Anaemia, diabetes, and the foot: A short review

Merlin C Thomas

Article points

1. Anaemia is common among people with diabetes, and is closely linked to kidney disease.
2. Patients with diabetes and anaemia should be considered as being at high risk of foot disease.
3. Conclusive evidence that correction of anaemia improves wound healing and clinical outcomes in diabetic foot disease is lacking.

Keywords
- Anaemia
- Delayed wound healing
- Kidney disease

Professor Merlin C Thomas is NHMRC Senior Research Fellow, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia.

Anaemia is a common finding in patients with diabetes, which largely reflects the high prevalence of chronic kidney disease in this patient group (Stevens, 2012). However, even after adjusting for kidney function, people with diabetes are approximately twice as likely to have anaemia when compared to those without diabetes (Astor et al, 2002; Lorber and Reddan, 2006). By the time that the estimated glomerular filtration rate (eGFR) declines to <60 mL/min/1.73m^2, up to one-in-three individuals with diabetes will have anaemia (Thomas et al, 2003; 2006). Anaemia also develops earlier, and is more severe, in those patients with diabetic kidney disease (Ishimura et al, 1998; Bosman et al, 2001).

To keep haemoglobin levels constant, the healthy kidney maintains an inverse relationship between synthesis of the haemopoietic hormone, erythropoietin and the haemoglobin concentration. However, in diabetes, this relationship is uncoupled, so that in most people with diabetes and anaemia, renal erythropoietin production is not elevated (as it should be), but instead remains – inappropriately – in the range considered normal for those without anaemia (Inomata et al, 1997; Craig et al, 2005; Thomas et al, 2005). This state may be considered to be functional erythropoietin deficiency, as while renal erythropoietin production remains intact, it is indifferent to the increased haemopoietic demands associated with systemic inflammation, functional haematinic deficiencies, erythropoietin resistance, and reduced red cell survival. Therefore, anaemia slowly develops.

Anaemia has a negative impact on a patient's sense of well-being, impairing their ability to work and reducing quality of life, causing symptoms such as lack of energy, dizziness, breathlessness, poor appetite, impotence, reduced cognitive function, and decreased exercise tolerance (Lundin, 1989; Canadian Erythropoietin Study Group, 1990). For patients with diabetes, many of whom already have reduced capacities, a poor quality of life, and a high prevalence of comorbid macrovascular disease, anaemia comes as an unwelcome additional burden.

Anaemia may also influence the development and progression of diabetic foot disease. Endoneural hypoxia, due to reduced microvascular blood flow and altered vascular permeability, plays an important role in the progression of diabetic neuropathy. Factors that reduce endoneural oxygenation are known to accelerate nerve injury in diabetes, and falling haemoglobin levels have the potential to reduce tissue oxygenation. Certainly, anaemia is more common among patients with neuropathy (Bosman et al, 2001), particularly in those with autonomic changes, and in experimental models of diabetes, treatment

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with erythropoietin has been shown to protect against the development of neuropathy, as well as reverse established disease (Bianchi et al, 2004).

In small studies of patients with polyneuropathy and anaemia, treatment with erythropoietin has also been shown to improve motor nerve conduction velocity and compound muscle action potential (Hassan et al, 2003). Whether this is due to correction of anaemia or the direct neurotrophic effects of erythropoietin remains to be established. The potential for distinct neuroprotective actions are under active investigation in a range of conditions, from stroke to spinal cord injury. However, large clinical studies are required to establish any efficacy in patients with diabetic neuropathy.

Cutaneous oxygenation is also a major determinant of the risk of foot ulceration in diabetes and its outcome; indeed, diabetic foot wounds will not heal without adjuvant surgical treatment, unless the transcutaneous oxygen partial pressure is >30 mmHg (Kessler et al, 2003). Any reduction in haemoglobin level will also reduce skin and wound site oxygenation. The most well-known example is B-thalassemia minor, a condition associated with haemolytic anaemia and an increased risk of leg ulcers. However, the clinical effects of anaemia on wound healing in healthy individuals are marginal, possibly because of reduced blood viscosity, increased peripheral perfusion, vasoreactivity (Schmidt-Lucke et al, 2000), and elevated erythropoietin levels that accompany anaemia act to offset the negative effects of a reduced haemoglobin concentration.

However, each of these compensatory responses may be impaired in diabetes, particularly in patients with established microvascular complications.

Anaemia is a potent risk factor for critical limb ischaemia, lower extremity amputation, subsequent high level (leg or thigh) amputation, and prolonged institutionalisation following surgery (Lavery et al, 1997; van Houtum et al, 1998; Hokkam, 2009). This means that patients with diabetes and anaemia should be considered high risk, and afforded the frequent and fastidious foot screening that goes with other risk factors. However, while there is a strong rationale for correcting anaemia, currently there is no conclusive evidence that it improves clinical outcomes in patients with diabetic foot disease.

A few case reports (Turba et al, 1992; Keast and Fraser, 2004) have documented improved healing of recalcitrant pressure sores and chronic leg ulceration following correction of anaemia. Erythropoietin may also have direct effects on immune function and angiogenesis in granulation tissue during wound healing in experimental models (Vlahakis, 2006). However, some authors have reported an increase in peripheral vascular disease in patients with diabetes receiving peritoneal dialysis and erythropoietin (Wakeen and Zimmerman, 1998). This may partly reflect confounding-by-indication (i.e. patients treated with erythropoietin who originally had anaemia).

However, it is also possible that increases in total peripheral resistance and blood viscosity that follow the correction of anaemia may have negative effects in the diabetic foot patient. Similar actions may have contributed to a two-fold increase in strokes with darbepoetin-alfa, observed in the TREAT (Trial to Reduce Cardiovascular Events With Aranesp Therapy) study (Winkelmayer, 2011). The specific utility of anaemia correction on diabetic foot disease is yet to be tested in clinical trials using hard endpoints.

There is no doubt that erythropoietin is a performance-enhancing drug, particularly in patients who have poor performance and reduced quality of life, and most strikingly in those patients with baseline haemoglobin levels <100 mg/dL (Johansen et al, 2012). From the perspective of a patient with diabetes and foot disease (and, therefore, cardiovascular disease, heart failure, retinopathy, etc), even a modest reduction in fatigue may be valuable. However, the

purely palliative treatment of anaemia with erythropoietin is not without significant cost, both in terms of the drug itself, as well as the systematised management and follow-up programme required for its use. The recent advent of generic erythropoietins may change the balance of cost and benefits, and lead to the broader exploration of anaemia correction. The feet may be a good place to begin. ■

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