Nephrosclerosis: update on a centenarian

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ABSTRACT

Nephrosclerosis is an umbrella term defining changes in all compartments of the kidney, changes caused by hypertension and by ageing. Among other lesions, arteriosclerosis and arteriolohyalinosis play a major role in inducing glomerular ischaemic shrinking and sclerosis along with glomerulomegaly and focal-segmental glomerulosclerosis (FSGS). These lesions are accompanied by tubulointerstitial inflammation and fibrosis that predict the decline of renal function. Nephrosclerosis is a major cause of renal insufficiency in blacks of African descent with a severe, early form of renovascularopathy and ischaemia that fosters the generation of hypoxia inducible-fibroising factors. Not all antihypertensive drugs equally...

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protect the kidney from nephrosclerosis. Angiotensin II antagonists exert a favourable effect on hyperfiltration. Conversely, dihydropyridine calcium-channel blockers and vasodilators do not withstand the derangement of renal autoregulation.

**Keywords:** ageing, nephrosclerosis, hypertension, renal autoregulation, renal hypoxia, black race, FSGS

### INTRODUCTION

Nearly a century ago, Fahr [1] coined the term 'nephrosclerosis' to qualify the 'renal hardening' that accompanies hypertension. Volhard [2], in a treatise on Bright's disease, introduced the section 'Die Sklerosen' with '...und die dritte monosymptomatische Form ... welche sich klinisch durch Hypertonie und Herzhyper trophy, anatomisch durch eine primäre Sklerose der Nierenge fäße auszeichnet' [...] the third, monosymptomatic form (of renal sclerosis) is characterized clinically by hypertension and cardiac hypertrophy, and anatomically by a primary sclerosis of the renal vessels. The wording 'primary sclerosis' is interesting as it points to renal vascular lesions being the cause rather than the consequence of hypertension. This initiated a long debate on whether the kidney is the culprit or the victim in hypertension and nephrosclerosis [3]. In fact both of these views are correct. That primary hypertension leads to renal vascular lesions, focal-segmental glomerulosclerosis (FSGS), glomerular obsolescence and interstitial fibrosis has long been established. This should not, however, obscure the fact that renal vascular lesions can be observed in animal models as well as in some humans in the absence of, or preceding the onset of hypertension [4–7]. Ageing kidneys also display lesions whose appearance is close to that of hypertensive nephrosclerosis without necessarily stemming from high blood pressure (BP).

### HYPERTENSIVE NEPHROSCLEROSIS AFFECTS ALL THE COMPARTMENTS OF THE KIDNEY TISSUE

Both nephrosclerotic kidneys have the same size, which would not be the case in atherosclerotic renal disease [6]. Reduction of the kidney is not constant [8]. The kidney outline may be smoothly scalloped, which reflects the presence of underlying ischaemic areas. Whereas inflammatory interstitial changes may evoke chronic pyelonephritis, the pathologist does not find inflammatory cells under the pelvic and calyceal system. The subcapsular surface is finely granular in most cases, reflecting the subcortical arteriolosclerosis.

#### Intrarenal arterial stiffening

The main branches of the renal artery may display atherosclerotic changes. Arcuate and interlobular arteries show intimal thickening by myofibroblasts and dense collagen tissue. Elastic laminae are frayed and reduplicated forming concentric layers of elastic. The media is initially thicker than normal, before undergoing atrophy. The lumen is usually narrowed (Figure 1). It comes as no surprise that the blood flow can be curtailed to some areas of the kidney tissue.

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**Arteriolar sclerosis and hyalinosis**

Arteriolosclerosis of the afferent arteriole (AA) is correlated with the degree of hypertension, male gender and ageing [7]. Arteriolar hyalinosis is not necessarily a feature of nephroangiosclerosis. Nevertheless, this lesion is more severe in primary hypertension. The hyalin seen on electron microscopy appears as confluent finely granular material of varying electron density [8]. Hyalinosis affects the afferent and the efferent glomerular arterioles although in the latter plasma protein infiltration is less pronounced than in the diabetic kidney. From a functional viewpoint whereas arteriolosclerosis implies rigidity and resistance to the blood flow, arteriolarhyalinosis does not hinder pressure-induced dilatation, a phenomenon coined by Hill [7] as ‘arteriolomalacia’ leading to loss of autoregulation in the glomerular circulation.

**Glomerular lesions.** It was long considered that glomeruli undergo progressive ischaemic changes, well described in [8], ending in shrinkage and obsolescence. It has since been established that the nephrosclerotic kidney displays three populations of glomeruli: normal ones, small ischaemic fibrous glomeruli and enlarged glomeruli with lesions of FSGS. The FSGS variant is common in ageing rats and in the elderly human. It is particularly pronounced in blacks of African origin. In hypertensive kidneys, 90% of large ‘FSGS-type glomeruli’ are served by an AA with hyaline deposits [7].
**Tubulointerstitial lesions.** Tubulointerstitial lesions are conspicuous (Figure 2). Tubules may be lost or atrophic. Others are dilated with a flattened epithelium and wide open lumens filled with eosinophilic casts (so-called 'thyroid areas'). The interstitium is fibrous and interspersed with inflammatory cells of the monocyte/macrophage lineage. Inflammation—that can be as severe as in chronic pyelonephritis—may safely be ascribed to ischaemia: the same appearance has long been observed in kidneys of rats rendered ischaemic by compression of renal artery [8] and in atherosclerotic renal disease.

These inflammatory cells evidently explain the build-up of fibrosis. As in other nephropathies these changes are associated with a rarefaction of peritubular capillaries, long identified as a self-perpetuating process to chronic renal insufficiency [9–12]. More specific to sodium-sensitive hypertension is the fact that immunocompetent cells that proliferate in the nephroangiosclerotic kidney are accompanied by oxidative stress and increased Ang II activity [13]. From this viewpoint, hypertension can be considered to be initiating an interstitial autoimmune reactivity triggered or aggravated by dietary sodium.

**RENAL VASCULAR LESIONS ARE COMMON IN NEPHROPATHIES INDEPENDENTLY OF HYPERTENSION**

For decades pathologists have observed that chronic kidney diseases are commonly associated with vascular lesions, usually ascribed to hypertension and/or ageing. A more careful analysis of kidney biopsies demonstrates that this opinion is not always valid for ageing and not true of hypertension.

In 1975 Kincaid-Smith [14] studying 344 kidney biopsies from patients with minimal-change disease (MCD), membranous nephropathy (MN) or FSGS stressed that ‘the lesions in arteries and arterioles in patients with glomerular disease may be quite out of proportion to those which might be anticipated in relation to the patients’ age and blood pressure’.

Numerous articles illustrate the fact that vascular lesions play a major role in the progression of glomerulopathies to renal insufficiency [15–17].

We confirmed such findings in the analysis of 1450 kidney biopsies [4–6]. In 222 patients under 40 years of age with a diagnosis of GN, of whom 75% were normotensive at the time of kidney biopsy, vascular lesions were found in 20.3%, compared with only 6.2% in controls of similar age. In 283 patients aged 40–65 years, the incidence of vascular lesions was 60% in MN and 50% in MCD. In 227 patients older than 65, the incidence of renal vascular lesions was 80.8%. In IgA GN nephroangiosclerosis appeared early and often preceded the onset of hypertension. In 266 patients with interstitial nephritis, despite normal BP in the majority, renal vascular lesions were found in 66.4 and 76.5%, respectively, compared with an incidence of 24.6% in 73 controls. The same may apply to patients with polycystic kidney disease [18].

**RENAL VASCULAR LESIONS MAY PRECEDE THE ONSET OF HYPERTENSION**

That renal vessel changes may precede the onset of hypertension or appear in the absence of hypertension has been established in the human, especially in young blacks of African descent and in animal experimental models.

Tracy et al. [19] compared renovasculopathies 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. In one other study of autopsy specimens, the magnitude of early nephroangiosclerosis was also assessed in five different ethnic populations [20–22]. Blacks exceeded whites in the magnitude of incipient nephroangiosclerosis in all age groups. The findings by Tracy’s group point to the notion that nephroangiosclerosis, especially in young blacks, anticipates a rise in BP later in life, which leads to speculations on separate genetic traits converging with an unequal time-scale to hypertension and renovasculopathy.

Experiments that consisted in infusing low dosages of angiotensin II (Ang II) in rats confirmed that Ang II plays a major role in creating microvascular lesions in the absence of hypertension or without being proportionate to the rise in BP.

Griffin et al. [23] perfused rats subcutaneously with Ang II by minipump for 10–12 days. Ang II gradually raised systolic BP, suppressing plasma renin and increasing plasma Ang II. In the perfused mesenteric circulation, vasoconstrictor responses to norepinephrine, vasopressin and KCl were enhanced, but sensitivity of responses was not altered. This combination of changes suggested that vascular hypertrophy develops during slow pressor infusion of Ang II. Vessel myography was done after Ang II infusion with and without a pressor response. Ang II raised systolic BP, increased heart weight and produced myographic changes of vascular...
hypertrophy in the mesenteric circulation. Hydralazine given with Ang II prevented the rise of pressure and the cardiac effect but not the vascular changes.

Johnson et al. [24] infused a slow, moderately pressive dosage of Ang II over 14 days in rats. The renal lesions were out of proportion with the moderate rise in systolic BP and consisted of pronounced proliferation of vascular smooth muscle cells. The main effect of Ang II in glomeruli was to increase the expression of alpha-smooth muscle actin (α-SMA) by mesangial cells and desmin by visceral glomerular epithelial cells. Ang II-infused rats also developed focal tubulointerstitial injury, with tubular atrophy and dilatation, cast formation, an interstitial monocytic infiltrate and mild interstitial fibrosis with increased type IV collagen deposition. The injury was associated with a proliferation of distal tubule cells, collecting duct cells, an interstitial monocytic infiltrate and mild interstitial fibrosis with increased type IV collagen deposition and was accompanied by an increase in platelet-derived growth factor B (PDGF-B)-chain messenger RNA in the areas of interstitial injury. Renal interstitial cells also underwent phenotypic modulation in which they expressed α-SMA.

Other experiments point to factors other than Ang II in the genesis of kidney vascular lesions. Smeda et al. [25] treated spontaneously hypertensive pregnant rats with hydralazine. Their offspring were normotensive at birth and yet exhibited thickening of renal vascular walls. The authors raised the hypothesis that genetic nephrosclerosis might be the cause rather than the consequence of hypertension. In mice rendered hypertensive by knock-out mutation of the ACE gene, histology showed thickened and hypercellular renal vascular walls [26]. Genetic manipulations can yield mice with zero to four functional copies of the angiotensinogen gene. The former are hypertensive, the latter hypertensive. Kim et al. [27] found the most severe lesions in the hypotensive mice. A nil mutation of the angiotensinogen gene yields a homozygous hypertensive strain of mice [28]. As of the third week of life, their renal cortical vessels display lesions of nephrosclerosis along with hyperexpression of PDGF-B mRNA and TGF-β. In these angiotensinogen-deficient mice, intrarenal renin levels are very high. Taken together, these findings lead to the hypothesis that renin exerts a significant influence upon vascular cell proliferation [29].

**PATHOGENESIS OF THE RENAL SCLEROSIS**

Lesions lumped together under the umbrella term of ‘nephrosclerosis’ can be followed from arteries to arterioles, glomeruli and the tubulointerstitium. Hypertension is not a pre-requisite for these lesions to occur. In addition, most hypertensive patients, with the exception of blacks, are older than 40–50 years and ageing independently contributes to arteriolar, glomerular and interstitial changes. Two major pathophysiologic mechanisms are involved in the glomerular and tubulointerstitial lesions: loss of autoregulation and ischaemia.

**Loss of autoregulation of renal blood flow**

The glomerular tuft capillaries are arranged in series between two resistance vessels, the afferent arteriole (AA) and efferent arteriole (EA). Renal autoregulation is centred by the need to insulate the glomerular capillary framework from high hydrostatic pressure. Conversely Ang II-induced EA vasoconstriction maintains to some extent the glomerular filtration rate (GFR) when pressure drops in the pre-renal vessels. When a rapid pressure rise or drop occurs in upstream arteries and in the AA, the GFR is preserved by the interplay of the AA and AE vascular tone along with the tubuloglomerular feedback. The response of the AA to a rise in preglomerular BP is characterized by a rapid vasoconstriction, known as the myogenic response (MR) that requires <10 s for completion. Should autoregulation come into play at higher than normal pressures its curve would be shifted to the right. The mechanisms underlying the MR are complex and not all have been elucidated (reviewed by Armin [30] and Bidani et al. [31]).

These physiological notions apply to sound pre- and post-glomerular vessels. How do they operate in the case of microvascular lesions that characterize nephrosclerosis, that is, in conditions of chronic hypertension?

**Loss of autoregulation in animal models.** Observations in rats demonstrate that autoregulation of the renal blood flow is lost in case of long-standing hypertension. This is true of 5/6th nephrectomized rats [32–34], in rats with streptozotocin-induced diabetes [35] and in hypertensive deoxycorticosterone-treated rats [36]. In these models, the loss of autoregulation is ascribed to an altered myogenic response [31, 32]. Interestingly, pathologists do not necessarily find lesions of the renal microvasculature. That a spontaneous loss of autoregulation leads to glomerular lesions through hyperfiltration and shear-stress on the podocytes has been demonstrated in several genetically hypertensive rat species including the Dahl salt-sensitive rats [37], the Brown-Norway rats [38] and the fawn-hooded rats [39]. In the latter, the reactivity of renal microvessels to pressure and Ang II is reduced. A shift to the right of the autoregulation curve is explained by histologic lesions with a dilatation of afferent glomerular arterioles shown by microvascular casts [40]. It is confirmed by micropuncture studies showing an increased glomerular capillary pressure [41] with hyperperfusion of the glomerular capillaries.

**Loss of autoregulation in human kidney disease.** Christensen et al. [42] studied the effect of hypotension induced by an intravenous injection of clonidine in 16 diabetic proteinuric patients with glomerular lesions on kidney biopsy. Twelve were normotensive. Seven of the patients with nephropathy had an abnormal autoregulation of GFR, that is, a more than 10% reduction in relative GFR compared with only one in the control group. One patient only had arteriolar lesions. Extensive functional/morphologic correlations were carried out by Hill and co-authors in the ageing kidney [43] and in essential hypertension [44] (reviewed in [7]). These elegant studies allow the differentiation between lesions due to ageing and those caused by hypertension. However in both conditions a loss of autoregulation is involved.

**Loss of autoregulation and ageing.** As observed by Hill et al. [43], it was widely assumed in the past that hyaline
afferent arteriolosclerosis was responsible for ischaemic glomerular shrinking in the ageing and hypertensive kidney. However, glomerular lesions of FSGS in oversized glomeruli are now recognized in essential hypertension.

Hill’s group performed a morphometric kidneys study in ageing, normotensive patients (Figure 3). Afferent arterioles were divided into three types according to the presence or absence of hyaline deposits and whether these did or did not obstruct the lumen. Arterioles with non-obstructive hyaline deposits had lumens over twice as large as those without deposits. Their associated glomeruli had significantly greater total capillary area. Arterioles with obstructive deposits differed from those with non-obstructive deposits by their smaller lumens with a higher proportion of extra-cellular matrix (ECM) in the periglomerular region consistent with a later stage of lesion. Glomeruli were divided into normal, hypertrophic, glomeruli with features of FSGS, and ischaemic glomeruli. Hypertrophic glomeruli were larger, with greater total capillary area but showed no evident lesions. FSGS-type glomeruli were also larger, but showed an increase in ECM. The remaining capillaries showed an inverse relation with the amount of mesangial matrix, with a spectrum of sizes from enlarged to shrunken. Ischaemic glomeruli were small. There was a strong association between hypertrophic/FSGS-type glomeruli and non-obstructive hyaline arteriolosclerosis, found in 90.3% of such glomeruli, versus 29.1% for the remaining glomeruli. These findings demonstrate that hyaline deposits in dilated AAs are responsible for an ‘arteriolomalacia’ rather than an arteriolosclerosis. They strongly suggest that the dilatation of AAs hinders autoregulation and explains glomerular hyperfiltration leading to glomerulomegaly and FSGS.

**Loss of autoregulation and hypertension.** Hill’s group performed a similar morphometric study in kidneys from proteinuric and/or azotaemic hypertensive patients with no evidence of other renal disease [44]. Afferent arterioles in hypertensive kidneys showed a significant increase in lumen diameter and wall area, due primarily to shift from predominantly normal toward predominantly hyaline arterioles. Glomeruli in hypertensive kidneys were much larger than in normotensive ageing kidneys. This was due primarily to an increase in size of each type of glomeruli, as defined in [43]. There was an excellent correlation between arteriolar lumen diameter and mean glomerular capillary area for hypertrophic/FSGS-type glomeruli such that as arteriolar diameter increases, the mean glomerular capillary area increases. The morphologic correlates

**FIGURE 3:** Glomerular and arteriolar types. (A) A normal glomerulus and its associated AA (arrow) without hyaline deposits. (B) A hypertrophic glomerulus demonstrates the massive dilatation of hilar capillary and its first branches. Peripheral capillaries are dilated and a channel (arrowhead) leading to the EA is also dilated. The dilated AA (arrow) shows a massive non-obstructive hyaline deposit. (C) An FSGS-type glomerulus shows mesangial increase and sclerosis with capsular adhesions, particularly at hilum (arrowheads). Its associated AA (arrow) shows non-obstructive deposits. (D) An ischaemic glomerulus shows collapsing capillary loops with resulting small capillary lumens. Its AA (arrow) is without deposits (Periodic acid-Schiff, ×250). Reproduced with permission (Nature Publishing Group, Licence 3490220997436) from Hill et al. [43]. AA, afferent arteriole; EA, efferent arteriole; FSGS, focal-segmental glomerulosclerosis.
of loss of autoregulation, with AA dilatation and increase in glomerular capillary size, glomerular hypertrophy, and subsequent FSGS, were present on a focal basis in ageing kidneys and more extensively in hypertensive kidneys.

**Ischaemia and hypoxia**

Despite a very large blood flow the kidneys, which carry out complex and energy consuming cellular transport functions, operate under markedly reduced oxygen tension, with regional oxygen levels ranging from ∼50 mmHg in the cortex to ∼10–20 mmHg in the outer medulla [45, 46]. A reduction in renal oxygenation occurs in most chronic kidney diseases irrespective of aetiology. Virtually every renal disease has an ischaemic component. Renal ischaemia, or more specifically hypoxia, is almost invariably accompanied by renal fibrosis, which involves the renal interstitium but can also lead to glomerular focal or global sclerosis.

Hypoxia runs through the whole story of fibrogenesis leading to end-stage renal failure. Fine and Norman [47] elaborated the ‘chronic hypoxia hypothesis’ in which hypoxia can be considered as the main common pathway to tubulointerstitial fibrosis and decline in renal function [48–50]. This was substantiated by further researchers who adduced evidence on hypoxia-inducible fibrogenic factors.

Ang II, endothelin-1, TGF- and PDGF-B are associated culprits in fibrosis [51–56]. Ang II fosters secretion of endothelin-1 in cultured mesangial cells [51] and renal vasoconstriction induced by endothelin-1 is linked to Ang II [53]. Ang II increases the expression of the TGF-gene [55] and of interstitial PDGF B-chain mRNA [50], thus contributing to the build-up of ECM and especially collagen IV in the renal interstitium.

Hypoxia-inducible fibrogenic factors (HIF) have received much attention of late [57, 58]. Consistent with decreased renal oxygenation in CKD is the increased expression of the oxygen-sensitive α-subunit of hypoxia-inducible factor (HIF)-1 (reviewed in [46]). It is now recognized that pathways to ischaemic renal fibrosis are complex and comprise epithelial–mesenchymal transition [59].

**RENAL INSUFFICIENCY**

The diagnosis of hypertensive end-stage renal disease (ESRD) is one of exclusion and pathologic data rarely corroborate this classification [60, 61]. These patients may suffer from a variety of diseases, including accelerated hypertension, atherosclerotic disease of the large arteries and/or cholesterol crystal embolism. Often included are patients with an undiagnosed primary renal disease. Zucchelli and Zuccala [62], in 136 patients diagnosed as having ‘benign nephrosclerosis’, performed a thorough diagnostic workup, including kidney biopsy. The study found cholesterol emboli in 29.4%, renovascular disease in 26.5% and true nephrosclerosis in only 44.1%. In the United States, Schlessinger et al. [63] reached similar conclusions concerning the propensity to wrongly label patients as suffering from ‘nephrosclerosis’ in the absence of kidney biopsy.

A number of metabolic disorders are common in the hypertensive population. They contribute to creating kidney lesions that are also wrongly labelled as ‘hypertensive nephrosclerosis’. Among such factors stand the metabolic syndrome and obesity [64]. An excess of adipose tissue increases oxidative stress and inflammation [65], directly or through an increase of circulating Ang II [66, 67]. In any event these factors add their untoward effects to the progression of hypertensive nephrosclerosis.

No one would deny that hypertension, ageing or both are deleterious to the kidney. However although an increase in serum creatinine or decline in clearance has been reported in nephrosclerosis, progression to ESRD has not been documented [58, 59], except in the malignant phase of hypertension.

In an excellent review of the matter, Hsu [68] came up with the conclusion that the question of whether non-malignant hypertension actually causes renal insufficiency remains controversial. A meta-analysis of 10 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. Failure to evaluate the possibility that pre-existing renal disease could explain any observed association between elevated BP and subsequent loss of renal function is an important limitation of published studies. It follows that treatment of hypertension in white Europeans aims more at reducing the risk of left ventricular hypertrophy and brain damage than preventing the development to ESRD.

Actually this is true of populations of white European lineage and not in blacks of African ancestry. As developed above this subset of hypertensive patients seems to suffer from two inborn conditions: one causing a renovascularopathy beginning early in life and later accompanied by FSGS and the other consisting of a severe form of hypertension with a high risk of progression to malignant hypertension. Among genetic factors Kopp et al. identified genetic variations of the MYH9 gene that encodes a non-muscular myosin, myosin heavy chain 9 and confers a risk of hypertensive nephropathy among blacks.

Since, more recent analyses localized the strongest association within the neighbouring APOL1 gene that seems to represent a hundred-fold greater risk factor than the latter [69]. 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 [70]. In the African-African 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 [71] the study participants were more likely to have two APOL1 risk variants compared with controls. G1 and G2 also confer a greater risk of FSGS in this population. However in Caucasians and Asians, genetic variants appear to be involved in the propensity to hypertension and renal damage. Genetic variants in the angiotensinogen Ang II type 1 receptor and alpha-adducin genes may contribute to loss of renal function in Caucasian females [72]. Genome-wide association studies also suggest that uromodulin (Tamm–Horsfall protein) might be a risk factor for both chronic kidney disease and hypertension [73]. A functional common polymorphism of the ABCB1 gene has been reported...
to be associated with chronic kidney disease and hypertension in the Chinese population [74].

**ANTIHYPERTENSIVES: A DOUBLE-EDGE SWORD IN THE TREATMENT OF NEPHROSCLEROSIS**

Treating hypertension slows the pace to renal insufficiency. Nevertheless not all antihypertensive drugs equally protect the kidney from loss of autoregulation that causes glomerulomegaly and FSGS and from ischaemia leading to glomerular shrinking and interstitial fibrosis. Clonidine [42] hinders autoregulation. The di-hydropyridine calcium channel blockers amlodipine [75] and nifedipine [76] exert an untoward vasodilating effect on the AA. They demonstrate a deleterious effect in rat remnant kidneys and do not diminish proteinuria in diabetics [77–79]. Hydralazine exerts a generalized vasodilating effect on arterioles [25] and despite its antihypertensive action, although this specific point has not been studied, impairment of autoregulation is likely. Ang II-converting enzyme inhibitors (CEI) diminish the EA vasoconstriction. However in the case of upstream impairment of the blood flow, that is, atherosclerosis of the renal arteries and their branches they may suppress the last defence against glomerular ischaemia. There is a wealth of literature on acute renal insufficiency complicating CEI treatment in patients with atherosclerotic renal disease [6] but the risk of reaching a ‘critical perfusion pressure’ [80, 81] has also been observed in the absence of haemodynamically significant renal artery stenosis [82]. These observations lead to recalling the KDIGO recommendations on BP control in CKD that recommend avoiding excessive BP reduction in elderly patients [83].

A common clinical observation is that Ang II inhibitors usually induce a rise in serum creatinine levels, a rise interpreted as purely functional and negligible in terms of long-term risk to renal function. In any event it is conceivable that in the long term, an excessive reduction of the EA vasoconstriction aimed at reducing the glomerular capillary hydrostatic pressure might trade off glomerulomegaly and the resulting FSGS-type for glomerular ischaemic shrinking and fibrosis. This provocative speculation might be considered as a matter worthy of further investigation.

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**CONFLICT OF INTEREST STATEMENT**

The author declares he has no conflict of interest with regard to this article. This paper has not been submitted or published elsewhere.

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