The association between declining kidney function and diabetic foot disease

Caroline McIntosh and Claire MacGilchrist

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Article points

1. Individuals with diabetes and chronic kidney disease are at high risk of developing foot complications.
2. Diabetic foot ulceration is one of the most devastating complications of diabetes, associated with significant mortality and amputation.
3. Individuals with stage 4 or 5 chronic kidney disease are fivefold more likely to develop diabetic foot ulceration.
4. Strong associations exist between end-stage renal disease and lower-extremity amputation.

Key words

- Diabetic foot
- Foot ulcer
- Kidney
- Nephropathy
- Renal

Authors

Caroline McIntosh is Professor of Podiatric Medicine, Discipline of Podiatric Medicine, National University of Ireland Galway, Galway, Ireland; Claire MacGilchrist is Lecturer in Podiatric Medicine, Discipline of Podiatric Medicine, National University of Ireland Galway, Galway, Ireland

Diabetic foot disease and chronic kidney disease (CKD) are strong predictive risk factors for the development of diabetic foot ulceration (DFU). Individuals with CKD, particularly those with end-stage renal disease (ESRD), are known to be at high risk of developing foot complications, including DFU and lower-extremity amputation. The onset and progression of CKD can be monitored through the analysis of estimated glomerular filtration rate (eGFR). The emerging literature investigating declining kidney function in association with DFU primarily focuses on stage 4 and stage 5 ESRD (e-GFR <29). Previous studies have identified a temporal relationship between dialysis and foot ulceration. Further research is warranted to comprehensively analyse the relationship between DFD and diabetic nephropathy to truly understand the interrelationship between these common, microvascular complications of diabetes.

Diabetic foot disease (DFD) and chronic kidney disease (CKD) are strong predictive risk factors for the development of diabetic foot ulceration (DFU). Strong associations are reported within the literature between CKD, typically end-stage renal disease (ESRD) and lower-extremity amputation (LEA). Individuals with stage 4 or 5 CKD are fivefold more likely to develop DFU than pre-dialysis patients, while dialysis is independently associated with DFU (Ndip et al, 2010). DFU is one of the most devastating complications of diabetes; associated with significant mortality and amputation (Boulton et al, 2005). Few research studies have comprehensively assessed the progression of DFD in association with declining kidney function. The authors aim to review the current evidence base for the association between declining kidney function and diabetic foot disease.

Diabetic nephropathy

The complications associated with diabetes are multiple, but can broadly be classified into macrovascular and microvascular complications. Diabetic nephropathy (DN) is an example of a microvascular complication of diabetes characterised by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions and loss of glomerular filtration rate (GFR) (Lim, 2014). DN can been defined by the presence of proteinuria >0.5 g/24 hours (Gross, et al, 2005). DN gives rises to declining kidney function resulting in chronic kidney disease (CKD). It has been estimated that 20–40% of people with diabetes will develop CKD (Game et al, 2006; American Diabetes Association, 2014), including a significant number who will develop ESRD requiring renal replacement therapies (dialysis and or transplantation).

Glomerular filtration rate (eGFR) is considered to be the best overall parameter of overall kidney function (Lavery, et al, 2003); indeed, it is well established that current GFR and past GFR trajectory are good predictors of ESRD (Colhoun and Marcovecchio, 2018). The GFR test is a measure of serum creatinine, which is used in a formula along with factors such as age, weight and gender to give an estimated GFR (eGFR) which,

essentially is a measure of how well the kidneys are functioning. Other risk factors that can predict GFR decline include: increasing age, long duration of diabetes, HbA_{1c}, systolic blood pressure, albuminuria and retinopathy status (Colhoun and Marcovecchio, 2018).

Table 1 describes the stages of CKD as outlined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Diabetic foot disease

Diabetic foot disease (DFD) encompasses macrovascular and microvascular complications and can be defined as the presence of several characteristic diabetic foot pathologies (including neuropathy and ischaemia), which contribute to the pathogenesis of diabetic foot ulceration (DFU) (McIntosh, 2017). Significant morbidity and mortality is associated with DFD; approximately 25% of DFUs will not heal, and up to 28% may result in some form of lower-extremity amputation (Hingorani et al, 2016). Furthermore, five-year mortality associated with DFD (46–84%) far exceeds numerous long-term conditions, including various malignancies (Armstrong et al, 2007; International Best Practice, 2013). Indeed, Jeffcoate et al, (2018) report the 5-year survival rate following presentation with a new DFU to be 50–60%, while data derived from a Veterans Health Administration population reported that 1-, 2-, and 5-year survival was only 81%, 69,% and 29%, respectively (Jeffcoate et al, 2018).

NICE guidelines (2015) advocate the following risk stratification, which classifies patients into four levels of increasing risk of foot problems

1) Low risk; no risk factors except callus alone
2) Moderate risk; deformity or neuropathy or non-critical limb ischaemia
3) High risk; previous ulceration or previous amputation or on renal replacement therapy or neuropathy and non-critical limb ischaemia or neuropathy in combination with callus and/or deformity
4) Active diabetic foot ulceration; ulceration or spreading infection or critical limb ischaemia or gangrene or suspicion of acute Charcot arthropathy.

Table 1. Stages of chronic kidney disease as described by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (Levey et al, 2002; Vanholder, 2006).

Stage	Clinical features	Glomerular filtration (GFR) (mL/min/1.73m²)
I	*Kidney damage with normal or increased GFR	≥90
II	*Kidney damage with a mild decrease in GFR	60-89
III	Moderate decrease in GFR	30-59
IV	Severe decrease in GFR	15-29
V	Kidney failure	<15 or dialysis

*Other evidence of kidney damage may include any of the following:
- Persistent microalbuminuria/proteinuria/haematuria
- Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests e.g. polycystic disease, reflux nephropathy
- Biopsy proven chronic glomerulonephritis

In the following circumstances eGFR may not be accurate:
- Acute renal failure
- Patients less than 18 years of age
- Patients with advances muscle wasting and amputations
- Pregnancy

Chronic kidney disease and the diabetic foot

DFD and CKD have been identified as strong predictive risk factors for the development of foot ulceration and a pre-cursor for amputation. Individuals with ESRD undergoing dialysis are at further increased risk of ulceration and subsequent amputation (Ndip et al, 2010; Kaminski et al, 2012). Increased risk is further identified among dialysis dependant individuals with diabetes (Kaminski et al, 2012).

A close temporal relationship has been demonstrated between foot ulceration and the onset of dialysis for ESRD (Jeffcoate et al, 2018). One large study (*n*=326) of patients with diabetes and stage 4 or 5 CKD found that dialysis treatment was independently associated with foot ulceration (Ndip et al, 2010). Those with end-stage kidney disease (stages 4 and 5) are five times more likely to develop DFU, while there is a temporal association for those commencing dialysis and new episodes of foot ulceration (Ndip et al, 2010). Prevalence of other lower-limb complications (amputation, PAD, prior ulcer and neuropathy)

was twofold higher in the dialysis group (Ndip et al, 2010). Otte et al (2015) support the findings of Ndip et al (2010); they undertook a retrospective study of individuals attending a hospital setting due to CKD stages 3–5 including those on dialysis treatment. Medical records were reviewed for incidence of foot ulceration and LEA. Otte and colleagues found that CKD 4–5 and dialysis treatment are independent risk factors for foot ulceration and major LEA compared with CKD stage 3.

Lavery et al (2018) investigated the incidence of foot ulcers and amputations pre- and post-the initiation of dialysis in 150 consecutive patients with diabetes requiring haemodialysis. Interestingly, their findings differ to those of Ndip et al (2010) and Game et al (2006). Lavery et al (2018) found no increase in the incidence of ulcers or amputations post dialysis, but they did find a higher cumulative incidence of ulcers in the 30-month period prior to dialysis. These findings support the thoughts of Jeffcoate et al (2018) who stated that "it may be assumed that the ulceration … is the result of worsening renal function it is equally and possibly more likely that it is the inflammation associated with the ulceration that triggers the final decline in renal function".

The emerging literature investigating declining kidney function in association with DFD primarily focuses on stage 4 and stage 5 ESRD. As such, earlier stages of kidney disease are significantly under-reported. Otte et al (2015) is one of the few studies investigating earlier stages of CKD, however, this is only extended to include stage 3 CKD and does not explore the entire continuum of CKD. Yet, in the 'West of Ireland Diabetes Foot Study', Hurley et al (2013) observed a trend towards increased probability of impaired sensory and vascular function with declining eGFR. It was indicated that for every one unit decrease in eGFR observed, there was a 1% increase in the odds of having abnormal neurological function.

A recent systematic review and meta-analysis (Kaminski et al, 2015) explored the relationship between particular risk factors for DFD and CKD in adults with ESRD on dialysis. They identified an increased risk with previous foot ulceration (OR, 17.6), lower-extremity amputation (OR, 15.5), peripheral arterial disease (OR, 7.5), coronary artery disease (OR, 3.9), retinopathy (OR, 3.0) and higher serum phosphorus levels (MD, 0.40 mg/dL). The aforementioned meta-analysis was conducted on 30 studies (48,566 individuals of whom 47,639 on haemodialysis and 927 on peritoneal dialysis) and six key risk factors were investigated (diabetes, coronary artery disease, serum albumin, previous ulcer/and amputation, peripheral arterial disease and neuropathy). Only 15 (50%) studies investigated neuropathy as a risk factor and 14 (47%) studies recorded serum albumin levels. Data included in this review were largely retrospective and derived from cross-sectional study design and, therefore, not appropriate to identify any temporal association between risk factors and foot disease.

Nearly all studies investigating the relationship between declining kidney function in DFD focus on ESKD (stage 4 and stage 5). There is a distinct lack of published research investigating the entire continuum in kidney disease including mild and moderate stages of CKD. Robust, longitudinal studies are warranted to explore the associations between earlier stages of CKD and DFD progression.

Kellegher (2017) conducted a cross-sectional study of a consecutive cohort of patients presenting with active DFU (*n*=70). The aim of the study was to profile patients with active DFU who were treated within a tertiary hospital in the Republic of Ireland. Clinical profiling included patient specific, wound specific and disease specific characteristics. CKD was diagnosed using pre-defined cut off points for estimated glomerular filtration rate (eGFR). The eGFR was estimated using the Modification of diet in Renal Disease equation (Vanholder et al, 2006). CKD was defined on the basis of eGFR and categorised according to the US National Kidney Foundation (Vanholder et al, 2006). Stage II eGFR between 60–89 mL/min/1.73m^2, stage III 59–30 mL/min/1.76=3m^2 and stage IV eGFR between 1,529 mL/min/1.73m^2. Examination of the biomedical markers revealed CKD stage 2 and 3 were the most prevalent in the study population with rates of 31.4% and 24.2% of the study population, respectively. Kellegher's unpublished work suggests a high prevalence of early stage CKD (stages 2 and

3) in a population of patients with active DFU. While the sample size was limited, the findings suggest a potential relationship with early stage CKD and DFD.

Conclusion

Further research is needed to investigate whether a temporal association exists between declining kidney function and progressing DFD to explore if a 'tipping point' exists between the onset and progression of CKD and diabetic foot complications. Declining renal function may be an early marker in the onset of DFU and LEA. The opportunity exists to identify if eGFR, an easily accessible marker of kidney function, is a potential predictor for onset of DFD. This would have significant implications for the screening of patients with diabetes as eGFR is an easily accessible marker of kidney function readily available to all GPs in primary care, as is albumin to creatinine ratio another key marker of CKD. Identification of when best to implement aggressive treatment strategies clinically is unknown, and further developments in this field are essential to significantly advance the scientific knowledge regarding the development and interactions between these microvascular complications of DM. ■

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