Comorbidities in the diabetic patient with foot problems

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Article points

1. Engage an interdisciplinary team from the early stage in case of comorbidities.
2. Recognise and treat PAD as soon as possible in the patients with confirmed renal failure.
3. Keep blood pressure within the target range — care should be taken in patients with critical limb ischaemia.
4. Treat the whole patient, not the hole in the patient.

Key words

- Comorbidities
- End stage renal failure
- Interdisciplinary teamwork
- Optimal disease management

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The main causes of diabetic foot problems are neuropathy and peripheral vascular disease, in tandem with trauma and infection. The cornerstones of diabetic foot ulcer treatment are pressure relief, control of infection and maintenance of adequate blood supply to the affected limb. The course and outcome of diabetic foot complications, particularly ulceration, are strongly influenced by comorbidities, such as kidney disease, arterial hypertension, dyslipidaemia, congestive heart failure and mental illness. A holistic patient approach by a well-coordinated and skilled interdisciplinary team is mandatory if successful outcomes are to be consistently achieved.

Diabetes mellitus is complex to manage as it is a disease that is commonly concomitant with other comorbid conditions. As type 2 diabetes is predominantly a disease of middle-aged, overweight and older individuals, many individuals will have one or more concomitant illnesses, e.g. arterial hypertension and dyslipidaemia, heart failure, renal impairment due to diabetic nephropathy, poor eyesight, psychological problems and polypharmacy (Alonso-Morán, 2014). The significant impact of multi-morbidity, defined as presence of two or more long-term health conditions, has become widely recognised in recent years, warranting a specially dedicated issue of a NICE guideline dedicated to this in 2016 (Farmer et al, 2016; NICE, 2016).

Patients with diabetic foot problems are a particularly vulnerable group. For a decade, the diabetic foot has been considered the "cancer of diabetes", since the mortality of diabetic patients with foot ulceration is comparable to the mortality of patients with various malignancies (Armstrong et al, 2007). Due to the multifactorial aetiology of diabetic foot ulceration (DFU), the diabetic foot lies between specialties and requires management by a finely-tuned and skilled interdisciplinary team (Barshes et al, 2013). The interrelation between the comorbid conditions is complex and almost never unidirectional. There is no simple answer to the question which is the cause and which is the consequence. Multi-morbidities in patients with diabetic foot problems have been investigated in many studies (Prompers et al, 2007; Apelqvist et al, 2011; Morbach et al, 2012; Bruun et al, 2013; Choi et al, 2014; Hoffstad et al, 2015; Begun et al, 2016). Most of them have demonstrated that renal failure has a significant influence on the course and outcome of the diabetic foot, but have also confirmed the significant impact of other comorbid conditions.

This paper is an attempt to summarise the evidence for the influence of renal failure, congestive heart failure, dyslipidaemia, neurological disorders and mental illness on the outcome of diabetic foot disease, and to suggest the potential windows of opportunity to improve these outcomes.

Diabetic foot and the kidney

The lower-limb amputation rate among people with end-stage renal disease (ESRD) on dialysis therapy is high in the general population. On its own, ESRD increases the risk for lower-extremity amputation equivalent to three or more other comorbidities (including diabetes) (Tseng et al, 2005; Goldberg et al, 2012). However, the combination of diabetes and ESRD represents one

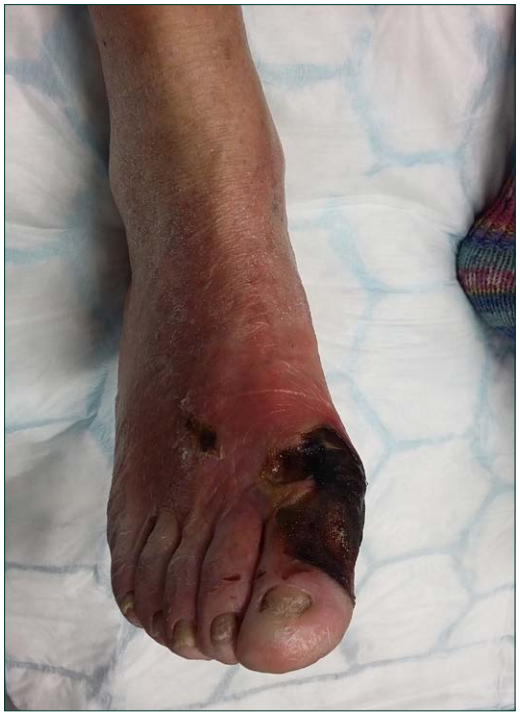


Figure 1. A 67-year-old female with type 1 diabetes for 35 years and peripheral arterial disease, who was blind due to proliferative retinopathy. The individual has end-stage renal disease and is on haemodialysis. After wearing shoes that were too tight, a blister developed on her right great toe. She tore the skin off by herself.

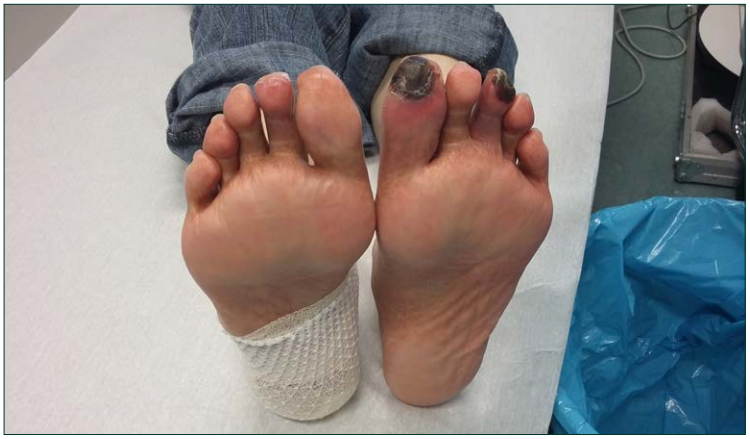
of the strongest risk factors for lower-extremity amputation (Kaminski et al, 2015; Gilhotra et al, 2016). Elevated urinary albumin excretion predicts peripheral arterial disease in type 1 diabetes patients independently of the conventional atherogenic risk factors of duration and control of diabetes (Deckert et al, 1996). Thus, chronic renal failure has been named a "vasculopathic state" (Luke, 1998; McGrath and Curran, 2000), since impaired renal function is associated with an increased prevalence of peripheral arterial disease (O'Hare et al, 2002). Rates of contralateral limb amputation are high both after minor and major amputation, and predicted by renal disease, atherosclerosis, and atherosclerosis with diabetic neuropathy (Glaser et al, 2013).

Due to various pathologies, e.g. uraemia, arterial medial wall calcification, etc, the results of the revascularisation procedures in patients with diabetes and ESRD are generally poor (Jaar et al, 2004). The association between renal failure and foot complications is so strong that Foster and co-workers have even used the term "renal foot" (*Figures 1 and 2*) (Foster et al, 1995).

There are multiple possible mechanisms for the association between diabetes mellitus, renal failure and the progression of macrovascular disease, including altered function of the renin-angiotensin system, arterial hypertension and hyperlipidaemia (Hinchliffe et al, 2006). Activation of the RANKL/NF-kappaB pathway may be involved in the development of medio-calcinosis of the arterial wall (Jeffcoate, 2004), which leads to reduced vessel compliance. Large fluid shifts in patients on dialysis might lead to fluctuations in blood pressure and oedema formation altering tissue perfusion. Haemodialysis induces changes in tissue haemoglobin concentrations and microvascular compliance and may significantly affect toe pressure of the lower extremities in people with diabetes (De Blasi et al, 2009; Kay et al, 2011). Haemodialysis leads to a transient fall in transcutaneous oxygen tension in the feet (Hinchliffe et al, 2006), which might become critical in those with established PAD.

Practical tip: Bearing this in mind, great care must be taken of patients' heels when receiving dialysis as they are often lying still on firm couches for up to 4–6 hours. Try to make it routine for patients to have their feet examined during their dialysis sessions.

Morbach et al (2001) have demonstrated that the coincidence of neuropathy and peripheral vascular disease was more common in diabetic patients on dialysis than in patients without renal impairment.



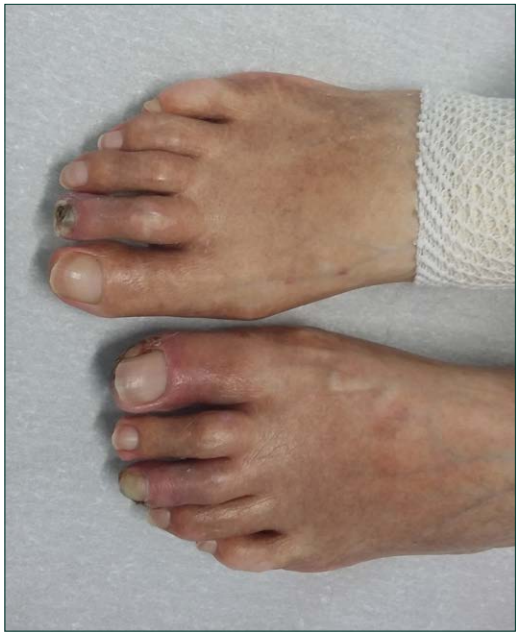


Figure 1. A 56-year-old female, with type 1 diabetes for 54 years, had a combined pancreas-kidney transplant two years ago. The individual also has peripheral arterial disease.

This leads to higher risk of unrecognised non-healing foot lesions. Chronic non-healing foot ulcers create a state of permanent inflammation with elevated circulating levels of various inflammatory cytokines, which could contribute to the progression of kidney failure (Game et al, 2013).

Clinical tip: Ensure that all foot ulcer patients have renal function tests at least once a year.

Diabetic foot and arterial hypertension

Most of the available papers addressing the issue of arterial hypertension and its impact on diabetic foot ulcer/amputation have confirmed a negative influence of arterial hypertension on the course of diabetic foot ulceration. Arterial hypertension is reportedly associated with an increased risk for diabetic microvascular complications (Tracey et al, 2016) and has been recognised as a risk factor for lower-extremity amputation in people with diabetes (Lee et al, 1993; Zubair et al, 2012; Jeon et al, 2017). However, one study from Brazil demonstrated a lower risk for foot ulcer and amputation in those with arterial hypertension (Parisi et al, 2016). The study of Budiman-Mak et al (2016) was the first to confirm the negative influence of systolic pressure variability on the course and outcome of diabetic foot disease.

The potential mechanisms through which arterial hypertension may exert influence on foot ulcer and gangrene development may be multiple — through the influence on arterial wall stiffness (Magalháes et al, 2011), inflammatory induced intimal thickening, altered rheology and plaque formation in the lower extremities or through negative impact on renal function.

Specific evidence for the target values of blood pressure in the patients with critical limb ischaemia is lacking. Good control of hypertension is necessary to avoid the progression of macrovascular complications (stroke, myocardial infarction and congestive heart failure). Overly aggressive antihypertensive treatment, however, may decrease limb perfusion and worsen the symptoms of claudication or critical limb ischaemia, therefore, great care must be taken to ensure that the rate of blood pressure fall is controlled. Acute drops in blood pressure can even lead to the need for amputation (Gardner and Afaq, 2008; Lambert and Belch, 2013). In the retrospective study by Im et al (2016), amputation rates at 12 months after below-knee arteries interventions in patients with critical limb ischaemia were higher in those with controlled hypertension.

Clinical tip: Ensure that hypertension is optimally managed pharmacologically, give lifestyle advice and routinely take blood pressures on those attending clinics with foot ulceration and those stratified at moderate/high ulcer risk.

Diabetic foot and dyslipidaemia

Hyperlipidaemia is a significant risk factor for the progression of atherosclerosis (Beckman et al, 2002). Its role in the pathogenesis of diabetic foot complications has also been confirmed in many clinical trials and meta-analyses (Zubair et al, 2012; Pei et al, 2014). A recent publication from Japan identified high-density lipoprotein (HDL) cholesterol levels as a predictor for lower-extremity amputation in patients with diabetes and foot ulcers. The contemplation of HDL cholesterol levels as a simple marker of the nutritional status was invalidated by the fact that neither triglyceride levels nor low-density lipoprotein (LDL) cholesterol levels were predicting this endpoint (Ikura et al, 2015). Pleiotropic effects of HDL, such as anti-oxidant and anti-inflammatory properties, may play a role (Tabet and Rye, 2009). Accordingly, the study by Sohn et al (2013), which included 83,593 cholesterol drug-naive patients with type 1 or 2 diabetes, was able to demonstrate a significant association between statin use and diminished amputation risk among patients with diabetes (Sohn et al, 2013). In the patients with critical limb ischaemia, statin use after angiography or endovascular intervention was associated with decreased mortality, improved patency of the target vessels and increased likelihood of amputation-free survival (Westin et al, 2014).

Clinical tip: Ensure all patients with foot ulcers are on lipid-lowering agents and monitor their effects. Additionally, check that lifestyle education has been given and understood.

Diabetic foot and cardiovascular disease/ heart failure

Patients with diabetic foot ulcers are at higher risk of all-cause mortality compared with patients with diabetes without a history of DFU. This risk is attributable, to a large extent, to a greater burden of cardiovascular disease (Brownrigg et al, 2012). DFU-patients not only have a higher prevalence of previous cardiovascular morbidity than their ulcer-free counterparts, they also show a higher incidence of new onset vascular events on a 5-year follow-up (Pinto et al, 2008). Together with the high frequency of cardiovascular disease, recent reports indicate that the presence of QT interval prolongation might contribute to the increased mortality rates in patients

Figure 3. A 72-year-old male, with type 2 diabetes for 15 years, arterial hypertension, hyperlipidaemia, peripheral arterial disease and congestive heart failure.

with diabetes and foot ulcers (Fagher and Löndahl, 2013) and those suffering above-ankle amputation (Fagher et al, 2015). Many investigators claim that diabetic foot disease can be regarded as an important cardiovascular risk marker (Löndahl et al, 2008; Tuttolomondo et al, 2015). Congestive heart failure is associated with lower ulcer healing rates, as well as with lower probability of healing overall (Rhou et al, 2015), probably due to lower perfusion and oxygenation in the extremities (*Figure 3*). A study from China demonstrated that the prevalence of congestive heart failure in diabetic foot ulcer patients was higher than in diabetic patients without foot ulceration. Furthermore, it was worse in those with higher Wagner grade ulcers (Xu et al, 2013).

Additionally, the presence of heart failure conferred a greater increased relative risk of a worse prognosis, slower healing rates and all-cause mortality was higher in those without heart failure (Xu et al, 2013). Aggressive cardiovascular risk management has been demonstrated to reduce mortality of diabetic patients with foot ulceration (Young et al, 2008).

The mechanisms through which congestive heart failure may exert adverse effect on wound healing are unclear. Tissue ischaemia may play an important role. Congestive heart failure may act at least partly through peripheral ischaemia. Oedema associated with congestive heart failure may also be a potential contributing mechanism as it may precipitate tissue ischaemia and impair healing by increasing the distance required for diffusion of oxygen from

capillaries to the ulcer, and it may reduce clearance of ulcer metabolites and degradation products from the ulcer site. Another possible mechanism contributing to the association between comorbid chronic heart failure (CHF) and ulcer healing may be renal insufficiency (Rhou et al, 2015).

Clinical tip: Patients with heart failure and lower-limb oedema should be advised to rest with elevated legs and to exercise the calf muscle pump to reduce oedema.

Diabetic foot and cerebrovascular disease

Diabetic foot problems are closely associated with cerebrovascular events. A history of cerebrovascular disease has been identified as an independent baseline predictor of diabetes-related lower-extremity amputation in a phase 1 Fremantle study (Davis et al, 2006). Transient ischaemic attacks (TIA) and ischaemic stroke are more prevalent before the onset of foot problems and on prospective evaluation (Tuttolomondo et al, 2015).

Clinical tip: Optimise protective footwear in this group of patients. Ensure that any protective footwear or insoles are regularly reviewed. This must include those with ulcers, but also moderate- to high-risk patients. Particular attention should be paid to the foot margins.

Diabetic foot and mental disorders

Foot problems are significantly associated with mental health symptoms in diabetic patients and caregivers. This may affect treatment in the foot clinic, outcome and quality of life (Hoban et al, 2015). The relationship between mental disorders and diabetic foot problems has been investigated by many. Williams et al have demonstrated that major depression is associated with a two-fold higher risk of incident diabetic foot ulcers and with a 33% higher risk of incident major lower-limb amputation in veterans with diabetes (Williams et al, 2010; 2011). In addition, Iversen et al (2015) confirmed a substantially increased risk of developing a foot ulcer in patients with symptoms of depression. In Ismail et al's study (2007), depression was present in one third of patients with diabetes and new foot ulceration. Minor and major depressive disorders were associated with an approximately threefold hazard risk for mortality compared with no depression.

The adverse effect of depression on outcomes in patients with diabetes may not be attributed to poorer glycemic, blood pressure, or lipid control (Heckbert et al, 2010). The biologic effects of depression are multifaceted: there is evidence for a neuroendocrine link between stress, depression and diabetes mellitus — depression has been linked to hypothalamic-pituitary-adrenal axis dysregulation and sympathetic nervous system activation (Golden, 2007; Lustman et al, 2008; Lin et al, 2010). Activation of the hypothalamic–pituitary–adrenal and sympathetic–adrenal medullary axes can modulate levels of matrix metalloproteinases and, thereby, wound healing (Yang et al, 2002).

Lastly, coping style and depression influence the healing of diabetic foot ulcers and there is also a significant independent effect of patients' illness beliefs on survival in patients with diabetic foot ulcers (Vedhara et al, 2010; 2016).

Clinical tip: Try to create a positive and friendly atmosphere in the foot ulcer clinic and use humour where possible. Patients should be treated as people not foot ulcers. Screening for depression with a simple tool is recommended.

Diabetic foot and palliative care

Comorbidities affect medicine and other treatment choices, functional status, surgical risk and quality of life. Foot ulcers and gangrene are no exception in end-of-life patients. The basic strategy in these patients must be to improve their quality of life, mainly by controlling wound-related symptoms (pain, exudate, odour and infection), providing psychological support and avoiding unnecessary procedures. Open empathic discussion with the patient and his relatives is mandatory to understand their views about the condition.

Early consultation with palliative care and pain specialists is highly recommended. Palliative care is a philosophy and a system for deciding care. In those patients where healing is unlikely, palliation can be the primary focus and can be used alone or integrated with usual chronic disease care. However, it should not be forgotten that patients who are likely to heal could still benefit from integrated palliative care (Chrisman, 2010; Dunning, 2016).

Miscellaneous

Body height, although not a comorbidity, is an independent predictor of lower-extremity amputation among patients with type 1 and type 2 diabetes (Tseng, 2006). Anaemia in patients with any condition, including diabetic foot ulceration, is associated with higher mortality, predominantly from infections (Almoznino-Sarafian et al, 2010), although not substantially proven may affect tissue oxygenation.

The role of nutrition in wound healing deserves special attention, since poor/malnutrition may affect immune system, collagen synthesis and wound tensile strength. Good quality randomised studies addressing this topic are scarce and direct benefit of use of nutritional supplements in human wound healing is not evidence based. Nevertheless, evaluation of patient's nutritional status is recommended and a balanced diet providing sufficient caloric (30–35 or even 40 kcal/kg) and fluid intake, as well as vitamins and minerals should be given (Maier et al, 2013; Quain and Khardori, 2015; Molnar et al, 2016).

Obesity in diabetic patients is associated with increased prevalence of foot ulcers (Vela et al, 1998; Sohn et al, 2011), the mechanism is unclear. In contrast to this, the risk of amputation is higher for non-elderly male patients with body mass index (BMI) <25 kg/m^2 compared to overweight individuals (BMI 25–29.9 kg/m^2), and lower for those with BMI ≥30 kg/m^2. While the amputation risk continues to decrease for higher BMI, amputation-free survival shows a slight upturn at BMI >40 kg/m^2 (Sohn et al, 2012). A more recent study investigated the effect of limb preservation status and BMI on the survival of patients with limb-threatening diabetic foot ulcers. Median survival time had positive correlation with BMI levels for patients with limb-preserved and minor lower-extremity amputation, but not for those with major LEA (Lin et al, 2017).

Finally, a study from Canada demonstrated that obesity does not appear to significantly impact inpatient amputation rehabilitation outcomes and, as such, should not be a deciding factor as to whether a patient is offered rehabilitation or not (Vivas et al, 2017). This association between obesity and amputation risk, amputation rehabilitation outcome and survival of patients with limb-threatening diabetic foot ulcers shows a pattern consistent with the 'obesity paradox' — fitness beats fatness — observed in many other health conditions.

Untreated severe obstructive sleep apnea has been demonstrated to delay ulcer healing due to prolonged overnight hypoxemia (Vas et al, 2016).

A problem that is all too often overlooked are polypharmacy and drug interactions, in particular, between antibiotics, anticoagulants and statins. These may result either in increased activity of the latter with bleeding complications or in diminished activity with resulting thrombo-embolic complications.

Conclusions and recommendations

Management of patients with diabetes and foot ulceration is a demanding task requiring a dedicated, well-coordinated and skilled interdisciplinary team. Special attention should be paid to the patients with renal impairment, in particular, to those with ESRD on haemodialysis and renal transplant patients. Foster et al have demonstrated decreased prevalence of gangrene and a fall in amputation rate in renal transplant patients after the introduction of a special foot clinic (Foster et al, 1995). Marn Pernat et al (2016) have demonstrated improved outcomes after implementation of routine foot check in patients with diabetes on haemodialysis. Good glycaemic regulation, treatment of hypertension and dyslipidaemia are the cornerstones of the holistic approach to the patient. Psychological problems should not be overlooked, and patient preferences and priorities never be neglected. Thus, clinicians should remember to 'treat the whole patient not just the hole in the patient'. ■

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