

Essential Hypertension, Progressive Renal Disease, and Uric Acid: A Pathogenetic Link?

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Hypertension and hypertension-associated ESRD are epidemic in society. The mechanisms responsible for renal progression in mild to moderate hypertension and those groups most at risk need to be identified. Historic, epidemiologic, clinical, and experimental studies on the pathogenesis of hypertension and hypertension-associated renal disease are reviewed and an overview/hypothesis for the mechanisms involved in renal progression is presented. There is increasing evidence that hypertension may exist in one of two forms/stages. The first stage, most commonly observed in early or borderline hypertension, is characterized by salt-resistance, normal or only slightly decreased GFR, relatively normal or mild renal arteriosclerosis, and normal renal autoregulation. This group is at minimal risk for renal progression. The second stage, characterized by salt-sensitivity, renal arteriolar disease, and blunted renal autoregulation, defines a group at highest risk for the development of microalbuminuria, albuminuria, and progressive renal disease. This second stage is more likely to be observed in blacks, in subjects with gout or hyperuricemia, with low level lead intoxication, or with severe obesity/metabolic syndrome. The two major mechanistic pathways for causing impaired autoregulation at mild to moderate elevations in BP appear to be hyperuricemia and/or low nephron number. Understanding the pathogenetic pathways mediating renal progression in hypertensive subjects should help identify those subjects at highest risk and may provide insights into new therapeutic maneuvers to slow or prevent progression.

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Hypertension is epidemic in our society and is the most common cardiovascular disease. In the United States, the prevalence of hypertension has increased markedly in the past 100 yr, from a frequency of 6 to 11% in the population in the early 1900s (1) to >30% today (2). The increase in hypertension does not simply reflect an increase in the aging population, because the prevalence of hypertension among individuals between the ages of 45 and 54 increased from 11% in the 1930s to 31% in 2000 (2,3). Hypertension was also nearly absent outside Europe and America in the early 1900s but now affects 25 to 30% of people throughout the world (4). This increase in hypertension tracks with the epidemic increase in obesity, metabolic syndrome, type II diabetes, and ESRD, raising the likelihood that these conditions are pathogenetically related and intricately linked to environmental and especially dietary changes that have occurred in the world population over the past 100 yr.

Hypertension is important in nephrology. According to the United States Renal Data System Report, hypertension remains the second most common cause of ESRD, accounting for nearly 80,000 patients in 2001 (5). The incidence of ESRD attributed to hypertension has increased nearly eight-fold since 1981, suggesting that hypertension should be considered as important as diabetes in the current epidemic of renal disease (5). Understanding the pathogenesis of hypertension and how it may lead to progressive renal disease is therefore critical.

Nevertheless, controversy exists over whether the diagnosis of essential hypertension-associated ESRD is correct for the large number of cases reported (6,7). There is no doubt that severe (malignant) hypertension may cause progressive renal failure and that lowering BP in this condition can slow or prevent progression (8). However, the issue is whether mild hypertension can cause progressive renal disease. Whereas epidemiologic studies show that the risk for ESRD increases stepwise as BP increases from 120 or 130 mmHg systolic pressure (9–13), opponents point out that in many cases pre-existing renal disease was not excluded (6,7). It is well known that hypertension often accompanies a decline in GFR regardless of cause (14). Because renal biopsy is not typically performed in essential hypertension, the possibility exists that cases diag-

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nosed as hypertension-associated ESRD could represent misdiagnosed cases of atheroemboli, ischemic nephropathy secondary to atheromatous disease, or glomerulonephritis (15,16). Furthermore, although some studies have reported an increased risk for renal progression in subjects with mild or moderate hypertension, especially blacks (17), it is often questioned whether the observations in this particular group can be carried over to the general hypertensive population. Finally, it has been difficult to show that antihypertensive treatment alters the risk for renal progression in subjects with mild hypertension (18–20), and in some cases renal function has worsened (21,22). Nevertheless, there are reports that antihypertensive treatment can slow renal progression in mild to moderate hypertension in both whites (23) and blacks (24).

In this review, we present new insights generated from recent experimental and clinical studies that should shed light on not only the role of the kidney in causing hypertension but also the role of hypertension in causing renal disease. Finally, we provide guidance for the identification of those hypertensive subjects most at risk for progression.

The Clinical Syndrome of Essential Hypertension

Essential hypertension is classically defined as hypertension that occurs in the absence of a known secondary cause. However, there are important clinical, pathologic, and hemodynamic features that characterize this entity. Clinically, hypertension frequently develops in subjects who are obese, have the metabolic syndrome, are hyperuricemic, or who have features of a hyperactive sympathetic nervous system (including type A personalities, subjects with a high baseline pulse, or a positive cold-pressor test). Other common characteristics include a positive family history, black race, the presence of low-level lead intoxication, and a history of low birth weight (25).

When hypertension first presents it is often termed “borderline,” in that the hypertension is either mild or intermittent. Early hypertension is also frequently salt-resistant, in that it is not significantly altered by changes in dietary salt intake. In the older subject, hypertension is usually salt-sensitive. Pathologically, hypertension is highly associated with small-vessel disease (arteriosclerosis), particularly involving the preglomerular vessels in the kidney (26–28). The classic finding consists of medial hypertrophy of the interlobular and arcuate arteries that may progress to medial fibrosis (fibroelastic thickening) associated with neointimal hyperplasia. Afferent arterioles are also affected and may show thickening and/or hyalinosis, in which there is subendothelial deposition of homogenous eosinophilic material (26–29). Although these changes are seen in the majority (>95%) of subjects with hypertension, some subjects with mild or early hypertension may demonstrate minimal arteriolar disease (26–29), although evidence for arteriolar spasm is usually present (inferred from an abnormal concentric overlapping of vascular smooth muscle cells) (28). Hypertension that is more severe or prolonged is usually associated with more severe renal arteriosclerotic changes (29,30), and in subjects with malignant hypertension the vascular lesions may result in

severe concentric hypertrophy (onion-skin vessels) and even fibrinoid necrosis (31).

The prominent involvement of the preglomerular vasculature is accompanied hemodynamically by evidence of increased resistance of the afferent arteriole (32), with a marked decline in renal plasma flow and relative preservation of GFR (33). Cortical vasoconstriction is the result, with relative preservation of blood flow in the deeper portions of the kidney (34,35). In addition to vascular involvement, biopsy and autopsy studies demonstrate that there is substantial tubular injury with features of ischemia, often accompanied by mild inflammatory cell infiltration (28). Glomeruli may show evidence for ischemia with collapse of the glomerular tuft and eventual obsolescence (36). However, a subset of subjects with essential hypertension may have enlarged glomeruli with segmental scars resembling focal glomerulosclerosis (36–38). This type of injury has been termed “decompensated glomerulosclerosis” by Bohle and Ratschek (37).

Natural history studies before effective antihypertensive therapy documented that 35 to 65% of subjects with essential hypertension developed proteinuria, with one third developing renal insufficiency and 6 to 10% dying from uremia (39–41). The greatest risk was for subjects with sustained systolic BP >200 mmHg (39). The risk for mortality and for renal insufficiency (measured by inulin clearance) correlated with the severity of renal arteriosclerotic lesions (42). The mortality risk also correlated with the severity of microvascular changes in the retina, with the survival for grade 3 (cotton wool exudates/hemorrhages) and grade 4 (papilledema) disease being only 0 to 20% at 5 yr (43–45). It is thus apparent from the historical literature that many untreated hypertensive subjects developed renal insufficiency; however, it is likely that many of these subjects had severe, accelerated, or malignant hypertension.

Experimental Insights into the Cause of Hypertension

Recent studies by our group and others have provided new insights into the pathogenesis of essential hypertension. Specifically, we have demonstrated in animals that hypertension often involves two stages.

The first stage of hypertension is primarily initiated by *extrarenal stimuli*, which may by themselves raise BP but which all have in common the induction of renal vasoconstriction. Examples include hyperuricemia (46–48), angiotensin II (49,50), catecholamines (51), endothelial dysfunction with impaired release of nitric oxide (52), or various agents such as cyclosporine (53). During the initial phase, the renal arteriolar structure is normal or only minimally abnormal; however, the arterioles are functionally constricted, resulting in a decline in renal plasma flow and renal ischemia with tubular injury and interstitial inflammation (46–53). Similar changes can be shown by exposing animals to systemic hypoxia (54).

The initial BP response depends in part on the type of external stimuli, and whether renal vasoconstriction is intermittent or constant. Intermittent activation of the sympathetic nervous system may result in intermittent elevations in BP (51); endothelial dysfunction caused by systemic depletion of nitric oxide results in constant elevations in pressure (52); and cyclosporine

administration in rats may result in only mildly elevated BP initially (53).

The second stage is characterized by renal cortical vasoconstriction that persists despite removal of the original stimulus (55). This is associated with the development of structural changes in the kidney, characterized primarily by arteriosclerotic changes (disease of the afferent arteriole) and interstitial inflammation, similar to the changes observed in most subjects with essential hypertension. Studies in animal models have suggested that both the arteriolar and interstitial changes have a key role in the hemodynamic response. Thus, the interstitial inflammatory changes (characterized by monocyte/macrophages and T cells) may have a role in mediating the renal vasoconstriction by producing oxidants and angiotensin II that inactivate local nitric oxide. In contrast, the structural changes in the arteriole may have a key role in helping to maintain the renal ischemia that drives the interstitial inflammatory reaction (55).

Hemodynamically, the renal vasoconstriction is associated with a decline in cortical plasma flow, a decline in single-nephron GFR, and a decrease in the ultrafiltration coefficient, K_f (48,50). Nevertheless, overall GFR is normal or only minimally decreased (47,48,50). This suggests that there is a compensatory increase in juxtamedullary nephron GFR (48,50). In this regard, it is known that juxtamedullary nephrons, which account for 25 to 30% of all nephrons, are unlike cortical glomeruli in that they are capable of increasing their GFR up to three-fold under physiologic conditions (56).

Relevance of Stages of Hypertension with the Development of Salt Sensitivity

Sodium retention results and BP increases whenever there is persistent renal vasoconstriction, because of glomerular (decreased K_f and/or GFR) and tubular (increased Na re-absorption) mechanisms (55, 57). However, differences in salt sensitivity are reflected in part by the stage of the hypertension. Thus, when the renal vasoconstriction is mediated primarily by humoral mechanisms, and when arteriolar disease is mild, the constriction is relatively uniform and hence an increase in renal arterial pressure will relieve ischemia uniformly throughout the kidney. Sodium handling then returns to normal but at an expense of a higher BP and a parallel shift in the pressure natriuresis curve, resulting in a salt-resistant form of hypertension (58). In contrast, as arteriolar disease develops, the variability in the lesions will result in heterogeneous perfusion, with some regions of the kidney remaining ischemic and others overperfused. Glomerular and peritubular capillary hypertension is then likely to develop, with focal loss of capillaries and the development of renal ischemia. As a consequence, the hypertension will be more of a salt-sensitive type because ischemia will continue to drive sodium re-absorption (55,57). In addition, a heterogeneous response of renin is likely to occur, which would also play a role in the hypertensive response as proposed by Sealey *et al.* (59).

A key issue then relates to the mechanisms involved in the induction of arteriolar disease. In this regard, arteriolar changes are particularly severe if induced by angiotensin II, hyperuri-

emia, or blockade of the nitric oxide system (46–50,52,60), whereas the arteriolar changes are relatively minimal with catecholamines or hypokalemia (51,61). The arteriosclerotic changes are also focal (particularly occurring at branch points) in some genetic strains, such as in the Dahl salt-sensitive rat, whereas the congenital narrowing of the arterioles are more uniform in the relatively salt-resistant spontaneously hypertensive rat. Interestingly, in most of these models the arteriopathy can be shown to be mediated by angiotensin II (60,62,63). The mechanism likely involves activation of NADPH oxidases and the generation of oxidants that causes local vascular smooth muscle cell proliferation and activation (64,65).

Relevance of Stages of Hypertension with the Progression of Renal Disease

The stage of hypertension and the type of arteriolar injury would likely have a major impact on the risk for renal progression. Thus, in the first stage the renal arteriolar structure remains largely intact. As a consequence, the arteriolar vasoconstriction will function adequately from the autoregulatory standpoint to prevent excessive transmission of systemic pressures into the glomerular and peritubular capillaries. Glomerular pressure will remain normal, and the risk for renal injury in this setting would be relatively minimal.

An appropriate analogy for this stage is the spontaneously hypertensive rat. In this hypertensive strain, there is a congenital reduction in afferent arteriolar diameter that results in renal ischemia. An increase in BP ensues, but the autoregulatory response of the preglomerular vasculature is functional and vasoconstricts appropriately to prevent the development of glomerular and peritubular capillary hypertension (66,67). In addition, renal ischemia is minimal because the increase in systemic and renal perfusion pressure will act to relieve it (55).

In contrast, the risk for renal injury is greater in the second stage of hypertension, particularly depending on the nature and type of the arteriolar injury. Thus, if the structural changes in the renal microvasculature are nonuniform, then the ischemia-induced increase in BP would result in heterogeneous perfusion of the renal parenchyma. In this scenario, some glomeruli would be overperfused and others underperfused for the same renal arterial perfusion pressure. The overperfused glomeruli may develop intraglomerular hypertension, whereas the underperfused glomeruli may become ischemic, resulting in persistent stimulation of juxtaglomerular renin release (59).

There is also increasing evidence that preglomerular arteriolar disease may also impair the autoregulatory response (47,48,68). Thus, in experimental hyperuricemia, the development of the preglomerular arteriolar lesions has been shown to result in reduced renal blood flow and glomerular hypertension, and both the arteriolar lesions and hemodynamic changes do not occur if hyperuricemia is prevented with allopurinol (47,48). Similar findings have been demonstrated in the remnant kidney model (68). We have postulated that the deposition of extracellular matrix into the arteriolar walls affects its ability to constrict appropriately for the degree of systemic BP elevation (48). The development of glomerular hypertension would then result in glomerular hypertrophy and the “decompensated

glomerulosclerosis" lesion, and this is observed in chronically hyperuricemic rats (69) and in rats with remnant kidneys (68). Interestingly, renal autoregulation is relatively maintained in rats with preglomerular arteriolar disease induced by transient exposure to angiotensin II, and in these animals glomerular hypertension did not develop after salt-loading (50). Whether this is because the vascular disease is more uniform and whether autoregulation would continue to remain intact as the vascular disease worsens are unclear.

Clinical evidence provides support for these pathways. Thus, early borderline hypertension is often salt-resistant (70) with minimally decreased renal plasma flow and normal GFR (71), and this corresponds with the renal hemodynamic changes associated with minimal renal arteriolar lesions (42). Younger subjects with short-duration (mean, 3 yr) hypertension also do not show any increase in peritubular capillary hydrostatic pressure with salt-loading, consistent with a normal autoregulatory response (72). In contrast, older hypertensive subjects tend to be salt-sensitive (70), have lower renal blood flow (73), have more prominent renal arteriolar changes (30), and worse renal function (30); some studies suggest that the age-dependent decline in GFR in our population may largely relate to the presence of hypertension (74). Subjects with salt-sensitive hypertension are also more likely to demonstrate renal progression compared with salt-resistant subjects and to have microalbuminuria (75). This latter condition is also associated with vascular changes in their retina (76), reduced renal function (76,77) and severe hypertension (78). Finally, subjects with salt-sensitivity and microalbuminuria demonstrate an increase in calculated glomerular hydrostatic pressure with salt loading in contrast to salt-resistant subjects, suggesting an impaired autoregulatory response (75).

Clearance studies also provide insight into the mechanisms of renal progression in subjects with essential hypertension. Renal plasma flows (RPF) (measured by p-aminohippurate clearance) decrease stepwise from 616 to 660 ml/min in normal subjects to 532 ml/min in borderline hypertensive subjects, to 475 to 505 ml/min in subjects with essential hypertension, to 317 ml/min in malignant hypertension (71,79). The level of GFR correlates with the changes in renal plasma flow (80) but does not show detectable decrease until the RPF falls to <450 to 475 ml/min (79). Interestingly, studies by Talbot *et al.* in the 1940s showed that the changes in renal plasma flow and GFR also correlate with the severity of the renal arteriolar lesions (by biopsy) (42). Thus, as arteriolar scores increased from 0 to 4, renal plasma flow decreased stepwise from 625, 552, 470, 440, to 283, with a decrease in GFR from 94, 104, 91, 89, to 64 ml/min (42). Interestingly, GFR did not decline until RPF decreased to <400 (late-stage hypertensive disease). One might posit that as the vascular disease worsens, the renal autoregulatory response also worsens, with some glomeruli displaying hypertension, whereas others remain ischemic. Eventually, however, renal perfusion pressures will not be able to sustain adequate glomerular pressures (even with maximal efferent vasoconstriction), and at this point glomerular obsolescence and collapse would occur. This is observed with severe, untreated, malignant hypertension (31).

Why Does Hypertension Progress in Some Subjects but in Others It Does Not?

These studies provide the necessary insight into better understanding why essential hypertension progresses in some subjects but in others it does not. Renal progression would be expected to occur if the renal autoregulatory response is impaired, resulting in increased glomerular hypertension. This concept is not novel and has been suggested by others (81–83). This could theoretically occur by several mechanisms. First, if the degree of hypertension was so severe that it exceeded the normal threshold for autoregulation. Studies of autoregulation have generally shown that glomerular pressure remains normal with systemic systolic pressure as high as 160 mmHg (84), although few studies have examined if autoregulation is maintained at higher pressures. However, one can observe renal injury developing in hypertensive kidneys in two-kidney one-clip hypertension when the systolic BP is >160 mmHg, suggesting that the threshold may be overcome (85). It is likely that this may represent one of the mechanisms by which malignant hypertension damages the kidney (86).

In subjects with mild or moderate hypertension, one would posit that alteration in the renal autoregulatory response would be necessary if one were to observe an increased risk for renal progression. One mechanism by which this may occur is in the setting of a reduced nephron number, such as in the remnant kidney model, in which even high-normal systemic pressures can be transmitted to glomeruli, resulting in glomerular damage (87). Another condition is experimental hyperuricemia, in which glomerular hypertension occurs even under conditions of mild systolic hypertension (47,48). As discussed, recent studies have correlated both of these conditions with the development of structural lesions of the renal arteriole (47,48,68).

Genetic mechanisms could also be operative. For example, the fawn-hooded rat has a genetic defect in renal autoregulation that results in early onset glomerular hypertension, followed by the accelerated development of renal disease (88). Numerous factors are known to govern renal autoregulation (84), including 20-hydroxyeicosatetraenoic acid (20-HETE) (89,90), and hence genetic alterations in any of these mediators could also lead to an abnormal autoregulatory response and increase the risk for progression in the subject with essential hypertension.

One can thus predict that the risk for renal progression is most likely to occur in the setting in which hypertension is severe or prolonged, when renal arteriosclerosis is severe, when nephron number is reduced, or in the setting of a genetic abnormality in the renal autoregulatory response. In this regard, a critical observation is that renal arteriolar injury may not simply reflect hypertension-related damage but also can occur independent of BP as a consequence of hyperuricemia (60). The mechanism appears to be mediated by direct entry of uric acid into both endothelial and vascular smooth muscle cells, resulting in local inhibition of endothelial nitric oxide levels, stimulation of vascular smooth muscle cell proliferation, and stimulation of vasoactive and inflammatory mediators (91).

Specific Characteristics that Favor an Increased Risk for Renal Progression in Essential Hypertension

There are certain characteristics that favor an increased risk for renal progression in the subject with essential hypertension (Table 1). An important risk factor is black race (92). Interestingly, several factors could account for this. First, blacks have been reported to have lower birth weights, which translates into fewer nephrons at birth (93). Second, they are known to have a significantly higher frequency of gout (94); in the African American Study of Kidney Disease Trial, mean uric acid was 8.3 mg/dl (95). Third, they also have higher serum TGF- β levels, which might theoretically result in more severe renal scarring (96,97). Other characteristics also may predispose them to hypertension, including diets low in potassium and high in salt (98), endothelial dysfunction (99), and increased vascular reactivity (100,101). Thus, it is interesting that clinical studies suggest that blacks have a defect in renal autoregulation with increased glomerular pressure (102), and that by renal biopsy they have more severe vascular and interstitial changes associated with glomerular hypertrophy and segmental sclerosis (103,104). The preglomerular vascular changes occur earlier and are more severe in blacks (105). It is perhaps not surprising that hypertension in blacks is primarily characterized by a high frequency of salt-sensitivity (106) and microalbuminuria (107).

A second major risk factor for renal progression in hypertensive subjects is the presence of hyperuricemia and/or gout. In the days before treatment of gout was available, as many as 25% of subjects died from renal failure (108,109). In addition, the majority (50 to 70%) had hypertension, 25% had albuminuria, 50 to 65% had decreased inulin clearances, 70 to 80% had decreased renal plasma flow, and 95% had histologic evidence of chronic renal injury (108–110). The primary histologic lesion in gout noted by early investigators was the presence of preglomerular vascular disease. The French academician, Henri Huchard (who coined the word hypertension), reported that gout was the most common cause of arteriosclerosis based on a large autopsy series (111). Other changes include focal glomerulosclerosis and tubulointerstitial fibrosis (108,112). Medullary urate crystals are also common but appear nonspecific (113).

Studies in the 1970s also demonstrated a strong association of

Table 1. Risk factors that favor an increased risk for renal progression in the subject with essential hypertension

Severe hypertension (systolic BP > 170 mmHg)
Prolonged hypertension
African American race*
Hyperuricemia and/or gout*
Chronic lead intoxication*
Obesity and/or features of the metabolic syndrome*
Diuretic use*
Reduced nephron number
Aging

*All conditions associated with hyperuricemia.

hypertension and renal disease with gout (114–116). For example, in one study approximately one third of subjects with gout had significant renal dysfunction in association with hypertension (114). Because most forms of mild hypertension are not associated with significant renal dysfunction, this association is particularly striking (117). Recent epidemiologic studies have further demonstrated that uric acid is a major and independent risk factor for the development of renal disease in the general population and in patients with glomerulonephritis and normal renal function (118–121). Experimental studies have reported that hyperuricemia induces systemic hypertension and renal injury via a crystal-independent mechanism, involving renal vasoconstriction mediated by endothelial dysfunction and activation of the renin-angiotensin system (46–48). Over time, the animals developed afferent arteriolar lesions, salt sensitivity, glomerular hypertension, glomerular hypertrophy, albuminuria, and eventually glomerulosclerosis (46–48,122). Thus, both experimental and human data clearly show that subjects with hyperuricemia and/or gout are at marked risk for hypertension with renal insufficiency.

A third major risk factor is low-level chronic lead intoxication. Studies in the 1800s linked chronic lead intoxication with the development of hypertension and renal disease (111,123), a finding that has been confirmed repeatedly in recent years (124–132). Subjects typically present with hypertension, slowly progressive renal insufficiency, and often have hyperuricemia and/or gout (124–132). Histologically, the renal lesion also appears like chronic hypertension, as characterized by prominent arteriosclerosis and tubulointerstitial fibrosis (133), leading Huchard to declare that lead intoxication was the second most common cause of arteriosclerosis (111). The relation of renal disease with lead levels can be demonstrated at levels well within the normal range (132), and subtle lead intoxication is now recognized in some parts of the world as a common cause of ESRD (134–136). In contrast, high blood levels of lead are not associated with hypertension but rather with proximal tubular injury with a Fanconi pattern, *i.e.*, intratubular nuclear inclusions (137,138).

A fourth major risk factor is obesity and the metabolic syndrome. It has become increasingly appreciated that obesity is associated not only with hypertension but also with an increased frequency of renal disease (139–144). Similar to the other conditions, obesity-associated renal disease is associated with vascular lesions, interstitial inflammation, glomerular hypertrophy and glomerulosclerosis, and with evidence for glomerular hypertension, as noted by elevated filtration fraction (141). The mechanism for the increased susceptibility for renal injury may relate to activation of the sympathetic and renin-angiotensin systems and/or the deposition of lipids in the renal parenchyma, resulting in increased interstitial pressure (139). Of additional interest is the finding that obesity-associated metabolic syndrome is almost always associated with hyperuricemia (145). Finally, this hypertension also tends to be salt-sensitive (146).

Although controversial, a fifth major risk factor appears to be diuretic use. Clinical and population-based studies have reported that diuretic usage does not slow but rather often accel-

erates renal progression in hypertensive subjects (21,22,147–155). The usage of diuretics in the EWPHE (22,153), Syst-Eur (149), SHEP (150), INSIGHT (151), and ALLHAT (152) studies were all statistically associated with a greater decline in renal function compared with the other treatment groups. Diuretics also exacerbate renal disease in a model of experimental hypertension (156). The mechanism is likely multifactorial (155), but it is of interest that even low-dose diuretic therapy is associated with an increase in serum uric acid (157,158).

It may appear surprising that diuretic usage is associated with worsening renal disease in hypertensive subjects given the known protective effects of diuretic on hypertension-related heart failure and stroke. However, the degree of protection for coronary events with diuretics is also less than expected for the decrease in BP observed (159–161), and this increase in cardiovascular events and mortality can be attributed in part to the effect of diuretics to raise uric acid levels (162,163). There is also a *post hoc* analysis in the LIFE trial that the added benefit of losartan to prevent cardiovascular events compared with β -blockers could be explained in part by its effect to lower uric acid (in addition to its well-known effect to block the angiotensin type 1 receptor) (164). Finally, it is interesting that diuretics prevent hypertension in experimental hyperuricemia but, unlike angiotensin-converting enzyme inhibitors, do not block the development of the renal arteriopathy (60). Similarly, a study in humans found that angiotensin-converting enzyme inhibitors are able to cause regression of retinal microvascular disease in hypertensive patients but diuretic therapy was without benefit (165). Again, these studies in composite suggest that diuretics, likely by raising uric acid levels and stimulating the renin-angiotensin system, may accelerate the development of renal microvascular disease and thereby predispose the patient to renal progression. Nevertheless, this does not negate the fact that diuretics are often a necessary part of the antihypertensive regimen in difficult-to-control hypertension.

A final risk factor is aging. It is well known that aging is associated with a high frequency of preglomerular vascular lesions (including hyalinosis and arteriolar thickening), with impaired renal function, and with salt-sensitive hypertension (70). There is even morphometric evidence that the arteriolar lesions may predispose to impaired autoregulation (166). The mechanisms responsible for the development of the renal lesions are undergoing study but can be largely prevented by long-term treatment with agents that block the renin-angiotensin system (167).

Summary and Hypothesis

Hypertension is epidemic in our society and is currently considered the second most common cause of ESRD. In this review, we have presented evidence that hypertension may exist in two stages (or forms). In the setting in which arteriolar disease is minimal, the arteriole may continue to appropriately autoregulate to prevent transmission of systemic pressures to the glomeruli. In this setting, which likely affects a substantial portion of the population, renal disease progresses slowly over time, and GFR remains relatively preserved. However, under conditions in which significant renal arteriolar disease devel-

ops, such as in the setting of severe hypertension, marked reduction in nephron number, or hyperuricemia, then the autoregulatory response becomes impaired and renal progression occurs much more rapidly. It is intriguing that most of the major groups associated with an increased risk for progression, namely, black race (94,95), subjects with gout or hyperuricemia, subjects with chronic lead ingestion (125,128), severe obesity/metabolic syndrome (145), and chronic diuretic use (155,158), all have relatively high uric acid levels. We suggest that uric acid may have a key role in initiating renal arteriolar lesions in these patients and thus in increasing their risk for early progression. There is also evidence that an elevated uric acid may potentiate the effects of angiotensin II to induce renal vasoconstriction (168), which could possibly be mediated by its effect to upregulate angiotensin type 1 receptors on vascular smooth muscle cells (169).

Thus, we propose trials to determine if reducing uric acid may have a role in slowing renal progression in subjects with hypertension. Although there is mixed literature on the role of reducing uric acid on slowing renal progression in gout, with both positive and negative results reported (170,171), most studies were limited by poor controls, short duration of therapy, or inadequate reduction of uric acid (117). Furthermore, it is important to recognize that when the microvascular disease develops, it is the vascular disease that will drive renal progression, much like the renal microvascular disease drives the salt-sensitive hypertension (25,55). Hence, studies to examine the role of uric acid in renal disease are best if they focus on the initiation of the process more than on its maintenance.

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