysfunction at the level of the glomerular microcirculation, although the case remains open for debate. In support of the relationship between blood pressure and glomerular injury in humans, Weir *et al*. [28] showed that systolic blood pressure is an important explanatory factor for proteinuria in the Chronic Renal Insufficiency Cohort study, with an $r = 0.40$. Interestingly, in a study of 29 African Americans and 33 French Canadian Whites, African Americans had increased renal plasma flow and glomerular filtration rate, and had a greater increase in response to norepinephrine infusion [29]. In kidney biopsies from 22 patients with advanced essential hypertension, Hill *et al*. [30] further found increased arteriolar diameter and wall area in hypertensive kidneys, and a correlation between arteriolar diameter and glomerular size, which would support the vascular flow dysregulation hypothesis. In a painstaking study of eight aging kidneys, Hill *et al*. [21] found a strong correlation, at the level of individual glomeruli, between glomerulomegaly and arteriolar hyalinosis, and concluded that the latter represented a failure of glomerular autoregulation; if this is correct, then increased flow and possibly increased pressures could support insudation of plasma proteins as a mechanism for hyalinosis.

No worker in the field of nephrosclerosis pathology has worked more diligently over the years than Richard Tracy; for selected references, see [31–35]. In brief, he argues what he describes as a contrarian hypothesis that renal arteriosclerosis (intimal fibroplasia of interlobular arteries) increases with age in populations around the world, that blood pressure also rises with age, but that the arteriosclerosis precedes the hypertension. Thus, the arrow of causation connects arteriosclerosis to hypertension, and not the reverse. Arteriosclerosis initially affects certain branches of the interlobular arteries (resistance vessels, with diameters <0.3 mm); this vascular fibroplasia reduces glomerular blood flow and activates the renin–angiotensin system locally, thereby increasing sodium reabsorption in nearby nephrons and increasing systemic blood pressure. Although arteriosclerosis contributes to nephrosclerosis, it may not be the only factor.

APOL1 AND HYPERTENSION-ATTRIBUTED KIDNEY DISEASE

Genetic variants in *APOL1* have been found to be strongly associated with kidney disease, including ESKD [36,37], FSGS [38], HIV-associated nephropathy [38], and hypertension-attributed CKD [16▪▪,36], as summarized in Table 2. Two *APOL1* variants are pathogenic, termed G1 and G2; the renal disease risk is almost entirely recessive: specifically, either homozygosity for either variant or dual heterozygosity confers risk. Recent work has extended these observations. In the AASK study, study participants were more likely (23%) to have two *APOL1* risk variants compared with controls (12%), whereas the percentages with one risk variant allele were similar between cases (42%) and control (45%). The presence of two *APOL1* risk alleles was also associated with more proteinuria at baseline urine protein/creatinine ratio more than 0.6 g/g, odds ratio 6.3, with 48% having two *APOL1* risk alleles, suggesting more severe kidney disease, and was associated with a greater chance of progressing to serum creatinine more than 3 mg/dl or ESKD during follow-up (odds ratio 4.6), with 40% having two *APOL1* risk alleles (Table 2).

Several points can be made about this genetic risk. First, about one-quarter of African Americans with hypertension-associated CKD, as defined within AASK, have two *APOL1* risk alleles. On the other hand, three-quarters of such patients do not have the risk genotype – and as in other kidney diseases (FSGS, HIV-associated nephropathy), one *APOL1* risk allele does appear not to confer increased risk. Thus, *APOL1* variants may not account for all the increased African-American predispositions to clinically diagnosed hypertension-attributed disease. Second, the presence of the *APOL1* risk alleles marks hypertensive individuals who have more proteinuria at presentation and who progress faster, despite the use of effective therapies and optimal levels of blood pressure control, at least as these are presently conceived. Further, even when more severe phenotypes are considered, that is, heavier proteinuria or progression to more advanced levels of renal insufficiency, the majority of subjects lack two *APOL1* risk alleles. With regard to progression of kidney disease in the AASK study, there was no interaction between *APOL1* genotype and response to any particular antihypertensive therapy or blood pressure goal during the controlled trial phase, which suggests that there is no favored therapeutic approach for these high-risk patients compared with other patients. Third, although studies are in progress, we still do not know whether the histology differs between those with two *APOL1* risk alleles and others – specifically whether they have more segmental glomerulosclerosis and/or more solidified glomerulosclerosis (rather than obsolescent glomeruli) compared with other subjects. Fourth, it was noted above that among African Americans, ESKD attributed to hypertension has a peak incidence at ages 30–59 years and this disease process likely began some 10–25 years before. This aligns fairly well with the incidence peak for FSGS (ages 15–39) associated with genetic variation in *APOL1* [38]. Thus, it may be that age-dependent onset of *APOL1* nephropathy, with injury initiating in the second, third, and fourth decades of life, leads to what are presently thought of as two diseases (FSGS and hypertension-attributed nephrosclerosis), but that may arise due to similar biologic mechanisms.

How does the new information about *APOL1* change our views of hypertension-attributed CKD? It suggests a model in which genetically influenced ‘primary’ kidney disease in individuals with two *APOL1* risk alleles and manifesting as arterionephrosclerosis may lead to hypertension, rather than the reverse. Not all *APOL1* two-risk allele subjects develop CKD, and therefore other genetic or environmental factors must contribute. Although there could be a dominant effect of a single *APOL1* risk allele, it has not been shown in the AASK study or in other studies of glomerular disease to date.

What causes arterionephrosclerosis in African Americans who lack two *APOL1* risk alleles and in those of European and Asian descent? Certainly hypertension may play a role, but we may need to broaden our thinking to include other possible causes of microvascular pathology, as listed in Table 3. These include age [39], diabetes [40], obesity [41], oxidative stress [42], and smoking [43]. The syndrome of nodular glomerulosclerosis with marked arteriosclerosis has been associated with cigarette smoking [44,45]. A number of genetic mutations, including *FBN1* (Marfan syndrome), *ABCC6* (pseudoxanthoma elasticum, PXE), *MGP* (Keutel syndrome), and *GGC6* (PXE-like), have been associated with arterial remodeling and vascular disease, although not associated with arterionephrosclerosis [46]; it now appears that *APOL1* variants are a primary cause of arterionephrosclerosis. Notably,

diabetic nephropathy and nodular glomerulosclerosis are associated with thickened glomerular basement membranes, which is not a feature of either *APOL1* nephropathy or most cases of arterionephrosclerosis. We have little understanding about what is distinctive about diabetic nephropathy and nodular glomerulosclerosis that would lead to basement membrane thickening, but presumably this arises by mechanisms that are different from mechanisms driving the arterial pathology.

HOW DO *APOL1* VARIANTS CAUSE KIDNEY DISEASE?

Despite on-going efforts by several research groups, the mechanisms by which *APOL1* disease-associated variants disrupt cellular metabolism remain unknown. ApoL1 protein is expressed in two locations in normal kidney tissue, within the glomerular podocyte and the arteriolar endothelial cells, and at a third location in FSGS and HIV-associated nephropathy, within glomerular arterioles and interlobular arteries [47]. ApoL1 is also present in the circulation, possibly released from liver; this could contribute to kidney disease, although the decreased allograft survival in allografts with two *APOL1* risk alleles [48] and the lack of effect of risk alleles in transplant recipients [49▪] argue that in the transplant setting, local ApoL1 production within the kidney is pathogenic. It is tempting to speculate that ApoL1 expression in the arterial wall could have a biologic role, and that the ApoL1 pathogenic variants G1 and G2 might alter cellular physiology so as to promote arteriosclerosis. It may be relevant that ApoL1 is a lipid-binding protein, so that variants may alter lipid physiology in the arterial cells and might drive arteriosclerosis.

CONCLUSION

The clinical diagnosis of hypertension-attributed CKD and the pathologic diagnosis of arterionephrosclerosis are undergoing reevaluation. The AASK study has demonstrated that careful selection among African Americans can yield a population that has predominantly arterionephrosclerosis but that present therapies have limited efficacy to prevent progression to ESKD, and that individuals with *APOL1* risk variants comprise about one-quarter of the study population and tend to progress to more advanced levels of CKD. *APOL1* variants are not the whole story in African Americans with arterionephrosclerosis and do not contribute to this disease in those who are not of West African descent. It seems plausible that other genes, environmental factors, aging, obesity, chronic inflammation, and oxidative stress, and perhaps essential hypertension, all may contribute to arterionephrosclerosis in different individuals.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 358–359).

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KEY POINTS

- The mainstream view has been that benign hypertension causes arterionephrosclerosis, the histology that underlies hypertension-attributed kidney disease.
- A contrarian view is that the arterial changes track more closely with systemic atherosclerosis than with hypertension, and that arterionephrosclerosis may be a vascular disease arising as a consequence of aging, obesity, inflammation, oxidative stress, chronic inflammation, and related factors.
- It is unclear whether *APOL1* nephropathy constitutes a continuum or distinct endophenotypes, of which arterionephrosclerosis is one.
- *APOL1* variants explain a major part of the predisposition of individuals of West African descent to develop arterionephrosclerosis. *APOL1*-associated arterionephrosclerosis tends to progress despite achievement of optimal blood pressure and the use of what are believed to be optimal renoprotective therapies.

Table 1

Rate of hypertension-attributed ESKD

Age at ESKD (y)	White subjects	Hispanic subjects	African-American subjects	African-American/ White incidence ratio
15–19	1.8	–	4.5	2.5
20–29	7.4	15	45	6.1
30–39	16	30	152	9.5
40–49	28	53	302	10.8
50–59	26	134	528	20.3
60–69	118	191	840	7.1
65–69	192	318	1107	5.8
70–74	326	446	1347	4.1

Annual rates of hypertension-attrributed ESKD per million population in the United States are shown for the year 2010, unadjusted. Note that the racial disparity, with African-American individuals at particular risk, peaks between ages 30 and 59. Source: URDS Annual Report 2012. ESKD, end-stage kidney disease.

Table 2

APOL1 renal phenotypes

Phenotype	*APOL1* 2 risk alleles, odds ratio	*APOL1* 2 risk alleles, prevalence
General population	NA	12–14%
HIV-associated nephropathy	29	72%
Focal segmental glomerulosclerosis	17	72%
AASK study phenotypes		
All subjects (clinically diagnosed arterionephrosclerosis)	2.6	23%
Baseline urine protein/creatinine ratio >0.6 g/g	6.3	48%
Serum creatinine >3 mg/dl during follow-up	4.6	40%
Hypertension-associated end-stage kidney disease	7.3	ND

APOL1 nephropathy presents in ways that are morphologically distinct and might represent endophenotypes, although more work in morphology and mechanism is needed to clarify how distinct these endophenotypes really are. Shown are the odds ratios for individuals with two *APOL1* renal risk alleles and the proportion of study subjects with two *APOL1* risk alleles for various renal syndromes compared with African Americans without kidney disease, some of whom had hypertension. Original reports are as follows: general population [36], HIV-associated nephropathy [38], focal segmental glomerulosclerosis [38], AASK study phenotypes [16▪▪], and hypertension-associated end-stage kidney disease [36].

Table 3

What beyond hypertension might contribute to arteriosclerosis?

Correlates and causes shared by atherosclerosis and arteriosclerosis
Aging
Diabetes, obesity, metabolic syndrome, hyperlipidemia
Oxidative stress, chronic inflammation, smoking
Hemodynamic shear stress
Increased calcium phosphate product
Angiotensin II, aldosterone

Atherosclerosis affects large-sized and medium-sized arteries and is characterized by focal injury to the arterial intima, with local lipid accumulation and macrophage infiltration. Arteriosclerosis affects the resistance arteries, generally <0.3 mm, and is characterized by diffuse remodeling of the arterial media, with intimal hyperplasia and particularly with medial hypertrophy and smooth muscle cell proliferation. The cause and correlates of atherosclerosis and arteriosclerosis show considerable overlap.