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Atherosclerosis of the Renal Artery as a Morphological Cause Chronic Kidney Disease

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Abstract: The paper presents the result of successful staged surgical treatment of a patient with ischemic kidney disease caused by atherosclerotic lesions of the renal arteries. Clinically, the patient had signs of ischemic kidney disease in the form of severe azotemia, arterial hypertension. The postoperative period was uneventful. Currently, there has been no progression of azotemia , there are no indications for renal replacement therapy, blood pressure has been stabilized at target values. This clinical observation shows the need for a thorough examination of patients with azotemia and hypertension for the presence of renal artery stenosis.

Key words: ischemic kidney disease, atherosclerosis, narrowing of the renal artery.

Patients with chronic kidney disease (CKD) are at an increased risk of premature mortality, mainly from cardiovascular causes. The association between CKD on hemodialysis and accelerated atherosclerosis was described >40 years ago. However, more recently, it has been suggested that the increase in atherosclerosis risk is actually observed in early CKD stages, remaining stable thereafter. In this regard, interventions targeting the pathogenesis of atherosclerosis, such as statins, successful in the general population, have failed to benefit patients with very advanced CKD. This raises the issue of the relative contribution of atherosclerosis versus other forms of cardiovascular injury such as arteriosclerosis or myocardial injury to the increased cardiovascular risk in CKD. In this review, the pathophysiogical contributors to atherosclerosis in CKD that are shared with the general population, or specific to CKD, are discussed. The NEFRONA study (Observatorio Nacional de Atherosclerosis en NEFrologia) prospectively assessed the prevalence and progression of subclinical atherosclerosis (plaque in vascular ultrasound), confirming an increased prevalence of atherosclerosis in patients with moderate CKD. However, the adjusted odds ratio for subclinical atherosclerosis increased with CKD stage, suggesting a contribution of CKD itself to subclinical atherosclerosis. Progression of atherosclerosis was closely related to CKD progression as well as to the baseline presence of atheroma plaque, and to higher phosphate, uric acid, and ferritin and lower 25(OH) vitamin D levels. These insights may help design future clinical trials of stratified personalized medicine targeting atherosclerosis in patients with CKD. Future primary prevention trials should enroll patients with evidence of subclinical atherosclerosis and should provide a comprehensive control of all known risk factors in addition to testing any additional intervention or placebo.

Stenotic damage to the renal arteries leads to chronic renal hypoperfusion and impaired filtration function. At the same time, morphological changes in an ischemic kidney are associated with both hypoperfusion and recurrent microembolism of the distal bed. This is accompanied by activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. As a result, a persistent increase in blood pressure and the development of complications from the cardiovascular system are formed [10]. Unilateral ischemic kidney injury leads to increased sodium excretion in the contralateral kidney. This compensatory mechanism allows you to compensate for volume overload for a long time. It should be noted that long-term bilateral narrowing of the renal arteries or damage to the artery of the only functioning kidney can lead to the development of chronic renal failure or transient pulmonary edema. [6]. With unilateral damage to the renal artery, the incidence of chronic renal failure is 3.18%, with bilateral stenosis it can reach 55% [3].

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Early reports of renal artery occlusion leading to renal failure were anecdotal, and usually were reported when a positive outcome was achieved with surgical intervention. Meyrier *et al*, however, examined the importance of renovascular disease as a cause of renal impairment and concluded that it was responsible for between 0.5 and 0.9% of the end-stage renal failure program, depending on whether retrospective or prospective analysis was performed. Our group prospectively examined by angiography all patients presenting to a single unit without a proven renal diagnosis, but who had evidence of atherosclerotic disease. This evidence was assessed on the basis of either proven episodes of cerebrovascular, cardiac or peripheral vascular disease or signs of these diseases. We found that these patients accounted for 14% of those over the age of 50 years who were going onto dialysis

Mailloux *et al* have looked at a large dialysis population and calculated that 25% of patients over the age of 60 years have atherosclerotic renovascular disease as the cause of renal failure

In the United Kingdom it is the patient group over the age of 60 years where there has been considerable expansion in the last decade, and therefore, if this trend continues, the importance of atherosclerotic disease will be magnified in the future. It is interesting that both of these articles excluded dialysis patients who had a known renal diagnosis. We have recently reported a patient with adult polycystic kidney disease who reached end-stage renal failure; an investigation in fact revealed renovascular disease as well. The patient did not need dialysis after angioplasty

Peripheral vascular disease is common in older age groups and can be present in association with other causes of renal failure. Specifically, the presence of femoral bruits was found in 85% of cases in one series.

The clinical absence in these patients of iliac or femoral bruits in the presence of vascular disease makes the likelihood of atherosclerotic renal artery stenosis (ARAS) in these patients unlikely in the author's experience. However, a number of patients may have no symptoms of peripheral vascular disease because of comorbid conditions preventing them reaching their claudication distance. In these patients the presence of iliac/femoral bruits is clinically useful. The important issue yet to be clarified is whether or not this is an important cause of renal disease in older type 2 diabetics (non-insulin-dependent diabetes mellitus). In one post-mortem series, 50% of the patients identified as having atherosclerotic renal disease had type 2 diabetes

However, ARAS or even just severe atherosclerotic aortic disease is associated with atheroembolic disease as well as renal artery narrowing. It is unclear how common this problem is as a cause of renal disease in the older population because of the difficulty in interpreting renal biopsy material if it does not contain a cholesterol cleft

The only absolute way to exclude the diagnosis is on a nephrectomy or post-mortem specimen where multiple sections from many areas can be examined.

One feature that has been reported in association with atherosclerotic renal disease with great frequency has been proteinuria. These reports have tended to be anecdotal, but nephrotic range proteinuria has been reported in both renal artery stenosis and atheroembolic disease

It is difficult to ascertain from the literature the true incidence of proteinuria in atherosclerotic nephropathy, but Harden *et al*, in their report on renal artery stenting, give a median proteinuria of 0.95 g per day for their patients with severe atherosclerotic renovascular disease

Demonstration of two specific histological changes not related specifically to experimental ischemic damage. As stated earlier in this article, atheroembolic disease is well described in patients with severe aortic atheroma and also in those with atherosclerotic renal artery narrowing, although in most instances both are present

It has also been shown to be the histological diagnosis in 10% of a large series of patients over the age of 65 years

Recently, focal segmental glomerulosclerosis has been described in association with renal artery stenosis by Thadhani *et al*

In the experimental rat model the predominant features were of interstitial damage, with the authors commenting that the “structure of the glomeruli were suprisingly well preserved” although there was some mild focal segmental mesangial sclerosis

The second piece of evidence is the very variable functional response to revascularization. Even in those studies with a positive outcome there was a progressive loss of function in a large minority of patients

We have recently reported a group of patients with single functional kidneys in whom there was a progressive loss in renal function. Angioplasty was performed and a good initial response was found with a fall in creatinine in all four patients. However, there was a subsequent decline in renal function after the initial improvement, and this was thought to be due to restenosis, yet angiography showed no evidence of restenosis.

This suggests that processes independent of a reduction in renal blood flow were present in these cases. There was proteinuria in three of the four patients suggesting parenchymal disease. Using estimations of individual kidney function, we have not been able to demonstrate an overall improvement in renal function within three months of angioplasty.

The response to angioplasty is variable with a small number of patients benefiting, but in a large number of patients in the published series, progressive renal dysfunction occurred in spite of angioplasty.

The third piece of evidence is based on the clinical observation that a number of patients investigated for atherosclerotic renovascular disease are found to have two equally sized kidneys with a unilateral renal artery stenosis but with impaired renal function. This is not a pattern seen in fibromuscular dysplasia, although it may be a consequence of different age groups for the two conditions. Preliminary results are available using single kidney glomerular filtration rates, which show that size and function based on routine ultrasound bipolar length estimations do not correlate in patients with atherosclerotic renal disease both in kidneys with and without stenosis.

However, it is also an important clinical observation that a number of patients present with severe ARAS and yet relatively preserved renal function but severely symptomatic “flash pulmonary edema.” It is easy to imagine that atheroembolic disease will be present in both kidneys if there is severe aortic atheroma even if there is only a unilateral renal artery narrowing. However, it is important to realize the dramatic production of cytokines by any atherosclerotic lesion. These patients on angiography invariably demonstrate severe aortic atheroma. Figure 1 shows the substances that are produced in atherosclerotic plaques. Many of them under different circumstances have been demonstrated as producing changes in renal and glomerular function. However, the studies that have sought to demonstrate *in situ* transcription of these cytokines within the kidney could not detect upstream production. Cholesterol crystals give us an elegant demonstration of “downstream damage” from the atherosclerotic lesion. It is important to note that the atherosclerotic disease is invariably limited to the first centimeter of the renal artery. In many respects aortic wall disease spills over into the renal artery rather than into intrinsic renal artery disease, as can be seen in fibromuscular dysplasia. The only substance produced by the endothelium that would be degraded between the atherosclerotic aorta and the glomerulus is nitric oxide.

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