The diabetic ischaemic foot – a challenging but treatable condition

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Over the last 25 years there has been considerable progress in the treatment of the diabetic foot as shown by an increased limb survival rate in patients attending multidisciplinary clinics. The initial reduction in amputations was achieved by advances in the care of the diabetic neuropathic foot. When the diabetic foot clinic at King's College Hospital was set up in 1981, it led to a 50% reduction in major amputations, and was able to prevent almost all major amputations of neuropathic feet.[1] At that time, it was difficult to achieve similar results with the ischaemic foot as advanced occlusive arterial disease could not be reversed. With the onset of modern techniques of angioplasty and distal bypass, however, the foot clinic was able to achieve a further 50% reduction in major amputations of the ischaemic foot.[2] Such technical advances in revascularisation have been underpinned by intensive multidisciplinary care of these patients in an integrated care pathway which also manages their considerable comorbidities and multiple diabetic complications, including almost always neuropathy.[3]

An improved understanding of the pathophysiology of the diabetic ischaemic foot provided the rationale for this active approach towards revascularisation and the advent of new procedures, notably angioplasty and bypass of the arteries below the knee, made it possible, supported by increasingly sophisticated arterial imaging techniques such as Duplex and magnetic resonance arteriography.[4] It was previously thought that a microangiopathic arteriolar occlusive disease was responsible for tissue necrosis in the diabetic foot and by implication revascularisation was not useful.[5] Tissue necrosis is now believed to result from poor tissue perfusion caused by narrowing and occlusion of the arteries of the leg, in particular the arteries below the knee, although this is often complicated by a septic occlusive vasculitis of the digital arteries. The practical implication of such a new understanding was that the two important pathologies, namely occlusive tibial disease and infection, were in reality amenable to treatment and thus cure.

Catheter-based revascularisation by means of angioplasty had a major impact in the diabetic patient when its use was extended from the iliac and femoral arteries to those below the knee utilising very narrow catheters originally developed for the coronary arteries. Such endovascular procedures have been feasible and successful in the tibial and peroneal arteries of the diabetic patient.[6] More recently, subintimal angioplasty has been used to recanalise long arterial occlusions in the tibial arteries.[7] Angioplasty must be applied when tissue loss is not extensive and when arterial stenoses and occlusions are still suitable for this procedure. Furthermore, angioplasty has become an important part of the management of the infected ischaemic foot. The diabetic ischaemic foot commonly presents with infection[8] and needs aggressive antibiotic treatment and possible surgical debridement, as well as optimal tissue perfusion to survive.

Patients may, however, present late when there is considerable tissue loss, often secondary to infection, accompanied by extensive occlusive arterial disease which is not amenable to angioplasty. In these circumstances, distal arterial bypass, in particular to the dorsalis pedis artery, which may be relatively spared, has been established as a valuable procedure in conjunction with surgical debridement, adjunctive plastic surgery and antibiotic therapy.[9] Diabetic ischaemic foot patients with end-stage renal disease are the most difficult to treat because of the presence of diffuse disease, greater involvement of the distal and pedal vessels, and extensive tissue necrosis.[4] Bypass can, however, be performed safely and effectively in patients who have undergone renal transplantation[10] and in a dialysis-dependent patient population.[11]

Angioplasty and bypass should not be regarded as competing treatments but as complementary. It is important that they are each applied in a timely and appropriate manner within the organisational framework of a weekly joint vascular clinic, attended by vascular surgeon, diabetologist, podiatrist and nurse and a vascular radiology meeting also attended by the interventional radiologist and vascular laboratory scientist. Angiograms are reviewed and joint decisions made as to the suitability of angioplasty (which is now often performed as a day-case procedure), or alternatively arterial bypass after due review of the patient's comorbidities. After either procedure, patients are followed up closely in the diabetic foot clinic to assess the clinical outcome and the need for further intervention. These patients are the most complex of diabetic patients with a high mortality[12] and the diabetic foot clinic should take them on for life to coordinate their revascularisation procedures, aggressively treat their infections and manage their comorbidities within a multidisciplinary forum.

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The management of proteinuria in diabetes

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The development of proteinuria in a person with diabetes remains the basis of a diagnosis of clinical or overt nephropathy. The appearances of circulating proteins in the urine is mostly dependent upon the permeability of the glomerular basement membrane (GBM), but intra-glomerular capillary pressures and blood flows are also important.

Thickening of the GBM is an early pathological feature of diabetic nephropathy.[1] This is a result of an accumulation of matrix proteins, due to a combination of excess production and decreased breakdown. Excess production may be a response to increased tension in the capillary wall secondary to haemodynamic forces, whereas the decreased breakdown may be secondary to glycaemia-induced inhibition of proteinases. Moreover, glycation of the matrix proteins alters their conformation and electrostatic charge and may prevent enzyme breakdown. The net result of these processes is to make the membrane more permeable to macromolecules, initially to smaller charged proteins, such as albumin, but later to largely more neutral molecules such as immunoglobulins.[2]

In parallel, and perhaps partly causing these pathological changes, are increases in glomerular capillary pressures and flows which animal studies have shown to be a result of afferent and efferent capillary vasodilatation.[3] The afferent capillary appears to be more dilated, thus leading to a net increase in intraglomerular capillary pressure. These changes lead to an increase in glomerular filtration rate – so called hyperfiltration – which has long been recognised as a feature of newly diagnosed human diabetes.

Lowering systemic (and by inference, intraglomerular capillary) blood pressure reduces proteinuria in diabetic and other nephropathies.[4] The development of drugs that inhibit angiotensin II production by blocking the renin angiotensin system (RAS) are particularly effective in this regard. Early clinical observations led to the discovery of activation of the local RAS in the diabetic kidney, and that blockade reduced both hyperfiltration and capillary pressure by reversing arteriolar vasodilatation.[5] Moreover, the demonstration of angiotensin II receptors on glomerular podocytes suggests another mechanism whereby RAS blockade may reduce proteinuria.

The development of sensitive assays for albumin revealed that diabetic patients had increased albuminuria as an early feature of nephropathy.[6] This discovery led to the concept of microalbuminuria or incipient nephropathy, now conventionally defined as an excretion rate of 20–200 μg/min (30–300 mg/day). Microalbuminuria thus provided a surrogate marker for nephropathy and its reduction has been used as a measure of clinical efficacy in nephropathy treatment and prevention.

Use of RAS blocking drugs (specifically angiotensin-converting enzyme inhibitors (ACEI)) in type 1 diabetes has not been shown to prevent the development de novo of microalbuminuria.[7] In hypertensive type 2 patients, however, trandolapril was effective in reducing the incidence of microalbuminuria.[8] Meta-analysis of studies of ACEI in microalbuminuric type 1 patients has shown a 60% reduction in progression to clinical proteinuria (urinary albumin excretion >300 mg/day) and a more than three-fold increase in the likelihood of reverting to normoalbuminuria.[9] In hypertensive microalbuminuric type 2 patients the angiotensin receptor blocker (ARB), irbesartan, achieved similar results.[10] It is notable in both these reports that high doses of the RAS blocking drugs were required. None of these reports, however, reduced the rates of end-stage renal failure or cardiovascular disease. In type 1 diabetic patients with clinical proteinuria, captopril significantly reduced the numbers doubling their baseline serum creatinine (equivalent to halving glomerular filtration rate) by almost 50%.[11] In type 2 diabetes, ARBs had a smaller but still significant effect on the main endpoint.[12,13] Interestingly both studies found a correlation between the magnitude of proteinuria reduction and the effect on doubling of serum creatinine.

Taken together, these studies have led to a near universal adoption of RAS blockade as first-line therapy for diabetic patients with hypertension and/or increased albuminuria.[14] They represent a classic example of how a clinical observation of efficacy leads to greater understanding of basic physiology which leads to better drug targeting and dosimetry. As a consequence of these treatments and other interventions the average period between development of clinical proteinuria and end-stage renal disease has doubled from 7 to 14 years over the last 30 years.[15] This is truly a 'career lifetime advance'.

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