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Clinical manifestations and diagnosis of chronic kidney disease resulting from atherosclerotic renal artery stenosis

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INTRODUCTION AND DEFINITION — Many but not all patients with atherosclerotic renal artery stenosis have chronic kidney disease (CKD) that is primarily due to a reduction in blood flow induced by the stenosis. In general, clinically apparent CKD (marked by an increase in the serum creatinine) occurs when the stenosis threatens the entire renal mass. Hence, patients with CKD resulting from atherosclerotic renal artery stenosis usually have high-grade stenosis of both renal arteries or stenosis to a solitary functioning kidney.

However, renal artery stenosis may be an "incidental" finding in patients who have CKD that is caused by a separate disorder (eg, diabetic nephropathy). It can be difficult to distinguish between patients whose disease is induced by renal artery stenosis and those who have an alternative cause of CKD.

Ischemic nephropathy is discussed in this topic. Determining which hypertensive patients to evaluate for renal artery stenosis, establishing the diagnosis of renal artery stenosis, and treatment of patients with unilateral or bilateral atherosclerotic renal artery stenosis are presented elsewhere. (See "Evaluation of secondary hypertension" and "Establishing the diagnosis of renovascular hypertension" and "Treatment of unilateral atherosclerotic renal artery stenosis" and "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney".)

In addition, the diagnosis and treatment of fibromuscular dysplasia are discussed in other topics. (See "Clinical manifestations and diagnosis of fibromuscular dysplasia" and "Treatment of fibromuscular dysplasia of the renal arteries".)

DEFINITION AND TERMINOLOGY — Chronic kidney disease (CKD) that results from atherosclerotic renal artery stenosis is frequently called ischemic nephropathy [1-3]. Broadly speaking, "ischemic nephropathy" can refer to a reduction in glomerular filtration rate (GFR) produced by any cause of diminished renal blood flow. In principle, this could include ischemic acute tubular necrosis, intrarenal arterial or capillary obstruction due to vasculitis, coagulation or hemolytic disorders (such as a thrombotic microangiopathy or sickle cell disease), or immune deposits (as with glomerulonephritis).

However, the term ischemic nephropathy is most commonly applied in patients who have CKD due to partial or complete obstruction of one or more extrarenal arteries [1], usually in patients with atherosclerotic disease. Thus, for the purposes of this review, ischemic nephropathy refers to the progressive loss of GFR resulting from atherosclerotic renal artery stenosis.

Although renal injury can develop in any kidney or kidney region beyond a critically stenotic artery, the injury may not be clinically apparent, largely due to adequate function of the unaffected contralateral kidney. As noted above, clinically apparent disease (marked by an increase in the serum creatinine) occurs primarily when the stenosis threatens the entire renal mass. Hence, patients who are diagnosed with ischemic nephropathy usually have high-grade stenosis of both renal arteries or stenosis to a solitary functioning kidney.

PATHOGENESIS — Loss of renal function in renovascular disease can result from a usually reversible consequence of antihypertensive therapy or can reflect progressive narrowing of the renal arteries and/or progressive intrinsic renal disease. Studies in human subjects demonstrate that, despite a moderate reduction in renal

perfusion pressure (up to 40 percent) and in renal blood flow (mean 30 percent), glomerular filtration is reduced but tissue oxygenation within the kidney cortex and medulla can adapt without the development of severe hypoxia [4,5].

However, more advanced vascular occlusion, corresponding to a 70 to 80 percent narrowing of the renal artery [6,7], leads to demonstrable cortical hypoxia that can be measured by blood oxygen level dependent magnetic resonance (BOLD-MR) [8]. In animal studies, this tissue hypoxia produces rarefaction of microvessels, as well as activation of inflammatory and oxidative pathways that lead to interstitial fibrosis [9]. These inflammatory changes and fibrosis are also evident in human "pressor" kidneys that were removed to treat hypertension in patients with a totally occluded renal artery [10]. Although vascular occlusion can initiate these processes, long-standing parenchymal injury characterized by inflammation and fibrosis eventually becomes an irreversible process. At some point, restoring renal blood flow provides no benefit.

EPIDEMIOLOGY — Ischemic nephropathy is an increasingly recognized disorder [1,11-16]. However, few prospective studies have examined the incidence or progression of chronic kidney disease (CKD) among patients with renal artery stenosis. In addition, renal artery revascularization among patients in these studies infrequently produced a meaningful recovery of renal function, which would have supported the diagnosis [17]. Thus, the true incidence and prevalence of ischemic nephropathy is unclear.

Various studies have reported that 5 to 22 percent of patients 50 years or older who have advanced CKD have renal artery stenosis [12,18-23]. However, the renovascular lesions may have been "incidental" in some if not many of these patients. The following examples illustrate the range of findings:

- The natural history of ischemic nephropathy was evaluated in a study of 51 patients with angiographically confirmed bilateral renal artery stenosis (defined as 90 percent or greater stenosis to one kidney and 50 percent or greater to the contralateral kidney) who were followed for up to five years [23]. The median estimated glomerular filtration rate (eGFR) declined from 39 to 24 mL/min per 1.73 m^2 over five years, and 12 percent of patients developed end-stage renal disease, although these individuals had advanced disease at baseline (eGFR 25 mL/min per 1.73 m^2). For various reasons, no patient was revascularized (eg, patient or clinician preference, "unsalvageable" kidneys, patient not suitable for the procedure, or lesion not amenable to the procedure), suggesting that findings may not be applicable to some patients diagnosed with ischemic nephropathy.

- In contrast, progression of kidney disease may be infrequent in those incidentally discovered to have renal artery stenosis. In a study of 593 patients who underwent angiography for peripheral artery disease, 397 had interpretable "drive by" renal angiograms [22]. Of these, 126 had more than a 50 percent stenosis of one or more renal arteries (38 had bilateral stenosis or stenosis to a single functioning kidney). The mean eGFR among these patients was 58 mL/min per 1.73 m^2. After 10 years, renal function remained stable and no patient developed end-stage renal disease.

- Renal artery stenosis is a common finding among patients initiating dialysis. This was shown in a study of 80 consecutive patients initiating hemodialysis as a single center [21]. Of the 49 patients who agreed to undergo computerized tomography angiography (CTA), bilateral renal artery stenosis (defined as a 50 percent or greater diameter reduction) was present in eight patients (16 percent). Three of these patients were not known to have renovascular disease and initiated dialysis with unexplained renal failure.

- Two randomized trials comparing percutaneous transluminal renal angioplasty with medical therapy alone primarily enrolled patients with CKD at baseline [24,25], although most patients had unilateral rather than bilateral stenosis. The incidence of renal endpoints in these trials (defined either as a 20 percent reduction in creatinine clearance or as a composite of acute kidney injury, end-stage renal disease, or renal death) was 19 percent during two to five years of follow-up.

- In a series of 95 patients undergoing surgical revascularization of totally occluded renal arteries, 49 percent had improved renal function, including some with end-stage renal disease who became independent from

dialysis [26]. In a study of 146 patients who had renal artery stenting, only 45 percent experienced stabilization or improvement of their renal function at five years [27]. Such reports provide de facto clinical evidence that some but not all atherosclerotic renovascular disease does produce hemodynamic limitations to kidney function that can improve after revascularization.

The epidemiology of renal artery stenosis in general is presented elsewhere. (See "Establishing the diagnosis of renovascular hypertension".)

CLINICAL MANIFESTATIONS — Patients with ischemic nephropathy typically present as follows:

- A persistent and progressive reduction in glomerular filtration rate (GFR) (ie, chronic kidney disease [CKD]).
- Lack of evidence supporting an alternative cause of renal disease, such as an abnormal urinalysis, proteinuria, a paraprotein, or use of a nephrotoxic drug. (See "Diagnostic approach to the patient with acute kidney injury (acute renal failure) or chronic kidney disease".)
- Findings that suggest the presence of renovascular disease, for example (table 1):
  - Severe hypertension that may be treatment resistant. However, a few patients with ischemic nephropathy are normotensive, which may be due in part to a reduced cardiac output [12].
  - An acute rise in serum creatinine following the administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). This usually, but not invariably, resolves after withdrawal of the drug.
  - Significant variability of serum creatinine concentration that may be due to changes in volume status [28].
  - Recurrent episodes of flash pulmonary edema and/or refractory heart failure.
  - Deterioration of renal function after placement of an endovascular aortic stent graft.

In addition, risk factors for atherosclerotic disease are often present, such as hyperlipidemia, cigarette smoking, and age greater than 50 years. Patients with ischemic nephropathy frequently have coronary artery disease or peripheral arterial disease in other vascular beds. (See "Establishing the diagnosis of renovascular hypertension", section on 'Incidental lesions'.)

In patients with renal artery stenosis, there is a reasonable correlation between estimated glomerular filtration rate (eGFR) and measured GFR (correlation coefficients range from 0.7 to 0.85 depending upon the estimating equation used) [29]. However, changes in measured GFR over time are not always accurately identified by temporal changes in eGFR. During approximately one year of follow-up, the direction of GFR change predicted by estimating equations was discordant with the true direction of GFR change in 28 to 40 percent of patients (depending upon the equation used).

DIAGNOSIS — In patients with clinical manifestations of ischemic nephropathy (see 'Clinical manifestations' above), a presumptive diagnosis of ischemic nephropathy can be made if there is radiologic documentation of significant stenosis of both renal arteries or of one renal artery to a solitary functioning kidney. Indications and options for radiographic imaging of renal artery stenosis and the interpretation of these tests are presented elsewhere. In general, these imaging tests to diagnose renal artery stenosis are warranted if a corrective procedure would be performed should significant renovascular lesions be identified. (See "Establishing the diagnosis of renovascular hypertension".)

As a practical matter, there are two diagnostic elements to consider in patients who could have ischemic nephropathy; these diagnostic elements can impact treatment decisions:

- **Is the vascular occlusive disease posing critical hemodynamic limitation to kidney function?** In general, luminal occlusion of at least 60 to 75 percent is required to limit blood flow and reduce perfusion

pressure [30,31]. This degree of stenosis is usually associated with a measurable translesional pressure gradient of 10 to 15 mmHg [32,33]. Doppler ultrasound criteria conventionally require peak systolic velocities above 180 to 200 cm/sec to identify more than 60 percent luminal occlusion that is verified by pressure gradients [32]. Identifiable levels of cortical hypoxia (measured by blood oxygen level dependent magnetic resonance [BOLD-MR]) are usually associated with translesional velocities above 385 cm/sec [8].

- **Is the condition of the kidneys such that restoring renal blood flow is likely to benefit function?** The condition of the kidneys can be assessed by considering the renal resistive index, the six-month trajectory of renal function, and the size of the kidneys, or by performing a kidney biopsy (which is not usually done). None of these factors predict the outcome of revascularization with certainty. Improved and validated methods to evaluate the salvageability of kidney function in this disorder are sorely needed. Some that have been proposed are as follows:

  - Renal resistive index – Some studies indicate that elevated resistive indices in segmental vessels (above 0.80) measured by duplex ultrasound denote poor prognosis for renal recovery [34] while a low resistive index is a favorable sign [35].
  - Trajectory of renal function – The most consistent predictor of good recovery of kidney function after revascularization has been a recent deterioration of renal function (ie, in the prior six to twelve months) [36].
  - Kidney size – Very small kidneys (less than 7 cm in longest diameter) are usually considered unlikely to recover after revascularization [37].
  - Kidney biopsy – Previous studies suggest that biopsy demonstrating preexisting atheroembolic changes and interstitial fibrosis indicate a limited potential for recovery [38]. Biopsies are not usually performed.
  - Comparison of kidney morphology with kidney function – Some investigators recommend assessing morphologic parameters, such as renal parenchymal volume and cortical thickness with MRI, and comparing these parameters with renal function measured by radionuclide scanning [39,40]. In a stenotic kidney, apparently normal morphology combined with reduced function may indicate a "hibernating kidney" that could be salvaged with revascularization.

A definitive diagnosis is not usually made. In practice, confirmation of the diagnosis is based upon stabilization or improvement of the glomerular filtration rate (GFR) after successful revascularization.

Angiography and revascularization are potentially hazardous, particularly within the severely diseased aorta. Potential complications of revascularization include atheroembolic renal disease and contrast nephropathy. In addition, as noted above, restoring blood flow alone may not reverse the renal disease. Hence, the clinical decision to pursue extensive diagnostic studies and renal artery intervention should weigh renal salvageability against comorbid diseases and risk.

DIFFERENTIAL DIAGNOSIS — Patients at risk for bilateral renal artery stenosis are also at risk for two other disorders that can present with similar clinical findings but cannot be corrected by surgery or angioplasty: hypertensive nephrosclerosis and atheroembolic renal disease.

Hypertensive nephrosclerosis has a similar clinical presentation to chronic ischemic renal disease: hypertension, slowly progressive chronic kidney disease (CKD), an unremarkable urine sediment, and possible evidence of atherosclerotic vascular disease. It is only the presence of the clinical clues described above that suggests the presence of renovascular disease. (See "Clinical features, diagnosis, and treatment of hypertensive nephrosclerosis".)

Atheroembolic renal disease can be precipitated by aortic manipulation or can occur spontaneously. It can generally be distinguished from bilateral renal artery stenosis or nephrosclerosis by an abrupt decline in renal function, evidence of extrarenal emboli (manifested by digital gangrene, livedo reticularis, or abdominal pain), and the transient presence of hypocomplementemia, eosinophilia, and/or eosinophiluria. Arteriography is

contraindicated in this setting since there is a high risk of inducing further embolization. (See "Clinical presentation, evaluation, and treatment of renal atheroemboli" and "Embolism from atherosclerotic plaque: Atheroembolism (cholesterol crystal embolism)".)

TREATMENT — Once a presumptive diagnosis of ischemic nephropathy is made, the management issues are as follows:

- All patients should receive medical therapy to control their hypertension in addition to routine chronic kidney disease (CKD) care and surveillance. Since these individuals have atherosclerotic cardiovascular disease, they should also be aggressively treated for secondary prevention of cardiovascular morbidity with aspirin, statins, cessation of smoking, and, in patients with diabetes, glycemic control. (See "Overview of the management of chronic kidney disease in adults" and "Secondary prevention of cardiovascular disease".)

- In addition to medical therapy and risk factor reduction, **some but not all patients should undergo revascularization** (usually achieved with percutaneous transluminal renal angioplasty plus a stent or, in selected patients, with surgery). This issue and the corresponding treatment recommendations are discussed elsewhere in detail. (See "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney", section on 'Treatment'.)

Results from studies of selected patients with ischemic nephropathy subjected to revascularization suggest that 25 to 30 percent will recover kidney function to a meaningful degree, approximately 50 percent will have little immediate change in kidney function but will "stabilize," whereas approximately 20 percent will have a rapid deterioration of kidney function, possibly related to the procedure [1]. (See "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney", section on 'Treatment'.)

SUMMARY AND RECOMMENDATIONS

- Many but not all patients with atherosclerotic renal artery stenosis have chronic kidney disease (CKD) that is primarily due to a reduction in blood flow induced by the stenosis. In general, clinically apparent CKD (marked by an increase in the serum creatinine) occurs when the stenosis threatens the entire renal mass. Hence, patients with CKD resulting from atherosclerotic renal artery stenosis usually have high-grade stenosis of both renal arteries or stenosis to a solitary functioning kidney. However, renal artery stenosis may be an "incidental" finding in patients who have CKD that is caused by a separate disorder (eg, diabetic nephropathy). It can be difficult to distinguish between patients whose disease is induced by renal artery stenosis and those who have an alternative cause of CKD. (See 'Introduction and definition' above.)

- CKD that results from atherosclerotic renal artery stenosis is frequently called ischemic nephropathy. Broadly speaking, "ischemic nephropathy" can refer to a reduction in glomerular filtration rate (GFR) produced by any cause of diminished renal blood flow. However, the term ischemic nephropathy is most commonly applied in patients who have CKD due to partial or complete obstruction of one or more extrarenal arteries, usually in patients with atherosclerotic disease. (See 'Definition and terminology' above.)

- Despite a moderate reduction in renal perfusion pressure (up to 40 percent) and in renal blood flow (mean 30 percent), glomerular filtration is reduced but tissue oxygenation within the kidney cortex and medulla can adapt without the development of severe hypoxia. However, more advanced vascular occlusion, corresponding to a 70 to 80 percent narrowing of the renal artery, leads to demonstrable cortical hypoxia. In animal studies, this tissue hypoxia produces rarefaction of microvessels, as well as activation of inflammatory and oxidative pathways that lead to interstitial fibrosis. Although vascular occlusion can initiate these processes, long-standing parenchymal injury characterized by inflammation and fibrosis eventually becomes an irreversible process. (See 'Pathogenesis' above.)

- Patients with ischemic nephropathy typically present as follows (see 'Clinical manifestations' above):

- A persistent and progressive reduction in GFR (ie, CKD).
- Lack of evidence supporting an alternative cause of renal disease, such as an abnormal urinalysis, proteinuria, a paraprotein, or use of a nephrotoxic drug.
- Findings that suggest the presence of renovascular disease (table 1), for example: severe hypertension that may be treatment resistant, an acute rise in serum creatinine following the administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), significant variability of serum creatinine concentration that may be due to changes in volume status, recurrent episodes of flash pulmonary edema and/or refractory heart failure, and deterioration of renal function after placement of an endovascular aortic stent graft.
- In addition, risk factors for atherosclerotic disease are often present, such as hyperlipidemia, cigarette smoking, and age greater than 50 years. Patients with ischemic nephropathy frequently have coronary artery disease or peripheral arterial disease in other vascular beds.

- In patients with clinical manifestations of ischemic nephropathy, a presumptive diagnosis of ischemic nephropathy can be made if there is radiologic documentation of significant stenosis of both renal arteries or of one renal artery to a solitary functioning kidney. As a practical matter, there are two diagnostic elements to consider in patients who could have ischemic nephropathy; these diagnostic elements can impact treatment decisions (see 'Diagnosis' above):

  - Is the vascular occlusive disease posing critical hemodynamic limitation to kidney function? In general, luminal occlusion of at least 60 to 75 percent is required to limit blood flow and reduce perfusion pressure. This degree of stenosis is usually associated with a measurable translesional pressure gradient of 10 to 15 mmHg. Doppler ultrasound criteria conventionally require peak systolic velocities above 180 to 200 cm/sec to identify more than 60 percent luminal occlusion that is verified by pressure gradients.
  - Is the condition of the kidneys such that restoring renal blood flow is likely to benefit function? The condition of the kidneys can be assessed by considering the renal resistive index, the six-month trajectory of renal function, and the size of the kidneys, or by performing a kidney biopsy (which is not usually done). None of these factors predict the outcome of revascularization with certainty.

- A definitive diagnosis is not usually made. In practice, confirmation of the diagnosis is based upon stabilization or improvement of the GFR after successful revascularization. (See 'Diagnosis' above.)

- Patients at risk for bilateral renal artery stenosis are also at risk for two other disorders that can present with similar clinical findings but cannot be corrected by surgery or angioplasty: hypertensive nephrosclerosis and atheroembolic renal disease. (See 'Differential diagnosis' above.)

- Once a presumptive diagnosis of ischemic nephropathy is made, patients should receive medical therapy to control their hypertension in addition to routine CKD care and surveillance. Since these individuals have atherosclerotic cardiovascular disease, they should also be aggressively treated for secondary prevention of cardiovascular morbidity with aspirin, statins, cessation of smoking, and, in patients with diabetes, glycemic control. In addition to medical therapy and risk factor reduction, **some but not all patients should undergo revascularization** (usually achieved with percutaneous transluminal renal angioplasty plus a stent or, in selected patients, with surgery). This issue and the corresponding treatment recommendations are discussed elsewhere in detail. (See 'Treatment' above and "Treatment of bilateral atherosclerotic renal artery stenosis or stenosis to a solitary functioning kidney", section on 'Treatment'.)

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GRAPHICS

Clinical features of the different causes of secondary hypertension

Disorder	Suggestive clinical features
General	Severe or resistant hypertension
	An acute rise in blood pressure over a previously stable value
	Proven age of onset before puberty
	Age less than 30 years with no family history of hypertension and no obesity
Renovascular disease	An acute elevation in serum creatinine of at least 30 percent after administration of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)
	Moderate to severe hypertension in a patient with diffuse atherosclerosis, a unilateral small kidney, or asymmetry in renal size of more than 1.5 cm that cannot be explained by another reason
	Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema
	Onset of stage II hypertension after age 55 years
	Systolic or diastolic abdominal bruit (not very sensitive)
Primary renal disease	Elevated serum creatinine concentration
	Abnormal urinalysis
Oral contraceptives	New elevation in blood pressure temporally related to use
NSAIDs	
Stimulants (eg, cocaine, methylphenidate)	
Calcineurin inhibitors	
Antidepressants	
Pheochromocytoma	Paroxysmal elevations in blood pressure
	Triad of headache (usually pounding), palpitations, and sweating
Primary aldosteronism	Unexplained hypokalemia with urinary potassium wasting; however, more than one-half of patients are normokalemic
Cushing's syndrome	Cushingoid facies, central obesity, proximal muscle weakness, and ecchymoses
	May have a history of glucocorticoid use
Sleep apnea syndrome	Primarily seen in obese men who snore loudly while asleep
	Daytime somnolence, fatigue, and morning confusion
Coarctation of the aorta	Hypertension in the arms with diminished or delayed femoral pulses and low or unobtainable blood pressures in the legs

	Left brachial pulse is diminished and equal to the femoral pulse if origin of the left subclavian artery is distal to the coarct
Hypothyroidism	Symptoms of hypothyroidism
	Elevated serum thyroid stimulating hormone
Primary hyperparathyroidism	Elevated serum calcium

Graphic 56130 Version 6.0

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