Clinical features, diagnosis, and treatment of hypertensive nephrosclerosis

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INTRODUCTION

Hypertensive nephrosclerosis is a disorder that is usually associated with chronic hypertension. In addition to the level of blood pressure, other individual factors are involved. As an example, black patients have an approximate eightfold elevation in the risk of hypertension-induced end-stage renal disease (ESRD) [1]; this increase in risk may persist even with "adequate" blood pressure control. Although low birth weight and bias in diagnosis based upon the patient's race may be involved, the recognition of an association between two independent sequence variants in the apolipoprotein 1 (*APOL1*) gene on chromosome 22 and renal disease in African Americans, including focal segmental glomerular sclerosis and hypertension-related ESRD, provides a much more likely pathophysiologic mechanism [2] and suggests that hypertensive nephrosclerosis in black and white patients may be distinct diseases. In addition, the histologic features of hypertensive nephrosclerosis may be observed in patients with normal blood pressure. (See "Focal segmental glomerulosclerosis: Genetic causes", section on 'FSGS in African Americans'.)

PATHOLOGY

Hypertensive nephrosclerosis is characterized histologically by vascular, glomerular, and tubulointerstitial involvement (picture 1) [3]. The histologic pattern of renal injury in patients with malignant hypertension (ie, malignant nephrosclerosis) is different and is discussed separately:

- (See "Evaluation and treatment of hypertensive emergencies in adults".)

- (See "Moderate to severe hypertensive retinopathy and hypertensive encephalopathy in adults", section on 'Clinical manifestations and diagnosis'.)

Vascular disease — The vascular disease consists of intimal thickening and luminal narrowing of the large and small renal arteries and the glomerular arterioles. Two different processes appear to contribute to the development of the vascular lesions:

- A hypertrophic response to chronic hypertension that is manifested by medial hypertrophy and fibroblastic intimal thickening, leading to narrowing of the vascular lumen [4,5]. This response is initially adaptive, minimizing pressure-dependent wall stress [5].
- The deposition of hyaline-like material (plasma protein constituents, such as inactive C3b, part of the third component of complement) into the damaged, more permeable arteriolar wall [5].

Glomerulosclerosis — The glomeruli may show both focal global (involving the entire glomerulus) and focal segmental sclerosis [4-6]:

- Global sclerosis is thought to reflect ischemic injury, leading to nephron loss. This can be further categorized histologically as either solidified (in which the entire tuft is involved) or obsolescent (in which the tuft is retracted and Bowman's space is filled with collagenous-type material). The solidified form is more commonly associated with African Americans than with Caucasians and might contribute to the increased prevalence of nephrosclerosis in African Americans [6].
- Focal segmental sclerosis is typically associated with glomerular enlargement, which can be a compensatory response to nephron loss [7] but may also precede that loss [8]. However, the combination of hypertrophy and a rise in intracapillary pressure in these glomeruli may gradually lead to hemodynamically mediated segmental sclerosis [4].

The altered hemodynamics may be due, in part, to abnormal metabolism of nitric oxide. In the spontaneously hypertensive rat that exhibits severe glomerulosclerosis with age, the chronic administration of intravenous arginine (the precursor of nitric oxide) significantly reduced severe glomerular injury [9]. Renovascular disease may accelerate the development of the secondary sclerotic lesion by enhancing ischemic nephron loss [10]. (See "Secondary factors and progression of chronic kidney disease".)

Two observations in humans, in addition to the glomerular hypertrophy, are compatible with the importance of glomerular hemodynamics in progressive renal disease:

- Among initially untreated patients with mild hypertension, an elevated creatinine clearance (suggestive of glomerular hyperfiltration) at baseline has been related to a subsequent

significant rise in the plasma creatinine concentration and higher blood pressure levels [11] and to the development of moderately increased albuminuria (formerly called "microalbuminuria") [12]. (See "Secondary factors and progression of chronic kidney disease", section on 'Intraglomerular hypertension and glomerular hypertrophy'.)

- Part of the enhanced risk in black patients may be related to maternal malnutrition, leading to low birth weight, impaired renal development, and a reduction in nephron number. The decrease in the number of nephrons results in compensatory hypertrophy in the nephrons that are present and subsequent glomerulosclerosis [13]. The way by which the variants on the apolipoprotein 1 (*APOL1*) gene are translated into renal physiology has not been elucidated [2]. (See "Possible role of low birth weight in the pathogenesis of primary (essential) hypertension".)

Interstitial fibrosis and tubular atrophy — Vascular and glomerular diseases are associated with renal interstitial changes that are often severe. The etiology of the interstitial fibrosis and atrophy is incompletely understood. Studies in experimental animals have shown that severe stenosis of the main renal artery can induce tubular atrophy and an influx of inflammatory cells [14]. The interstitial disease in the ischemic kidney is, at least in part, an active immunologic process that may be initiated by ischemia-induced alterations in antigen expression on the surface of the tubular epithelial cells [14]. In this model of unilateral renal artery stenosis, the contralateral kidney, which is exposed to high blood pressure but no ischemia, develops similar tubulointerstitial changes [15].

CLINICAL MANIFESTATIONS

Nephrosclerosis is seen with normal aging [16] but is clearly exacerbated by chronic hypertension [17]. In addition, hypertension may aggravate mechanisms of cellular senescence in the kidney [18]. The overall incidence of progressive renal disease in hypertensives is relatively low and most affected patients have mild hypertension (see 'Incidence of renal failure' below). There are, however, three major groups at increased risk:

- Black patients
- Patients with more marked elevations in blood pressure
- Patients with underlying chronic renal disease, particularly those with diabetic nephropathy (see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults" and "Diabetic kidney disease: Pathogenesis and epidemiology")

Patients with nephrosclerosis typically present with a long history of hypertension, slowly progressive elevations in the blood urea nitrogen (BUN) and plasma creatinine concentration, and mild proteinuria. Black patients with these clinical features are particularly likely to have underlying nephrosclerosis. As an example, a renal biopsy was performed in 39 nondiabetic, hypertensive, black patients with chronic kidney disease who did not have marked proteinuria (total protein-to-creatinine ratio ≤2.0) [19]. Histologic changes compatible with nephrosclerosis as the sole disease were seen in 38 of the patients; the remaining patient may have had primary focal segmental glomerulosclerosis. Similar data are not available in white patients.

Hyperuricemia (independent of diuretic therapy) is a relatively early finding in benign nephrosclerosis and appears to reflect the reduction in renal blood flow induced by the vascular disease [20]. The urinalysis is typically benign with the sediment revealing few cells or casts.

Proteinuria — Protein excretion is usually mildly elevated (less than 1 g/day) in nephrosclerosis; this reflects the generally focal nature of the glomerular involvement [4]. However, more prominent proteinuria can occur, occasionally reaching as high 10 g/day [21], with such affected patients being more likely to have superimposed renovascular disease or malignant hypertension [10]. The proteinuria may be due to the less-affected glomeruli having undergone compensatory hypertrophy with a higher intraglomerular pressure.

Incidence of renal failure — An interesting clinical paradox is that benign hypertensive nephrosclerosis is one of the most common diagnoses in new patients starting maintenance dialysis. However, in the absence of one of the risk factors noted above, the rate of progression is generally slow and only a **few patients** with apparent primary hypertension (formerly called "essential" hypertension) develop progressive renal disease. This can be appreciated from the findings in three large trials:

- The Multiple Risk Factor Intervention Trial (MRFIT) in which the seven-year incidence of a doubling of the plasma creatinine concentration to more than 2.0 mg/dL (177 micromol/L) was less than 0.2 percent [3].

- The Hypertension Detection and Follow-up Program (HDFP) in which the five-year incidence of more than a 25 percent rise in the plasma creatinine concentration to above 2.0 mg/dL (177 micromol/L) was 1.3 to 1.4 percent [3].

- A retrospective report of 2125 patients in which the likelihood of attaining or maintaining a plasma creatinine concentration above 2 mg/dL (177 micromol/L) was less than 2 percent at five years [22]. Furthermore, 31 percent of these patients had proteinuria at entry (suggesting that they may have had coexisting renal disease), and there was no relation

between changes in the plasma creatinine concentration and the degree of diastolic blood pressure control (<95 mmHg versus ≥95 mmHg).

In the aggregate, these observations suggest four, not mutually exclusive, possibilities to explain the apparently high incidence of hypertensive nephrosclerosis as a cause of end-stage renal disease (ESRD):

- The number of hypertensive patients is so large that even the small percentage at risk constitutes a large number.
- The rate of progression is generally so slow that many patients at risk cannot be detected by five-to-seven-year studies.
- In the absence of a kidney biopsy, many patients (particularly nonblack patients) diagnosed as having hypertensive nephrosclerosis may actually have a different cause of kidney disease.
- African-American patients have a unique genetic variant that likely interacts with hypertension, which is responsible for their propensity to focal and segmental glomerulosclerosis and ESRD. (See "Focal segmental glomerulosclerosis: Genetic causes", section on 'FSGS in African Americans'.)

Long-term follow-up from the MRFIT trial, in which over 322,000 men were screened for possible entry, are compatible with the first hypothesis [23]. A direct correlation was found between the initial blood pressure (measured on only one occasion) and, at 16-year follow-up, the development of ESRD of any cause [22]. The adjusted relative risk increased from 1.0 in those with optimal blood pressure (<120/<80 mmHg) to 1.9 with high-normal blood pressure, 3.1 with mild hypertension, 6.0 with moderate hypertension, and 11.2 with severe hypertension (figure 1). There were also data compatible with a very low percentage of patients with a blood pressure of 140 to 159/90 to 99 mmHg being at risk. The age-adjusted rate of ESRD in this group was only 0.34 percent at 16 years.

DIAGNOSIS

The diagnosis of benign hypertensive nephrosclerosis is generally **inferred** from the characteristic clinical features and the exclusion of other kidney diseases since kidney biopsy is infrequently performed. Affected patients usually have a long history of hypertension that is typically accompanied by left ventricular hypertrophy, a relatively normal urine sediment, small kidneys, and, if previous information is available, slowly progressive renal insufficiency with gradually increasing proteinuria that is usually nonnephrotic [1,19,24]. In the future, recognition

of the variants on the apolipoprotein 1 (*APOL1*) gene on chromosome 22 will likely provide a sensitive and specific diagnostic tool in black patients [25].

Most important from a clinical viewpoint, the hypertension **precedes** the development of either proteinuria or renal insufficiency, and there is no other obvious cause of renal disease [26]. By comparison, patients with one of the other more common causes of the nephrotic syndrome, such as membranous nephropathy or minimal change disease, typically present with moderate to heavy proteinuria and edema. Other glomerular diseases may be heralded by signs and symptoms other than hypertension and mild to moderate proteinuria. (See "Glomerular disease: Evaluation and differential diagnosis in adults".)

When the historical data are incomplete, a clinical diagnosis of benign nephrosclerosis may be incorrect unless confirmed by renal biopsy [24]. This is particularly true in nonblack patients in whom hypertensive end-stage renal disease (ESRD) is much less common in the absence of malignant hypertension [26,27]. On the other hand, nephrologists are more likely to ascribe otherwise unexplained renal failure to hypertension in black patients [28].

There is one disorder that commonly presents with similar findings to hypertensive nephrosclerosis but is potentially **reversible**: ischemic renal disease due to bilateral renal artery stenosis [5]. These patients are more likely to have a history of severe or refractory hypertension, an acute elevation in blood pressure over a previously stable baseline, or relatively rapid deterioration of renal function due to more complete occlusion of one or both renal arteries or to removal of angiotensin-driven renal perfusion by angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) therapy. (See "Clinical manifestations and diagnosis of chronic kidney disease resulting from atherosclerotic renal artery stenosis".)

Although not commonly performed, a definitive diagnosis of hypertensive nephrosclerosis can be made only by renal biopsy. In general, we perform a renal biopsy in patients who have unexplained chronic kidney disease, normal-sized kidneys, and a progressive decline in glomerular filtration rate (GFR), proteinuria, or abnormal urine microscopy. (See "Chronic kidney disease (newly identified): Clinical presentation and diagnostic approach in adults".)

TREATMENT

The likelihood of progressing to renal failure is directly related to the degree of blood pressure control (figure 2). Episodes of accelerated hypertension (which may be unrecognized) can enhance the rate of disease progression [3]. On the other hand, effective treatment of the hypertension to a diastolic pressure below 90 mmHg usually prevents continued renal injury,

although, as noted above, there is little evidence that diastolic pressures of 95 to 100 mmHg are harmful to the kidney over a five-year period [22].

There are, however, two issues that are important to consider:

- Does the type of antihypertensive therapy matter (ie, are angiotensin-converting enzyme [ACE] inhibitors more protective in nephrosclerosis as they appear to be in many other forms of renal disease?)?
- What level of blood pressure control provides the maximum degree of renal protection?

There are, as yet, no definitive answers to these questions, but some data are available.

Choice of antihypertensive agent — ACE inhibitors and angiotensin II receptor blockers (ARBs) are the drugs of choice for renal protection in patients with proteinuric chronic kidney disease [29] (see "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults"). Whether they are also protective in patients with benign nephrosclerosis was best addressed in the African American Study of Kidney Disease and Hypertension (AASK). Such trials of antihypertensive therapy for hypertensive nephrosclerosis are lacking in other racial groups.

AASK trial — The issue of renal protection in black patients with presumed nephrosclerosis was also addressed in part in the African American Study of Kidney Disease and Hypertension (AASK) [30,31]. This trial included 1094 African Americans with longstanding hypertension, otherwise unexplained slowly progressive chronic kidney disease, and proteinuria (mean approximately 500 to 600 mg/day); as mentioned above, this pattern in black patients was shown to be almost always associated with histologic changes compatible with nephrosclerosis as the sole disease [19].

The patients were allocated to one of three drugs: ramipril (436 patients), metoprolol (441 patients), or amlodipine (217 patients) and to one of two blood pressure goals, 125/75 or 140/90 mmHg. The primary end point was the rate of change in glomerular filtration rate (GFR); the secondary clinical composite outcome was the time to first event including a 50 percent reduction in GFR, an actual decrease in GFR of 25 mL/min per 1.73 m^2, the onset of renal failure, or death. The main conclusions of the trial were similar using the serum creatinine concentration or iothalamate clearance to estimate GFR [32].

At interim analysis, all patients receiving ramipril were compared with all those receiving amlodipine [30]. Among patients with proteinuria, the rate of loss of GFR after the first three months and incidence of the secondary composite end point were significantly **lower** in the ramipril arm. This suggested that there would be no additional information gained from continuing those with less proteinuria, and the amlodipine arm was terminated.

At study end, after approximately four years, the average blood pressure was 128/78 and 141/85 mmHg in the lower and usual blood pressure group, respectively [31,33]. The mean rate of change in GFR and the rate of the secondary composite end point were **similar** with both blood pressure goals, suggesting that the lower blood pressure goal may not provide further benefit in slowing progression of the renal disease. (See 'Goal blood pressure' below.)

With respect to the different antihypertensive agents, the following results were reported:

- Patients treated with ramipril had a significantly **decreased** risk of the secondary clinical composite outcome when compared with those treated with metoprolol (6.9 versus 8.7 percent per year, risk reduction 22 percent, 95% CI 1-38 percent) or amlodipine (risk reduction 38 percent, 95% CI 14-56 percent). There was no significant difference between the amlodipine and metoprolol groups.
- Significant differences in the slope of the GFR were not consistently observed with any of the drug group comparisons.

Subjects who did not progress to end-stage renal disease (ESRD) during the AASK trial continued to be followed for a total of 10 years. This follow-up study suggested that neither aggressive blood pressure lowering nor the benefits of ACE inhibition affected the long-term rate of chronic kidney disease progression among these patients [34]. Despite an achieved mean blood pressure of 133/78 mmHg, for example, the majority of patients (67 percent) had a yearly decline in GFR of greater than 1 mL/min per 1.73 m^2. However, the benefits of ACE inhibition were probably obscured by the fact that patients who did not receive ramipril during the trial switched over and received ramipril during the extended follow-up (ie, 80 to 90 percent of all participants received an ACE inhibitor during the cohort phase).

On the other hand, the effects of ACE inhibition and a more aggressive blood pressure goal in the AASK trial differed according to whether or not patients had proteinuria, with benefits observed in proteinuric but not nonproteinuric patients. This observation was also evident in a subsequent analysis with extended follow-up [35]. These issues, and our recommendations for therapy in patients with hypertensive nephrosclerosis and other nondiabetic renal disease, are discussed separately:

- (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'AASK trial of antihypertensive therapy'.)
- (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Management'.)

- (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'AASK trial of goal blood pressure'.)

Recommendations for treatment of hypertension in black patients with relatively normal renal function are discussed elsewhere. (See "Treatment of hypertension in black patients".)

Goal blood pressure — Recommendations regarding goal blood pressure for patients with presumed hypertensive nephrosclerosis are discussed elsewhere. (See "Antihypertensive therapy and progression of nondiabetic chronic kidney disease in adults", section on 'Blood pressure goal'.)

Progression despite blood pressure control — In some patients, the plasma creatinine concentration and degree of proteinuria continue to rise despite seemingly good control of the systemic blood pressure. Why such patients are susceptible to progressive renal injury is not known [5]. It is possible, for example, that the variants on gene apolipoprotein 1 (*APOL1*) may play an important role in this setting or that some of these patients have a different renal disease that is exacerbated by hypertension. A discussion that also reviews the mechanisms by which the institution of antihypertensive therapy can lead to an acute, reversible decline in GFR can be found elsewhere. (See "Effect of antihypertensive treatment on kidney function in primary (essential) hypertension".)

Not surprisingly, patient survival in those who progress to dialysis is generally less than that in patients with primary glomerular diseases. This increase in risk, which is also seen in diabetics, largely reflects the associated extrarenal vascular disease. (See "Patient survival and maintenance dialysis".)

Improvement of renal function — Although hypertensive nephrosclerosis is usually progressive, long-term improvement in renal function is observed in a minority of patients. This was shown in a post-hoc analysis of the AASK trial mentioned above, in which GFR was estimated a median of 16 times during 12 years of follow-up [36]. A positive slope (indicating an improvement of GFR) was present in 3 percent of patients; the GFR in these individuals improved at a rate of 1.1 mL/min per 1.73 m^2 per year. Compared with patients whose renal function did not improve, those whose renal function improved were younger (51 versus 55 years), had lower median baseline urine protein-to-creatinine ratios (0.04 versus 0.07 g/g), and were more likely to have been randomly assigned to the lower target blood pressure (77 versus 49 percent). (See 'AASK trial' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic kidney disease in adults".)

SUMMARY AND RECOMMENDATIONS

- Hypertensive nephrosclerosis is a renal disorder associated with chronic hypertension. Risk factors include black race associated with genetic variants, severe hypertension, and underlying chronic kidney disease, especially diabetic kidney disease. (See 'Introduction' above and 'Clinical manifestations' above.)
- Characteristic histologic findings include vascular, glomerular, and tubulointerstitial lesions. (See 'Pathology' above.)
- Patients present with a long history of hypertension that is typically accompanied by retinopathy and left ventricular hypertrophy and which precedes the development of either proteinuria or renal insufficiency. (See 'Clinical manifestations' above.)
- Patients present with elevations in blood urea nitrogen (BUN) and serum creatinine concentrations. Protein excretion is usually less than 1 g/day, although greater amounts can occur. Hyperuricemia may be observed. The urinalysis is typically benign, with the sediment revealing few cells or casts. The rate of progression of renal disease is generally slow.
- The diagnosis of hypertensive nephrosclerosis is generally inferred from the characteristic clinical features; confirmation by renal biopsy is rarely indicated. Other obvious causes of renal disease should be excluded, especially bilateral renal artery stenosis. Patients with renal artery stenosis are more likely to have severe or refractory hypertension, an acute elevation in blood pressure over a previously stable baseline, or relatively rapid deterioration of renal function due to more complete occlusion of one or both renal arteries or to removal of angiotensin driven renal perfusion by angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) therapy. (See 'Diagnosis' above.)
- Effective treatment of the hypertension usually slows progression of renal injury. It is not clear whether ACE inhibitors and ARBs, which are the drugs of choice for renal protection in patients with proteinuric chronic kidney disease, are also protective in patients with benign nephrosclerosis without proteinuria. (See 'Choice of antihypertensive agent' above.)

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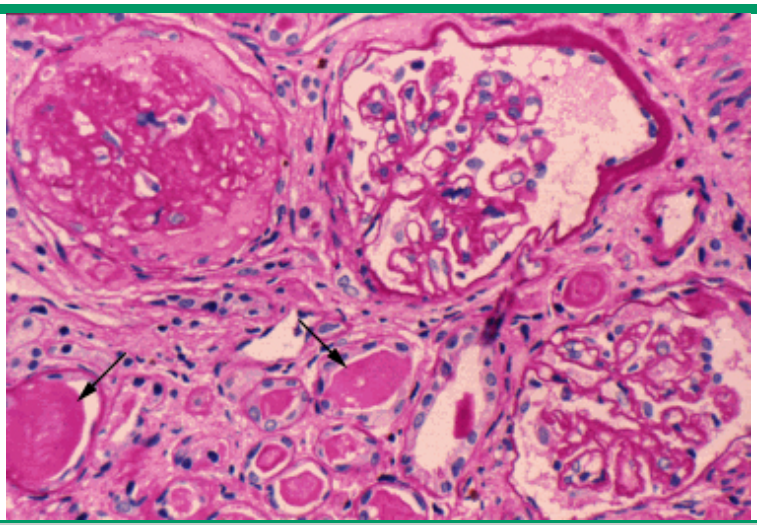
GRAPHICS

Benign nephrosclerosis

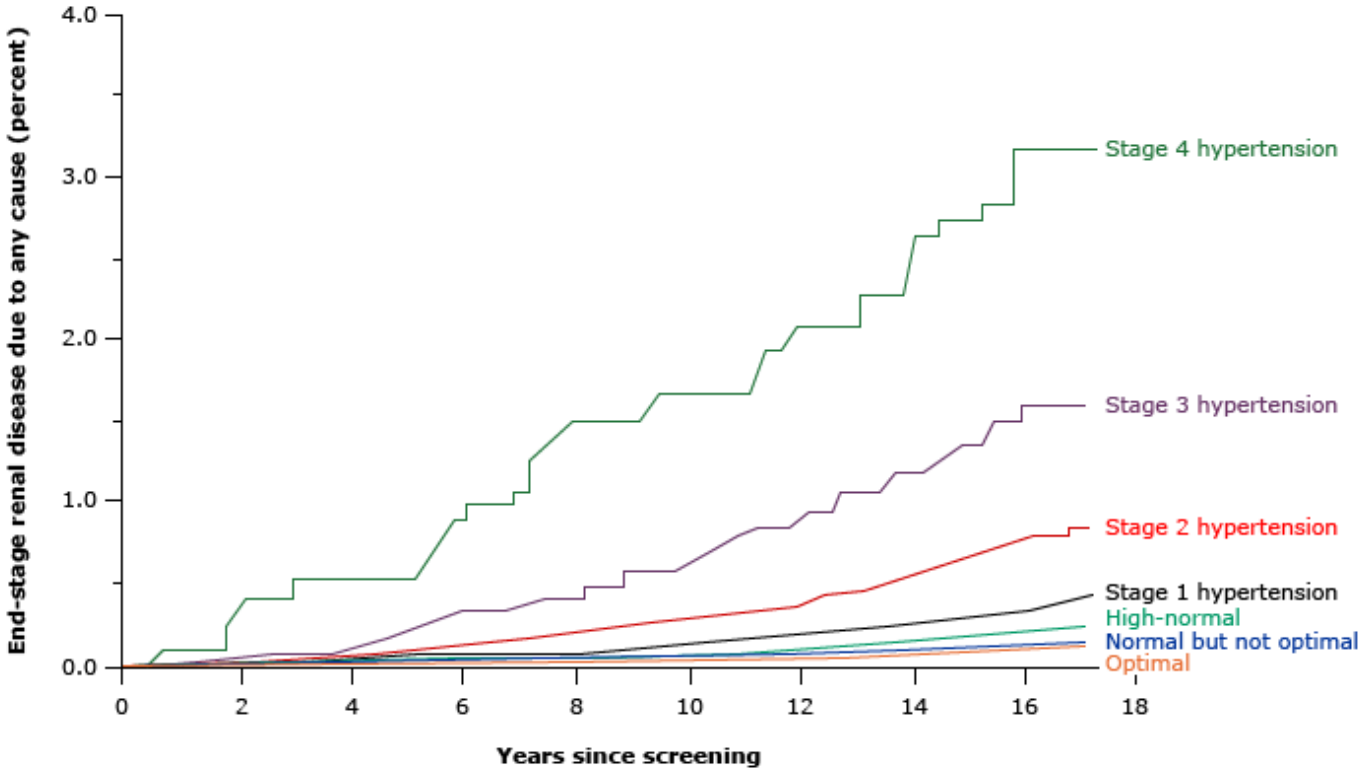


Light micrograph in benign nephrosclerosis showing a completely sclerotic glomerulus (upper left) adjacent to two shrunken glomeruli that are still intact. There is also prominent tubular atrophy and dilatation with intratubular hyaline casts (arrows). These changes are induced by ischemia resulting from arterial and arteriolar thickening (not shown).

Courtesy of Helmut Rennke, MD.

Graphic 53909 Version 2.0

Relation between hypertension and development of ESRD

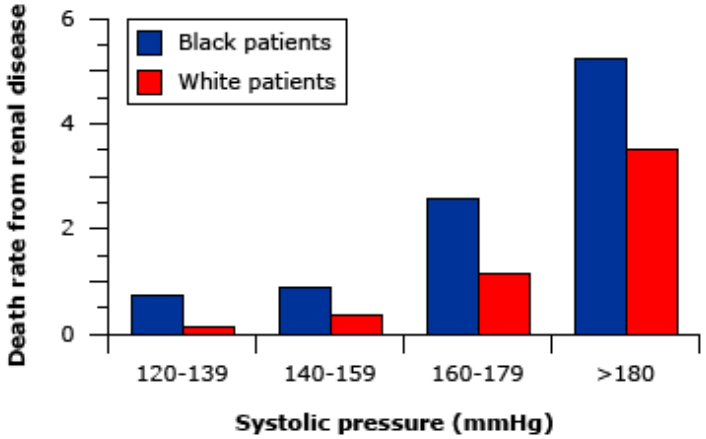


Cumulative incidence of end-stage renal disease (ESRD), due to any cause, according to blood pressure category in 332,544 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) trial. The adjusted relative risk increased from 1.0 in those with optimal blood pressure (<120/<80) to 1.9 with high-normal blood pressure, 3.1 with mild hypertension, 6.0 with moderate hypertension, and 11.2 with severe hypertension. Patients with stage 1 hypertension or lower blood pressure were at very low risk of ESRD at 16 years (≤0.34 percent).

Redrawn from: Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med 1996; 334:13.

Graphic 69454 Version 5.0

Blood pressure and kidney-related mortality in Black patients



Relative risk of death from all causes of renal disease in Black patients and White patients according to systolic blood pressure in almost 350,000 males screened for the Multiple Risk Factor Intervention Trial. Patients with higher systolic pressures and Black patients were at increased risk. A similar trend was seen for increasing diastolic pressures.

Data from Flack JM, Neaton JD, Daniels B, Esunge P. Ethnicity and renal disease: lessons from the Multiple Risk Factor Intervention Trial and the Treatment of Mild Hypertension Study. Am J Kidney Dis 1993; 21 Suppl 1:31.

Graphic 62524 Version 7.0