The diabetic foot and renal disease

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Abstract

Diabetic foot disease is one of the most costly complications of diabetes in the UK, and frequently co-occurs with chronic kidney disease (CKD), including end-stage renal disease, in people with diabetes. In addition to the common pathologies underlying each complication of diabetes it is not clear whether each may have an influence on the other. Those with end-stage renal disease are at particular risk of the development of diabetic foot disease, and this risk increases dramatically when renal replacement therapy commences. However, it is now also recognised that the presence of a diabetes-related foot ulcer may accelerate decline in renal function, such that the commencement of renal replacement therapy may be advanced. Potential mechanisms for this include chronic inflammation with circulating inflammatory cytokines and/or repeated episodes of acute kidney injury, particularly in those who have hospital admissions for their diabetic foot disease. Given the poor outcome of foot disease and CKD in this patient cohort, renal units and diabetes foot services should work closely together to ensure that patients are seen regularly by preventative podiatry services, and to ensure that pathways are in place for rapid referral should new foot disease be noticed.

Key words: diabetic foot disease, ulcers, amputation, CKD, dialysis

Introduction

Diabetic foot disease is one of the most costly complications of diabetes in the UK, estimated to cost the NHS approximately £1billion in 2014-15.[1] The majority of the cost is related to the treatment of diabetic foot ulceration in community settings. It is also a leading cause of hospitalisations and amputations.[2,3] The incidence of diabetic foot ulceration (DFU) is thought to be between 2-6% in those living with diabetes, with a lifetime incidence of up to 34%.[4,5]

Chronic kidney disease (CKD) is also common in those living with diabetes and is thought to affect approximately 40-60% of those with a DFU.[6] In the most recent UK Kidney Organisation annual report it was reported that 8,254 adult patients started renal replacement therapy (RRT) for end-stage renal disease (ESRD) in the UK in 2022. Diabetes remained the most common identifiable primary renal disease and continues to account for an increasing proportion of patients starting RRT.[7]

The two conditions, diabetes and CKD, share common pathological risk factors, particularly microvascular disease and atherosclerosis of the supplying arteries. As such it is hardly surprising that the two conditions frequently coexist. Whether these two common complications of diabetes simply co-exist or whether it is possible that they have a bidirectional relationship, with each condition potentially worsening the other, will be explored below.

Risk factors for diabetes-related foot disease and link to CKD

The causes of diabetes-related foot disease are well known. Risk assessment relates to the assessment of neuropathy (loss of protective sensation), peripheral arterial disease and assessment of deformity of the foot.[8]

Uraemia

One factor that may explain an increase in risk of development of foot ulceration in diabetes in those with CKD is the neuropathy caused by the uraemia of renal failure. Uraemia is known to be an independent cause of neuropathy in ESRD. It is the most common neurological complication of CKD, and is said to affect about 90% of dialysis patients.[9]

In patients with CKD, the severity of diabetic peripheral neuropathy is directly correlated with the duration of diabetes, the degree of glycaemic control and the degree of uraemia.[10]

Peripheral arterial disease (PAD)

The link between diabetes, PAD and CKD is well recognised. Data from the US NHANES reported that prevalence of PAD in patients with diabetes was 3-fold higher than those without diabetes, and the risk of PAD increased over 6-fold in patients with eGFR <60 as compared with eGFR ≥60 mL/min/1.73m^2.[11]

The presence of PAD is known to be even higher in people with ESRD,[12,13] and tissue oxygenation may be worsened by both anaemia and by tissue oedema. Both large and small vessel arterial calcification are more prevalent,[14] and this is particularly important in the more distal arteries where the pedal arch may be compromised.[15] One recent study showed that in a cohort of 419 people who underwent distal angiography, those with severe CKD were five times more likely to have loss of patency of the pedal arch due to calcification than those with no CKD.[15]

Renal replacement therapy (RRT) and diabetes-related foot ulceration

In addition to the exacerbation of risk factors for the development of DFUs, as described above, it has been noted that there is a temporal association between the onset of RRT and the incidence of the first foot ulcer in a cohort of patients with diabetes.[16] None of the pathology described above completely explains this.

Circulatory changes during dialysis

One possible explanation is that dialysis induces changes in the circulation of the foot. One small study looking at tissue oxygenation as measured by trans-cutaneous oxygen pressure ($TcpO_2$) in patients with diabetes but who had no previous history of foot ulceration or amputation, showed a trend towards a fall in $TcpO_2$ during and after haemodialysis.[17] A further small study examining the cutaneous microcirculation of the foot before, during and after haemodialysis using a micro-lightguide showed an increase in blood flow in those without diabetes, whereas in patients with diabetes the blood flow fell.[18]

Other factors

Other factors considered possible explanations for this increase in risk of development of foot ulceration include lack of appropriate footwear, or prescribed footwear no longer fitting appropriately when oedema may change peri-dialysis; change in emphasis of care

and inability of patients to access podiatry whilst attending dialysis, and immobilisation with pressure on vulnerable and unprotected heels whilst dialysing.

All of these factors mean that the risk of a poor outcome from diabetes foot ulcers is worse for those on dialysis, with major amputation at six months post presentation with a new ulcer being of particular concern. Data from the National Diabetes Foot Care audit of England and Wales showed that patients undergoing RRT are at very high risk for major amputation, with those on RRT being twice as likely to have a major amputation within six months of presentation than those not on RRT.[19]

Effect of diabetes-related foot ulcers on the renal system

The role of inflammation in neuropathic diabetic foot disease has been extensively discussed recently with particular relation to the pathogenesis of the acute Charcot foot,[20] where it is thought that a foot ulcer may be one of the inflammatory precipitating factors. However, it is also recognised now that there is an inflammatory component to uncomplicated diabetic foot ulcers. One study of the histology of non-infected neuropathic diabetic wound biopsies showed a diffuse and intense inflammatory reaction, which reduced as healing progressed with appropriate off-loading.[21] In addition, local inflammation is known to precede skin breakdown; the foot is said to "heat up" before it breaks down.[22]

These markers of inflammation are not, however, restricted to the foot but may be measured systemically. Studies have found elevated levels of IL6, hs-CRP and fibrinogen, as well as adiponectin and resistin, even in the absence of infection.[23,24]

Inflammation, acute kidney injury and chronic kidney disease

Equally, it is recognised that systemic inflammation is key to the development of acute kidney injury (AKI). A large body of work, mainly in animals, demonstrates that the pathophysiology of AKI is characterised by an inflammatory cascade that propagates and extends the initial renal insult.[25] Other studies showed that damaged or infected cells in distant tissue may release cytokines that increase the development of AKI by upregulating inflammatory responses in the kidney.[26] Although clinical studies are few, there is evidence that a systemic inflammatory response in hospitalised patients with non-severe pneumonia correlates with the incidence and severity of AKI.[27]

If AKI does occur, there is now clinical evidence that this may contribute to the development and progression of CKD,[28,29] and that progression is much more likely in those pre-existing CKD.[30] In a study of exclusively diabetic patients, a single episode of AKI was associated with a more than three-fold increase in the risk of progression to CKD stage 4.[30]

Finally, a study from France showed that in a cohort of hospitalised people with diabetes, those who were admitted with active foot disease had the highest risk of later renal events (end-stage renal disease or a doubling of serum creatinine).[31]

Taken together, these data provide evidence to support the fact that the presence of a chronic diabetic foot ulcer may accelerate a decline in renal function either through an increase in circulating inflammatory cytokines or repeated episodes of AKI, or both. And thus, the development of a foot ulcer may be the reason that people with diabetes and these co-morbidities are accelerated into ESRD and RRT.

Management of people with diabetes on RRT with foot disease

The Joint British Diabetes Societies have produced a series of guidelines on the management of people with diabetes on the haemodialysis unit, and management of foot disease is just one chapter within these guidelines.[32]

Essentially, recommendations for care of people with diabetes on haemodialysis differ little in terms of national recommendations in the care of those at risk of foot disease whilst recognising that all patients undergoing RRT are considered at high risk of future ulceration,[8] and that many have a considerable burden of other co-morbidities. Daily self-foot checking is recommended by Diabetes UK for those assessed at high risk of developing foot disease,[33] although given the difficulty that many people with diabetes, particularly those with other co-morbidities, have in being able to see all areas of their feet and given the very high risk of limb loss in this population, it has been suggested that additional foot checks be done on the dialysis unit. Indeed, monthly foot checks implemented at one large haemodialysis facility in the USA resulted in a 17% decrease in major amputations.[34] The heels of those with diabetes should be protected with an appropriate pressure relieving device whilst the person is dialysing.[32]

Should a new foot problem be identified then rapid referral (within one working day) is recommended by NICE,[8] for review within one further working day by a multidisciplinary footcare team (MDFT). These referral timescales are greatly facilitated where there is a close working relationship, or full integration, between dialysis units and MDFTs, a position that is sadly only the case in a minority of units in England and Wales.[35]

Conclusion

Diabetes-related foot disease is common, as is CKD, and they have shared pathogeneses. However, each may influence the other. If a patient with diabetes has CKD, and particularly if they are on RRT, this considerably worsens the outcomes of diabetic foot disease, in particular the risk of major amputation. Conversely, it is now increasingly recognised that the development of a foot ulcer may accelerate the decline in renal function, particularly in those with pre-existing CKD, such that this may mean patients need to start RRT sooner than anticipated. Given the poor outcome of foot disease and CKD in this patient cohort, renal units and diabetes foot services should work closely together to ensure that patients are seen regularly by preventative podiatry services, and to ensure that pathways are in place for rapid referral should new foot disease be noticed.

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