Nephrosclerosis: A Term in Quest of a Disease

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Key Words

Nephrosclerosis · Hypertension · Aging · Black race · Genetics · *APOL1* · FSGS · Renal autoregulation · Renal hypoxia · Antihypertensive drugs

Abstract

For a century, nephrosclerosis was ascribed to nonmalignant hypertension and aging. However, it was intuitively perceived that hypertension may follow rather than explain this nephrovasculopathy. Hypertensive nephrosclerosis was long considered a major cause of end-stage renal failure (ESRD). This is especially true in blacks of African descent but not in other ethnic populations. The term ‘nephrosclerosis’ is still an easy way out to classify a patient with renal insufficiency. This leads to neglect the possibility of an overlooked nephropathy complicated by hypertension and to believe that drastic blood pressure control may retard the progression to ESRD. Several clinical and experimental lines of evidence lead to the understanding that nephrosclerosis, especially in blacks, is a genetic renovasculopathy that precedes the rise in blood pressure. The identification of coding region variants in *APOL1* encoding apolipoprotein L-1 in black but also white and Asians opens new lines of research on the genetics of nephroangiosclerosis and of FSGS. Metabolic derangements, such as obesity, oxidative stress, dyslipidemia and atherosclerosis may be considered confounding factors with regard to nephrosclerosis. Histomorphometric studies led to sorting out the lesions due to aging from those stemming from hypertension. They shed new light not only on

glomerular lesions that comprise ischemic obsolescence but also on glomerulomegaly and focal-segmental sclerosis, the latter due to a loss of renal autoregulation. It appears that the control of hypertension is not credited with the expected benefit for slowing the decline of renal function. ‘Nephrosclerosis’ can be considered an umbrella term of poor significance that should be replaced by its pathologic description, that is, *arterionephrosclerosis* and incite to elucidate the various genetic and metabolic factors that lead to a lesion in quest of a specific disease.

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Introduction

The term ‘nephrosclerosis’ (‘kidney hardening’) was coined in 1918 by the German clinicians and pathologists Franz Volhard and Theodor Fahr [1, 2]. The etymology refers to the callous consistence of kidneys cut after removal at autopsy. Hardening suggests tissue fibrosis and can apply to most chronic kidney diseases but Volhard distinguished three variants of ‘nephrosclerosis’, the third one linked to hypertension. The notion of arterial hypertension was known by physiologists but a practical way of measuring it dated back from less than a decade [3]. Volhard observed that the third variant in his classification was associated with vascular lesions and attributed the renal sclerosis to a consequence of vascular lesions rather than to hypertension causing renal vessel changes. A far-reaching concept of Volhard was his idea

that hypertension results from a pressor substance released from ischemic kidneys, contributing to a further rise in blood pressure with subsequent renovascular injury and aggravation of hypertension. Most interestingly Goldblatt stated in 1960 [4] that *'the important question of which comes first, the high blood pressure or the renal lesion, remains unsolved.'*

Over the half-century that followed, the relations between hypertension and kidney damage were more academic than clinically relevant. The first kidney biopsies entered into practice at the end of the 1950s and there were no efficient antihypertensive drugs before the first beta-blocker was marketed in 1964. At that time and for decades a patient with long-standing, poorly controlled hypertension and declining renal function was diagnosed as suffering from 'hypertensive nephrosclerosis' and of the renal lesions that accompany aging. The two variables correlate with each other, both progressing simultaneously and resulting in kidney fibrosis, glomerular ischemic obsolescence along with glomerular hypertrophy and focal-segmental sclerosis (FSGS).

Nephrosclerosis: An Umbrella Term in Quest of a Definition

Many renal clinicians still do not distinguish hypertensive nephrosclerosis from kidney aging and other conditions with kidney sclerosis, often associated with hypertension, such as obesity and oxidative stress, smoking, atherosclerosis and dyslipidemia. 'Nephrosclerosis' is the easy way out for classifying a case of chronic renal insufficiency in a hypertensive and/or aging patient in the absence of kidney biopsy.

It is interesting to follow the description of 'nephrosclerosis' by pathologists over fifty years.

In 1963, Solomon Papper introduced his chapter on nephrosclerosis in [5] with: *'— in its traditional application, nephrosclerosis refers to the pathologic processes associated with the following disorders involving the renal vasculature: arteriosclerosis, arteriolar (benign) nephrosclerosis, and the accelerated (malignant) phase of hypertensive disease.'* The reader does not find any mention of glomerular changes except six words referring to *'Complete hyalinization in some ischemic areas.'* Ischemia is mentioned but the black racial predominance of nephrosclerosis is totally overlooked.

Following twenty years of personal research, Heptinstall in his classic third edition of 'Pathology of the Kidney' [6] offered in 1983 a comprehensive picture of arte-

rial and arteriolar lesions, including glomerular afferent arteriole hyalinosis, tubulointerstitial inflammatory fibrosis and glomerular obsolescence interpreted as an early ischemic lesion. However, the notion of glomerular hypertrophy and FSGS was still missing.

Secondary FSGS that complicates hypertensive nephrosclerosis is a recent concept. While FSGS being a subset of idiopathic nephrotic syndrome has been a matter of keen interest for four decades, the notion of FSGS as a feature of (arterio)nephrosclerosis appeared only timidly in one report of the African-American Study of Kidney Disease [7] and is now accepted as an important relevant lesion with a genetic background [8].

Confounding Issues: Obesity, Atherosclerosis, Dyslipidemia, Glucose Intolerance, Salt, Smoking and What Not?

Discussing all the conditions associated with hypertension, renal function impairment and proteinuria – conditions too often labeled as 'Nephrosclerosis' – would by large exceed the space allotted for this minireview. We shall skip discussing here a wealth of literature on glucose intolerance, salt intake and smoking. Yet, two examples are worth developing: obesity linked with oxidative stress and interstitial fibrosis and atherosclerosis linked with dyslipidemia.

Obesity is a confounding variable [9]. An excess of adipose tissue increases oxidative stress and inflammation directly or through an increase of circulating angiotensin II (Ang II) [10]. These factors add their untoward effects to the progression of 'hypertensive nephrosclerosis' or create kidney lesions wrongly labeled as such.

Hypertensive patients are commonly atherosclerotic. Kasiske [11] investigated the relationship between atherosclerotic vascular disease and age-associated changes in the normal human kidney and renal histology from 57 individuals with mild systemic atherosclerosis (Group I), compared to 57 sex- and age-matched individuals with moderate-to-severe atherosclerosis (Group II). Patients in Group II had twice as many sclerotic glomeruli as those in Group I. The mean glomerular area of non-sclerotic glomeruli was 20% greater in Group II than in Group I suggesting that there were compensatory increases in glomerular size in Group II. Interstitial fibrosis was similar in both groups. Both age and intrarenal vascular disease exhibited highly significant, independent associations with glomerulosclerosis.

Interstitial Fibrosis of Nephrosclerosis Results from Hypoxia, and Glomerular Hypertrophy and FSGS from a Loss of Renal Autoregulation

The main feature of nephrosclerosis is interstitial inflammatory fibrosis. It has long been demonstrated that fibrosis entraps the peritubular capillaries and largely contributes to the decline in renal function [12]. The fact that nephrosclerosis is complicated by downstream ischemia and interstitial fibrosis ascribed to a curtailment of blood supply to the kidney had been proved in animal models of renal artery stenosis [6]. However, the renal blood flow – one fifth of the cardiac output – is out of proportion with the need of preserving the viability of two organs whose weight does not exceed ≈ 350 g.

It is more appropriate to ascribe renal fibrosis to hypoxia, a theory defended by Fine and Norman [13–16] and amply developed by subsequent studies substantiated by hypoxia-inducible factors [17, 18].

A loss of autoregulation of renal blood flow resulting from an impairment of the afferent arteriole myogenic response [19–21] is a second mechanism by which an increase in glomerular capillary hydrostatic pressure leads to glomerulomegaly and FSGS. This was demonstrated in several models of genetically hypertensive rats [22–27] and confirmed by renal arteriolar casts [28] and micro-puncture measurements [29]. These experiments confirm that in these rat models, the glomerular afferent arterioles are dilated and that the glomerular capillary hydrostatic pressure is increased.

Taken together hypoxia and loss of autoregulation explain well the two components of nephrosclerosis. One is inflammatory interstitial fibrosis and the other consists of two populations of glomeruli: some ischemic and obsolescent, while the others hypertrophied and undergoing focal-segmental sclerosis.

Antihypertensive Therapy May Aggravate the Progression to Glomerular Hypertrophy, FSGS and Proteinuria

No one would deny that treating hypertension is beneficial to kidney function, even if the risk of end-stage renal disease is not documented in hypertensive nephrosclerosis. However, some antihypertensive drugs may have an untoward effect on the glomerular lesions. As developed above, a loss of renal autoregulation contributes to increasing the hydrostatic pressure in glomeruli and thereby leads to glomerulomegaly and FSGS. Some

drugs such as clonidine [30], di-hydropyridines [31, 32] and hydralazine [33] hinder renal autoregulation. Ang II antagonists may complicate nephrosclerosis with acute kidney insufficiency in the absence of atherosclerotic renal disease [34] and it is conceivable that overcorrection of hypertension with this class of drugs that act on the glomerular efferent arteriole might in the long-term trade off glomerulomegaly and FSGS for ischemic glomerular obsolescence [35].

Hypertension and Aging Both Lead to Nephrosclerosis and FSGS But Kidney Histology Reveals That They Are Not the Same Entity

A meticulous, painstaking histomorphometric study by Hill and co-authors shed a new light on the similarities and the differences in the so-called nephrosclerosis of hypertensive patients versus normotensive aging subjects. Hill's group sorted out afferent arterioles (AA) into three types based on the presence or absence of hyaline deposits and whether these did or did not obstruct the lumen.

In the aging kidneys [36], arterioles with nonobstructive hyaline deposits had lumens more than twice larger than those without deposits. The glomeruli they served had a greater total capillary area. Arterioles with obstructive deposits had smaller lumens with a higher proportion of periglomerular extra-cellular matrix (ECM). Hypertrophic glomeruli exhibited a greater total capillary area but showed no evident lesions. FSGS-type glomeruli were also large and showed an increase in ECM. Ischemic glomeruli were small. There was a strong association between large/FSGS-type glomeruli and AAs with nonobstructive hyaline deposits. These findings demonstrated that hyaline deposits in dilated AAs are – to coin the term cleverly used by Hill – responsible for an 'arteriolomalacia' rather than an arteriolosclerosis. They suggest that the dilatation of AAs hinders autoregulation and explains glomerular hyperfiltration leading to glomerulomegaly and FSGS.

In kidneys from hypertensive patients [37] AAs showed an increase in lumen diameter due to shift from normal to hyaline arterioles. Glomeruli were much larger than in normotensive aging kidneys. This was due to an increase in the size of each type of glomeruli. There was a significant correlation between increased arteriolar lumen diameter and mean glomerular capillary area for hypertrophic/FSGS-type glomeruli. The morphologic correlates to loss of autoregulation, with AA dilatation and increase in glomerular capillary size, glomerular hyper-

Table 1. Main distinguishing features of primary focal-segmental glomerulosclerosis, hypertensive nephropathy and aging kidney

	Primary FSGS	Hypertensive nephropathy	Aging
Black/White ratio	≈66%/33%	Early nephrovascular lesions in young Blacks may precede the onset of hypertension	Lesions attributed to aging and not to aging and hypertension may be found in Blacks aged <40 years
Nephrotic range proteinuria	≈80%	No, except in Blacks with associated FSGS as part of nephrovasculopathy	No
Progression to ESRD	Risk of ESRD proportional to degree of 24 h proteinuria, histologic type and response to therapy	Rare in Whites in the absence of MH Frequent in Blacks	African Americans Annual rate per million population of hypertension attributed ESRD in the US Age 30–39: 9.5 Age 40–49: 10.8 Age 50–59: 20.3
Glomerular lesions	Podocytopathy Five variants according to the ‘Columbia classification’ From most severe (CG) to rather mild (TIP)	Three subsets of glomeruli: Normal Small, ischemic/fibrotic Hypertrophied with FSGS (mostly hilar variant)	(1) Two types of glomerular involution and sclerosis: Tuft retraction to hilum Afferent → Efferent arteriolar short circuit of blood flow to glomerular capillaries. Empty Bowman’s chamber. (2) A subset of dilated, hypertrophic/FSGS glomeruli
Glomerular afferent arteriole (AA)	Mostly arteriolosclerosis	Arteriolosclerosis and arteriolo-hyalinosis with AA dilatation	Afferent arteriole hyalinosis and dilatation with 90% of hypertrophic/FSGS glomeruli served by this type of AAs
Tubulointerstitial inflammation/fibrosis	Yes, out of proportion with the severity of glomerular lesions	Severe with interstitial inflammation and fibrosis. Microcystic tubules with casts (‘Pseudothyroid areas’)	Tubulointerstitial fibrosis and some inflammation. Less severe than in hypertensive nephropathy Mostly fibrous
Loss of renal autoregulation	Likely but not specifically documented	Yes	Yes
APOL1 G1–G2 risk factor	Yes, especially in African Americans	Yes, especially in African Americans	Yes in Blacks. Not specifically documented in Whites

FSGS = Focal-segmental glomerulosclerosis; ESRD = end-stage renal disease; MH = malignant hypertension; CG = collapsing glomerulopathy; TIP = tip-lesion.

trophy, and subsequent FSGS, were present on a focal basis in aging kidneys and extensively in hypertensive kidneys.

These studies show that nephrosclerotic kidneys comprise two populations of afferent arterioles and of the glomeruli they serve: dilated AAs with hyalinosis and hypertrophic/FSGS glomeruli as a result of loss of autoregulation, and arteriolosclerotic AAs with small obsolescent glomeruli as a consequence of ischemia [38] (table 1).

Hypertensive Nephrosclerosis: A Black Genetic Conundrum

The propensity of blacks of African ancestry to suffer from early and severe hypertension and renal damage has long been established and confirmed in the African-American Study of Kidney Disease (AASK) [7].

Tracy et al. [39–42] confirmed the predominance of renovasculopathies in blacks as compared with white

populations. This predominance was found on autopsies in three age groups of white and black males aged 25–54 years. The difference between whites and blacks was already present at 25–34 years of age. It is most interesting to see that in young members of this population the renal vascular lesions may precede the onset of hypertension. In further studies, the magnitude of early nephroangiosclerosis was also assessed in five different ethnic populations [47–49]. Blacks exceeded whites in the magnitude of incipient nephroangiosclerosis in all age groups.

Kopp et al. identified genetic variations of the *MYH9* gene that encodes a nonmuscular myosin, myosin heavy chain 9, and confers a risk of hypertensive nephropathy among blacks [43]. Although these initial studies implicated MYH9, more recent analyses localized the strongest association within the neighboring *APOL1* gene. Genovese et al. found two independent sequence variants (G1 and G2) in the *APOL1* gene encoding apolipoprotein L1 in African Americans with FSGS and hypertension-attributed end-stage kidney disease [44]. The *APOL1* gene that is very close to the *MYH9* gene seems to represent a hundred-fold greater risk factor than the latter. *APOL1* is a lysis factor for *Trypanosoma brucei brucei*, the parasite transmitted by the TseTse fly, the one that causes sleeping sickness. However, *T. brucei gambiense* resists to *APOL1* lysis and this could have induced a selection of a subset of African subjects genetically protected from *T. brucei brucei* sleeping illness but with a trade-off propensity to *APOL1* G1- and G2-induced podocyte injury.

So far, the role of *APOL1* mutations in the pathophysiology of hypertensive nephropathy in blacks has not been determined and the pathways to renal vascular lesions and FSGS in this population are unknown [8]. 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 [45]. ApoL1 protein is a lipid-binding protein present in the circulation and one can hypothesize that the G1 and G2 variants contribute to promoting arteriosclerosis. In any event, in the African-American population it appears that one allele (G1 or G2) does not confer a risk of progression to greater levels of proteinuria and more advanced chronic renal disease. In the recent AASK study on *APOL1* gene variants in African Americans [46] the 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 and controls. Moreover, these studies indicate that G1 and G2

confer an increased risk of primary FSGS in African Americans.

The genetic background of hypertensive nephrosclerosis in blacks might be still more complex, as another gene with an impact on oxidative stress has recently been identified by Chang et al. [47]. The authors examined whether genetic variants of the *GSTM1* gene, a member of a superfamily of glutathione S-transferases, influence the course of kidney disease progression in participants of the African-American Study of Kidney Disease (AASK) trial. *GSTM1* directly regulates intracellular levels of 4-hydroxynonenal (4-HNE) in vascular smooth muscle cells. Groups with and without the common *GSTM1* null allele, *GSTM1(0)*, differed significantly in the time to ESRD.

Hypertensive Nephrosclerosis: A Poor Explanation for End-Stage Renal Failure

Numerous authors demonstrated that nonmalignant hypertension follows a relatively slow course and that, when other causes of renal sclerosis have been excluded by thorough work-up comprising kidney histology, benign hypertension does not portend a significant risk of end-stage renal failure (ESRD) [48–52].

Moreover, it was shown that treating hypertension does not modify the renal prognosis of ‘hypertensive nephrosclerosis’ in white Europeans and in African-Americans. These studies excluded those demonstrating a benefit in chronic renal disease resulting from various nephropathies, such as diabetes mellitus, that do not deal with the same matter.

A meta-analysis by Hsu [53] of ten randomized controlled trials of antihypertensive drug therapy showed that patients randomized to antihypertensive therapy (or more-intensive therapy) did not show a significant reduction in their risk of developing renal dysfunction and not end-stage renal insufficiency. Hsu stressed the fact that failure to evaluate the possibility that preexisting renal disease could explain any observed association between elevated blood pressure and subsequent loss of renal function is an important limitation of published studies. It appears that treatment of hypertension in white Europeans aims more at reducing the risk of left ventricular hypertrophy and brain damage rather than preventing the progression to ESRD.

The same disappointing effect of antihypertensive therapy was also demonstrated in hypertensive blacks when the effects of two levels of blood pressure (BP) con-

trol were analyzed in a total of 1,074 African Americans with 'hypertensive renal disease' [54]. They were randomly assigned to one of two mean arterial pressure goals (102–107 mm or 92 mm Hg or less) and to initial treatment with either a beta-blocker an angiotensin-converting enzyme inhibitor or a di-hydropyridine calcium channel blocker. No additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower BP goal. Interestingly, in one recent study [55], for the same efficacy of BP control in black hypertensives of the AASK trial, the *APOL1* phenotype was associated with a more rapid decline in renal function than in subjects who did not carry the *APOL1* gene.

This leads to discussing the following 'second opinion' with regard to the benefits vs. untoward effects of antihypertensive drugs for the renal function of hypertensive patients. When *bona fide* physicians expect to protect the kidney from the assumed deleterious effects of high blood pressure upon renal arterioles and the glomeruli they serve, they indeed oppose the effects of hypertension on

the heart and on the brain but don't do much on the progression of arterionephrosclerosis and they may even aggravate the lesions and increase the degree of proteinuria [31, 34].

There is no better way to conclude than quoting Jeffrey Kopp [8] *verbatim*: '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'.

Conflict of Interest Statement

The author declares he has no conflict of interest with regard to this article.

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