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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Recognizing and managing fibromuscular dysplasia

ABSTRACT

Fibromuscular dysplasia typically occurs in young women and most commonly presents with hypertension, transient ischemic attack, stroke, or an asymptomatic cervical bruit. The disease is nonatherosclerotic and noninflammatory and most often affects the renal and carotid arteries, although almost any artery can be involved. On angiography, affected blood vessels characteristically resemble a string of beads in the most common type of fibromuscular dysplasia, medial fibroplasia. Patients with renal artery stenosis and hypertension or renal impairment should be treated with percutaneous transluminal angioplasty without a stent. Patients with fibromuscular dysplasia of the internal carotid artery should also be treated with angioplasty if they develop focal neurologic symptoms such as a transient ischemic attack or stroke.

MANY PHYSICIANS consider fibromuscular dysplasia to be rare, but it is not that uncommon: it is often simply overlooked or misdiagnosed.

When fibromuscular dysplasia occurs in the renal arteries (the most common location), its most usual presentation is the onset of hypertension at a young age (< 35 years). Many patients have an accompanying systolic and early diastolic epigastric bruit. When it occurs in the carotid arteries (the second most common location), most patients have an asymptomatic carotid bruit, but some also present with transient ischemic attack or stroke.

This article gives an overview of the disease, including how it typically presents, how it is diagnosed, and how it should be treated. Cases are provided to illustrate its different presentations and courses.

CHALLENGES OF AN UNUSUAL DISEASE

Because fibromuscular dysplasia is not commonly recognized, no large, randomized prospective trials have been done to help guide therapy. Recommendations must be based only on a few small case series, multiple case reports, and the recommendations of experts who frequently encounter this condition.

In recent years the Fibromuscular Dysplasia Society of America has made great strides in increasing awareness of this disease, educating and supporting patients and their families, and promoting research. Its Web site (**www.fmdsa.org**) offers a wealth of information for patients and physicians. Because funding from public and private sources is scant for less-common diseases, the society is funding an international patient registry to facilitate research in this important disease.

The Fibromuscular Dysplasia Society of America is making great strides in increasing awareness of this disease

CAUSE IS UNKNOWN

Fibromuscular dysplasia is not atherosclerotic and not inflammatory. Although a variety of genetic, mechanical, and hormonal factors have been proposed, the cause of fibromuscular dysplasia remains unknown. It is more common among first-degree relatives of patients with the disease, but many patients have no family history of fibromuscular dysplasia.

Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

Case 1: A 34-year-old woman with hypertension

A 34-year-old woman is found to have a blood pressure of 180/98 mm Hg and a systolic/diastolic bruit in the epigastrium. Her physician orders computed tomographic angiography, which reveals a macroaneurysm and beading in the branches of the renal artery, indicating medial fibroplasia (FIGURE 1).

The patient undergoes percutaneous balloon angioplasty of the right renal artery, followed by aortorenal bypass of the left renal artery. The procedures appear to be successful on postoperative angiography, and her blood pressure returns to normal (110/70 mm Hg), requiring no medications.

However, when the patient returns for follow-up 3 months later, her blood pressure has risen to 155/92 mm Hg. Her physician orders a duplex ultrasonography scan; her peak systolic velocity is markedly increased at 314 cm/second, and the end-diastolic velocity is quite high at 166 cm/second, indicating a very severe stenosis. Color power angiography shows beading.

The patient undergoes angioplasty a second time, and duplex ultrasonography performed after the procedure shows normal velocities (peak systolic velocity 184 cm/second; end-diastolic velocity 86 cm/second), indicating a technically excellent result.

The patient remains normotensive several years after the second procedure.

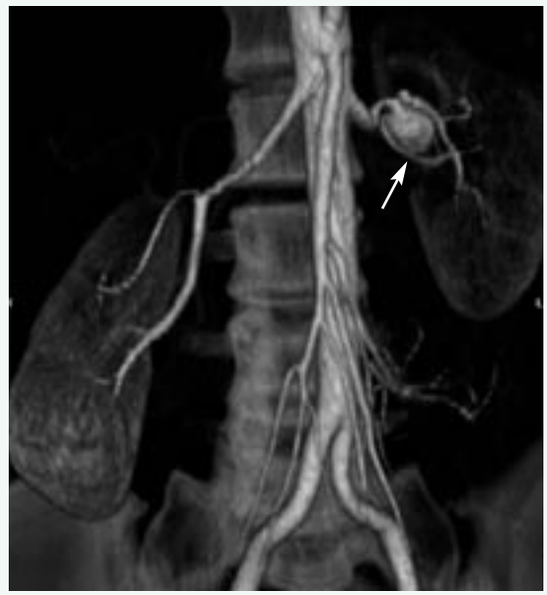

FIGURE 1. Medial fibroplasia and macroaneurysm in the left renal artery (arrow).

Comment. Because the patient had hypertension, treatment was clinically indicated. In addition, a macroaneurysm is one of the few indications for surgery.

AFFECTS RENAL, CAROTID, AND OTHER ARTERIES

Fibromuscular dysplasia can involve almost any artery, but it tends to affect some arteries more than others.[1]

Renal arteries. About 60% to 75% of cases of fibromuscular dysplasia involve the renal arteries, and about 35% of these cases are bilateral.

The carotid or vertebral arteries are involved in 25% to 30% of cases. Intracranial involvement is rare; however, carotid or vertebral artery involvement is associated with intracranial aneurysms in 7% to 51% of cases. The higher number includes patients presenting with subarachnoid hemorrhage. For this reason, all patients who present with carotid or vertebral fibromuscular dysplasia should undergo magnetic resonance angiography to determine if an intracranial aneurysm is present.

Mesenteric arteries. Isolated mesenteric disease occurs but is unusual. When present, it usually coexists with renal artery involvement.

Other arteries. Involvement of nearly every artery has been reported. A few cases of aortic as well as coronary artery involvement have been reported, but whether they are truly manifestations of fibromuscular dysplasia is debatable.

Multiple arterial involvement. In about 28% of cases, multiple arterial systems are involved, a condition that may mimic necrotizing vasculitis. The renal arteries are almost always involved. Pate et al[2] reported on seven patients with fibromuscular dysplasia of the renal arteries and, in the opinion of the authors, the coronary arteries as well. The involved coronary arteries had long, smooth

areas of narrowing, and unlike in severe diffuse atherosclerotic disease, all other coronary segments were angiographically normal.

THREE HISTOLOGIC TYPES

Fibromuscular dysplasia is classified histologically according to whether it predominately affects the arterial media, intima, or adventitia.[3]

Medial dysplasia

Medial dysplasia is further subdivided into three histologic types:

Medial fibroplasia accounts for about 75% to 80% of all cases of fibromuscular dysplasia.

On angiography, the affected artery resembles a string of beads in which the beads are larger in diameter than the normal artery (FIGURE 2). When it occurs in the renal arteries, the abnormality tends to be in the middle and distal portion of the main renal arteries and its branches. In contrast, atherosclerotic renal artery disease tends to be located at the origin or proximal portion of the artery.

On histologic cross-section of the artery, the media has both very thin and very thick areas without inflammatory cells. The thin areas may develop aneurysms in a minority of patients.

Perimedial fibroplasia accounts for fewer than 10% of cases of fibromuscular dysplasia. It tends to occur in girls between 5 and 15 years old. It may progress to renal failure if left untreated.

Like medial fibroplasia, perimedial disease also resembles a string of beads but with fewer beads and with diameters smaller than the normal artery size. Collateral arteries often form around the area of stenosis. Histologically, there is extensive collagen deposition in the outer half of the media.

Medial hyperplasia is rare. It appears angiographically as a concentric focal band and histologically as smooth muscle cell hyperplasia without fibrosis. Medial hyperplasia resembles intimal fibroplasia and may not be a distinct condition.

Intimal fibroplasia

Intimal fibroplasia accounts for fewer than 10% of cases of fibromuscular dysplasia. It can be progressive and multifocal and occur in any vascular bed. Patients with intimal disease are more likely to present with ischemic symptoms.

Two types of intimal fibroplasia are evident on angiography. One involves focal band-like narrowing. The other appears as long, smooth narrowing, which may be confused with other vascular diseases such as Takayasu arteritis in young subjects or giant cell arteritis in older patients.

Histologically, the intima is very thick, with circumferential or eccentric collagen deposition. No lipid or inflammatory component is evident. The internal elastic lamina may be fragmented or duplicated.

Patients with medial fibroplasia generally have an excellent prognosis. However, those with intimal disease involving multi-

Medial fibroplasia: Angiographic appearance

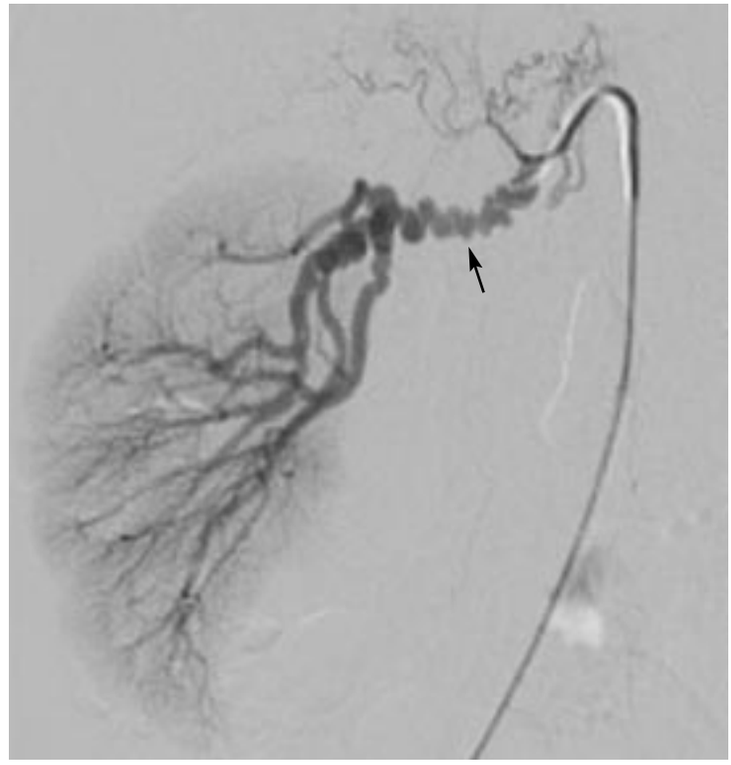

FIGURE 2. Medial fibroplasia of the renal artery, the most common histologic type and location of fibromuscular dysplasia. Note the "string of beads" appearance of the lesion (arrow), in which the beads are larger in diameter than the normal artery. The lesion typically affects the mid to distal portion of the artery but not the ostium.

ADAPTED FROM SLOVUT DP, OLIN JW. FIBROMUSCULAR DYSPLASIA. N ENGL J MED 2004; 350:1862–1871.

TABLE 1

Clues to the diagnosis of renal artery stenosis

Onset of hypertension in a patient younger than 35 years or older than 55 years
Exacerbation of previously well controlled hypertension
Malignant hypertension
Resistant hypertension
Systolic/diastolic epigastric bruit
Unexplained azotemia
Azotemia developing in a patient taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
Atrophic kidney or discrepancy in kidney sizes
Atherosclerosis elsewhere
Sudden development of pulmonary edema
Recurrent congestive heart failure

Fibromuscular dysplasia can be asymptomatic or can mimic necrotizing vasculitis

ple branches of the renal arteries may develop renal artery dissection or progressive renal impairment. In addition, patients with intimal disease in multiple vessels may not have as favorable a prognostic course.

Adventitial (periarterial) fibroplasia

Adventitial (periarterial) fibroplasia accounts for fewer than 1% of cases. Dense collagen replaces the fibrous tissue of the adventitia and sometimes enters the surrounding tissue.

CLINICAL PRESENTATION VARIES

Fibromuscular dysplasia can present in a number of ways, ranging from asymptomatic to a multisystem disorder with a clinical picture that mimics necrotizing vasculitis, involving mesenteric ischemia, renal vascular hypertension, renal failure, claudication, transient ischemic attack, or stroke.

Fibromuscular dysplasia most often presents as either the sudden onset of high blood pressure in a young woman or as a cervical or epigastric bruit in a young woman who is without symptoms. It has also been reported in older patients.[4] Although many young people who are thin have a benign systolic epigastric bruit caused by the crus of the diaphragm compressing the celiac artery, a systolic and diastolic bruit is never normal and is more indicative of fibromuscular disease than atherosclerosis. The diastolic component indicates severe stenosis that causes enough of a pressure gradient for blood to continue to flow during diastole.

Patients with carotid artery involvement usually present at around age 50 years. Many have nonspecific symptoms such as headache, neck pain, light-headedness, tinnitus, dizziness, or altered mentation. Evaluation for syncope, transient ischemic attack, stroke, amaurosis fugax (temporary loss of vision in one eye), subarachnoid hemorrhage, and arterial dissection should include fibromuscular dysplasia in the differential diagnosis. Any patient with the sudden onset of Horner syndrome (ptosis, constriction of the pupil, and facial anhidrosis) must be evaluated for spontaneous dissection of the carotid artery as well as for fibromuscular dysplasia.[5]

The presentation in infants and children younger than 4 years is especially likely to resemble vasculitis. Renal failure is a common presentation in infants and children but is uncommon in adults, although it is occasionally the presenting problem in adults with intimal disease.

Other uncommon presentations in adults include claudication, myocardial infarction, ruptured aneurysm, mesenteric ischemia, or bowel infarction.

A number of conditions are associated with fibromuscular dysplasia: eg, Ehlers-Danlos syndrome type IV, Alport syndrome, pheochromocytoma, and Marfan syndrome.

DIAGNOSIS OF RENAL ARTERY DISEASE

Fibromuscular dysplasia of the renal arteries may be detected incidentally or as part of an evaluation for hypertension. Clues to the diagnosis of renal artery stenosis are listed in **TABLE 1**.

Fibromuscular dysplasia is usually easy to differentiate from atherosclerosis: it tends to occur in young women at low risk for atherosclerotic cardiovascular disease, the coronary

TABLE 2

Results of balloon angioplasty in patients with fibromuscular dysplasia

AUTHORS	YEAR	NO. OF PATIENTS	TECHNICAL SUCCESS (%)	HYPERTENSION CURED (%)	HYPERTENSION IMPROVED (%)	MEAN FOLLOW-UP (MONTHS)
Sos et al[9]	1983	31	87	59	34	16
Baert et al[10]	1990	22	83	58	21	26
Tegtmeyer et al[11]	1991	66	100	39	59	39
Bonelli et al[12]	1995	105	89	22	63	43
Jensen et al[13]	1995	30	97	39	47	12
Davidson et al[14]	1996	23	100	52	22	NR
Klow et al[15]	1998	49	98	26	44	9
Birrer et al[16]	2002	27	100	74*		10
Surowiec et al[17]	2003	14	95	79*		NR
de Fraissinette et al[18]	2003	70	94	14	74	39

*The percentage shown is the total for cured and improved.
NR = Not reported

arteries are rarely involved, and renal artery angiography tends to reveal beading of the renal artery, with involvement in the middle to distal portions.

Duplex ultrasonography of the renal arteries

Duplex ultrasonography is a noninvasive test that is highly specific and sensitive for renal artery stenosis, whether it is caused by atherosclerosis or fibromuscular dysplasia.[6] Duplex ultrasonography involves comparing peak systolic velocity measurements with pulsed-wave Doppler in the aorta and in the renal artery. If the patient is suspected of having fibromuscular dysplasia, it is critical that the laboratory performing the test be told to completely evaluate the renal arteries, including the middle and distal portions of the artery, where the stenosis is likely to be.

A renal-to-aortic peak systolic velocity ratio of at least 3.5 suggests 60% to 99% stenosis. If, in addition, the end-diastolic velocity in the renal artery is at least 150 cm/second, then stenosis is very severe, in the range of 80% to 99%.

Gowda et al[7] found that a combination of color-flow duplex imaging and intravascular ultrasonography depicts blood flow and abnormalities better than renal arteriography, which is the traditional gold standard for diagnosing renal artery fibromuscular dysplasia.

Renal artery angiography

Catheter angiography remains the gold standard for the diagnosis of fibromuscular dysplasia. It is the only imaging technique that can identify disease in both the main renal arteries and the branch vessels.

There are no good studies of the sensitivity and specificity of magnetic resonance angiography in patients with fibromuscular dysplasia. The spatial resolution may not be good enough to detect disease in the branch vessels, and occasionally one may see beading on magnetic resonance angiography when no beading actually exists.

On the other hand, 64-row multidetector computed tomographic angiography can accurately detect fibromuscular dysplasia in the main renal arteries. However, branch disease may be missed with this imaging test as well.

Fibromuscular dysplasia is usually easy to differentiate from atherosclerosis

Case 2: A 50-year-old woman with an asymptomatic cervical bruit

A 50-year-old woman presents to our clinic after her internist discovered a cervical bruit during her annual physical examination. Carotid ultrasonography performed at another hospital was interpreted as showing "bilateral 50% to 55% stenosis of the internal carotid artery in the proximal portion."

The patient has never smoked, exercises regularly, and has no family history of heart or vascular disease.

Her blood pressure is 110/70 mm Hg in both arms. She has a long systolic bruit high up at the angle of the jaw on both sides. She has no epigastric bruit. Her total cholesterol concentration is 160 mg/dL, and the high-density lipoprotein cholesterol concentration is 75 mg/dL.

Comment. Since this relatively young patient had no atherosclerotic risk factors, it would be quite unusual for her to have carotid stenosis in the proximal portion of the carotid artery as reported. When we performed repeat ultrasonography, the proximal portion of the internal carotid artery was normal; however, the velocity in the middle to distal portion of the carotid arteries was markedly elevated at 190 cm/second, which is consistent with a 60% to 79% stenosis. There was marked turbulence, and beading was seen on color power angiography.

Magnetic resonance angiography of the carotid and vertebral arteries demonstrated typical findings of medial fibroplasia (FIGURE 3). An MRA of the intracranial circulation was performed (not shown) to search for intracranial aneurysms. None were found.

Because this patient had normal blood pressure, no symptoms, and no intracranial aneurysms, she was treated only with aspirin as antiplatelet therapy, and she was counseled about the signs and symptoms of transient ischemic attack and stroke.

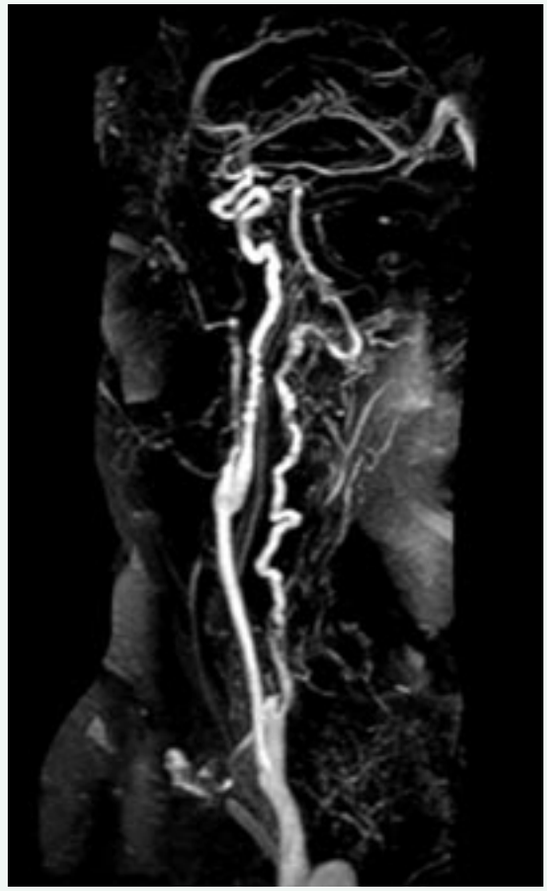

FIGURE 3. Magnetic resonance angiogram of the carotid and vertebral arteries. There is beading in the mid and distal carotid artery and multiple areas of the vertebral artery, consistent with a diagnosis of medial fibroplasia.

TREATMENT OF RENAL ARTERY FIBROMUSCULAR DYSPLASIA

The American College of Cardiology and the American Heart Association recently published guidelines for managing patients with peripheral arterial disease, renal artery disease, and aneurysm.[8]

Balloon angioplasty

Percutaneous balloon angioplasty is recommended for patients with renal artery stenosis due to fibromuscular dysplasia with clinical indications for intervention, ie:

- Recent-onset hypertension (even if well controlled with medication)
- Resistant hypertension

- Intolerance to antihypertensive medications
- Noncompliance with medications
- Renal impairment or loss of renal volume, eg, from ischemic nephropathy.

A number of studies since 1983 have evaluated the role of percutaneous transluminal angioplasty of the renal arteries in patients with fibromuscular renovascular disease and hypertension (**TABLE 2**).[9–18] Over the years, the technical success rate of the procedure has approached 100%. Angioplasty leads to cure or improvement of hypertension in a high percentage of patients with fibromuscular dysplasia. The procedure is safe when performed by an experienced operator, and most complications are minor.

Whether angioplasty is technically successful is often difficult to determine by angiography. Either intravascular ultrasonography at the time of angioplasty or duplex ultrasonography performed shortly after angioplasty can help to determine if the multiple areas of stenosis were adequately treated. We recommend that duplex ultrasonography be performed soon after renal angioplasty. If the velocity is elevated, then the renal artery stenosis has not been adequately treated and the patient needs to return for another procedure.

Stents are not primary therapy

Stents are not recommended as primary therapy, but only for rescuing a suboptimal balloon angioplasty or if a dissection occurs. Not only does balloon angioplasty alone usually offer definitive therapy, but if a stent in a middle or distal lesion results in restenosis, surgical revascularization may be more difficult since it would then involve repair of a branch renal artery.

Surgery

Surgery should generally be used only to treat macroaneurysms. Selected patients with complex arterial disease that extends into the segmental arteries can also be considered for surgery, but a trial of angioplasty is generally recommended first.

Watch and wait

Patients without hypertension and with normal renal function should have their kidney size monitored and clinical measures (blood pressure, renal function) followed.

The natural course of fibromuscular dysplasia is difficult to determine.[19] It is difficult to demonstrate progression of disease by angiography. Renal length and cortical thickness may be better indicators of disease progression.[20–22]

DIAGNOSIS AND TREATMENT OF CAROTID ARTERY DISEASE

Patients with a carotid artery bruit should undergo carotid duplex ultrasonography to determine if fibromuscular dysplasia of the carotid artery is present. It is important that the ultrasonographer image the carotid artery as distally as possible, or the fibromuscular dysplasia will be missed. If dysplasia is present, magnetic resonance arteriography of the intracranial circulation is needed to determine if an aneurysm is present.

It is generally recommended that patients with asymptomatic fibromuscular dysplasia be started on aspirin 81 mg daily for stroke prophylaxis. This is an empiric recommendation, since no randomized trials have been conducted in patients with carotid artery fibromuscular dysplasia. For a patient with a transient ischemic attack or stroke, percutaneous angioplasty and antiplatelet therapy are recommended. A stent is needed only if the angioplasty does not produce a technically satisfactory result or if dissection occurs. ■

Angioplasty cures or improves hypertension in most patients with renal artery fibromuscular dysplasia

REFERENCES

1. **Slovut DP, Olin JW.** Fibromuscular dysplasia. N Engl J Med 2004; 350:1862–1871.
2. **Pate GE, Lowe R, Buller CE.** Fibromuscular dysplasia of the coronary and renal arteries? Catheter Cardiovasc Intervent 2005; 64:138–145.
3. **Begelman SM, Olin JW.** Fibromuscular dysplasia. Curr Opin Rheumatol 2000; 12:41–47.
4. **Pascual A, Bush HS, Copley JB.** Renal fibromuscular dysplasia in elderly persons. Am J Kidney Dis 2005; 45:e63–e66.
5. **Schievink WI.** Spontaneous dissection of the carotid and vertebral arteries. N Engl J Med 2001; 344:898–906.
6. **Olin JW, Piedmonte MR, Young JR, DeAnna S, Grubb M, Childs MB.** The utility of duplex ultrasound scanning of the renal arteries for diagnosing significant renal artery stenosis. Ann Intern Med 1995; 122:833–838.
7. **Gowda MS, Loeb AL, Crouse LJ, Kramer PH.** Complementary roles of color-flow duplex imaging and intravascular ultrasound in the diagnosis of renal artery fibromuscular dysplasia: should renal arteriography serve as the "gold standard"? J Am Coll Cardiol 2003; 41:1305–1311.
8. **Hirsch AT, Haskal ZJ, Hertzer NR, et al.** ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive sum-

mary. J Am Coll Cardiol 2006; 47:1239–1312.
9. **Sos TA, Pickering TG, Sniderman K, et al.** Percutaneous transluminal renal angioplasty in renovascular hypertension due to atheroma or fibromuscular dysplasia. N Engl J Med 1983; 309:274–279.
10. **Baert AL, Wilms G, Amery A, Vermylen J, Suy R.** Percutaneous transluminal renal angioplasty: initial results and long-term follow-up in 202 patients. Cardiovasc Intervent Radiol 1990; 13:22–28.
11. **Tegtmeyer CJ, Selby JB, Hartwell GD, Ayers C, Tegtmeyer V.** Results and complications of angioplasty in fibromuscular disease. Circulation 1991; 83(suppl):I-155–I-161.
12. **Bonelli FS, McKusick MA, Textor SC, et al.** Renal artery angioplasty: technical results and clinical outcome in 320 patients. Mayo Clin Proc 1995; 70:1041–1052.
13. **Jensen G, Zachrisson BF, Delin K, Volkmann R, Aurell M.** Treatment of renovascular hypertension: one year results of renal angioplasty. Kidney Int 1995; 48:1936–1945.
14. **Davidson RA, Barri Y, Wilcox CS.** Predictors of cure of hypertension in fibromuscular renovascular disease. Am J Kidney Dis 1996; 28:334–338.
15. **Klow NE, Paulsen D, Vatne K, Rokstad B, Lien B, Fauchald P.** Percutaneous transluminal renal artery angioplasty using the coaxial technique. Ten years of experience from 591 procedures in 419 patients. Acta Radiol 1998; 39:594–603.
16. **Birrer M, Do DD, Mahler F, Triller J, Baumgartner I.** Treatment of renal artery fibromuscular dysplasia with balloon angioplasty: a prospective follow-up study. Eur J Vasc Endovasc Surg 2002; 23:146–152.
17. **Surowiec SM, Sivamurthy N, Rhodes JM, et al.** Percutaneous therapy for renal artery fibromuscular dysplasia. Ann Vasc Surg 2003; 17:650–655.
18. **de Fraissinette B, Garcier JM, Dieu V, et al.** Percutaneous transluminal angioplasty of dysplastic stenoses of the renal artery: results on 70 adults. Cardiovasc Intervent Radiol 2003; 26:46–51.
19. **Schreiber MJ, Pohl MA, Novick AC.** The natural history of atherosclerotic and fibrous renal artery disease. Urol Clin North Am 1984; 11:383–392.
20. **Goncharenko V, Gerlock AJ Jr, Shaff MI, et al.** Progression of renal artery fibromuscular dysplasia in 42 patients as seen on angiography. Radiology 1981; 139:45–51.
21. **Mounier-Vehier C, Lions C, Jaboureck O, et al.** Parenchymal consequences of fibromuscular dysplasia renal artery stenosis. Am J Kidney Dis 2002; 40:1138–1145.
22. **Mounier-Vehier C, Haulon S, Devos P, et al.** Renal atrophy outcome after revascularization in fibromuscular dysplasia disease. J Endovasc Ther 2002; 9:605–613.

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