

# Research Review

## EDUCATIONAL SERIES

### Management of Dry Skin in Diabetes Mellitus

#### About the Reviewers

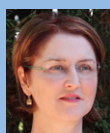


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Trish has served as the NSW Mentorship Director and thence Director of Training for NSW dermatology registrars. She is the current Honorary Secretary of the ACD and sits on the College Board. Trish also sits on the board of the Australasian Dermatopathology Society. She works in an advisory role to the Cancer Council Australia, for the yearly National Skin Cancer Action Week campaign.

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This overview of dry skin (xerosis) in patients with diabetes mellitus and its management covers key aspects of the underlying pathology, diagnosis and assessment, and treatment. Expert Commentaries by Hon. Associate Professor Marius Rademaker (Hamilton) and Dr Patricia Lowe (Sydney) provide clinical practice insight and recommendations. This article is intended as an educational resource for healthcare professionals involved in the care of patients with diabetes mellitus.

#### Introduction

Diabetes mellitus is a group of metabolic disorders characterised by inadequate insulin production or response, leading to alteration of glucose metabolism. The two main forms of diabetes mellitus are type 1 and type 2. Type 1 diabetes mellitus involves insulin insufficiency arising from progressive immune-mediated destruction of pancreatic  $\beta$ -islet cells. Type 2 diabetes mellitus involves end-organ insulin resistance, which may be accompanied by a progressive decrease in pancreatic insulin production.

Diabetes mellitus is associated with a variety of biophysical complications, including cutaneous manifestations. Up to two-thirds of patients who have diabetes mellitus experience some form of skin involvement,<sup>1-4</sup> including necrobiosis lipoidica, bullosis diabeticorum, periungual telangiectasia, and vitiligo in type 1 diabetes and acanthosis nigricans, diabetic dermopathy, diabetic thick skin, and pigmented purpuric dermatosis in type 2 diabetes mellitus. However, with a prevalence of  $\geq 40\%$ ,<sup>1,2</sup> dry skin is one of the most common cutaneous manifestations of diabetes mellitus and is the focus of this article.

#### Skin Barrier Function

Skin barrier function is primarily the responsibility of the stratum corneum, the outermost layer of the epidermis. It is composed of non-viable keratinocytes (skin cells), intercellular lipids and water, with moisture retention assisted by a surface film of natural oil (sebum).<sup>5-8</sup> Natural moisturising factor (NMF), derived from the breakdown of the filaggrin protein, is essential for maintaining water within keratinocytes. In addition to its vital role as a physical barrier, the stratum corneum is also involved in the maintenance of hydration and innate immunity.<sup>6,9</sup>

Adequate hydration of the stratum corneum is essential for maintaining its structural integrity and functionality.<sup>10</sup> Disruption of skin barrier function leads to increased evaporation, known as trans-epidermal water loss (TEWL), and compromised innate immunity.<sup>5-7</sup>

Generalised xerosis, as a consequence of skin barrier disruption, is associated with an increased risk of infection and various types of eczema (term used interchangeably with dermatitis) including atopic and allergic contact dermatitis.<sup>7,11</sup> In the general population, xerosis affects all ages and males and females equally. However, it increases in frequency with age, particularly in post-menopausal females. Xerosis is multifactorial in causation, including the following factors:

- Genetics, e.g. ichthyosis vulgaris
- Intercurrent systemic diseases, e.g. diabetes, hypothyroidism, renal disease
- Age:  $>50$  years, menopause
- Environmental factors: low humidity environment, e.g. winter, air-conditioned rooms, windy conditions
- Solar damage
- Excessive soap and water use
- Oral medications, e.g. statins, diuretics
- Intercurrent cutaneous diseases, e.g. atopic eczema.

## Cutaneous Effects

Dry scaly skin results from dehydration of the uppermost layers of the stratum corneum, abnormal cohesion between keratinocytes, and increased keratinocyte transit time with secondary epidermal thickening.<sup>12</sup>

As with some other endocrine disorders, diabetes mellitus can cause specific alterations in the functional and mechanical properties of the skin. Studies of the functional properties of the skin in patients with diabetes mellitus have variously implicated reduced hydration, decreased sebum secretion, and impaired skin elasticity.<sup>13,14</sup> Dry skin and reduced elasticity may lead to fissuring (cracking) of the skin, serving as a portal for entry for infective agents.<sup>15</sup> At this point in time, however, the precise influence of diabetes mellitus on the stratum corneum has not been fully elucidated.

In addition to possible disruptive effects on the stratum corneum contributing to dry skin in patients with diabetes mellitus, diabetic xerosis may be exacerbated by the microangiopathy and peripheral neuropathy that commonly affect these patients.<sup>12,16</sup> The microvascular network of the skin is substantially altered in diabetes mellitus and diabetic neuropathy, which predominantly affects the distal portions of the sensory motor innervation, may contribute to dry skin, especially of the feet.<sup>16,17</sup>

The pathophysiological mechanism underlying microangiopathy is not completely understood. However, hyperglycaemia-induced non-enzymatic glycation of structural and regulatory proteins leading to the formation and accumulation of advanced glycation end-products (AGE) has been proposed as playing a role in the microvascular complications of diabetes mellitus.<sup>12,17,18</sup> When it occurs in the skin, glycation creates new molecular residues and induces cross-links in the extracellular matrix of the dermis. The formation of such cross-links between macromolecules appears to contribute to altered skin properties in patients with diabetes mellitus similar to those observed in ageing and photoageing.<sup>12,18</sup> The accumulation of final glycation products appears to increase with age and is amplified by UV exposure.<sup>19,20</sup> Accumulation of AGE has been shown to lead to development of diabetic thick skin. Although glycation inhibitors and use of sunscreen have been postulated as potential treatments for diabetes-associated skin disorders, randomised controlled clinical trials demonstrating a clinically significant beneficial effect of these interventions on AGE-induced skin disorders in patients with diabetes mellitus are lacking.<sup>12</sup>

Given the apparent link between skin manifestations in diabetes mellitus and microangiopathy, one group of researchers performed a prospective study to investigate the relationship between skin disorders and diabetic neuropathy and nephropathy.<sup>21</sup> They concluded that skin disorders, including xerosis and diabetic foot disease, could serve as indicators of the presence of associated microvascular complications of diabetes mellitus.<sup>21</sup> In addition, the skin signs in diabetes patients have even been suggested as markers for the course of the disease or for the success of therapeutic interventions.<sup>17</sup>

## Diagnosis and Assessment

Xerosis is dry, scaly skin, which may become itchy and red. Typical signs and symptoms of xerosis include the following:<sup>22,23</sup>

- Excessively dry, dull, rough patches of skin
- Uneven and fissured (cracked) skin
- Raised or uplifted skin edges (scaling), flaking (desquamation), chapping
- Can affect any part of the skin, commonly limbs, heels and feet
- Pruritus (itching), which leads to rubbing and ultimately lichenification (leathery thickening) of the epidermis
- Can become inflamed (appears red).

The grading of xerosis is important as it helps to define skin changes and their severity, and possibly their propensity to progress to something more serious.<sup>16</sup> It also informs treatment, especially the selection of appropriate emollients and moisturisers from the broad range of products available.<sup>16</sup> Given that data from the Fremantle Diabetes Study (Phase II) indicates that self-assessment of diabetes-related foot problems by patients with diabetes mellitus is unreliable, education and regular monitoring by a healthcare professional may be necessary in diabetes mellitus patients who demonstrate signs of serious foot disease.<sup>24</sup>

A variety of non-invasive, or minimally-invasive, instrumental assessments that provide accurate and objective data on xerosis severity, the rate of desquamation, and the hydration level of the stratum corneum are available.<sup>16</sup> For example, electrometric devices can conveniently measure stratum corneum moisture, and the harvesting of superficial keratinocytes can provide information on the severity of xerosis.<sup>12,16</sup> Data gained via such methods add quantification to the subjective assessment by the patient and/or the healthcare professional. Biophysical measurements also reveal changes in the functional properties of the skin, which are not easily determined via visual and tactile examinations.<sup>16</sup>

Although instrumental assessments of dry skin are valuable because of their sensitivity and objectivity, their specificity is weaker. Thus, global evaluations, which are best obtained non-instrumentally, should not be dismissed. For these reasons, a triple-component approach, involving biophysical instruments, trained assessors and self-assessments, may increase the accuracy of xerosis assessments.<sup>16</sup>

	SCALING	ROUGHNESS	REDNESS	CRACKS FISSURES
<b>0 = absent</b>		Perfectly smooth and pliable		
<b>1 = slight</b>	Small scales only, surface lightly dull in colour	Slightly irregular and scratchy on tangential tactile evaluation	Small areas of minimal redness or diffuse faint redness	Single and superficial cracks in the examination field
<b>2 = moderate</b>	Small scales in combination with larger scales (>0.05mm), surface opaque or whitish	Definitely irregular and scratchy and possibly slightly stiffened on vertical tactile evaluation	Limited areas of definite redness or diffuse and obvious redness	Single or grouped superficial and more deep cracks
<b>3 = severe</b>	Larger and large scales (flake >1mm) are prominent, surface whitish	Advanced irregularly and scratchy feeling associated with some stiffening	Large areas of definite redness or diffuse and more pronounced redness	As for 2 but with deep cracks
<b>4 = extreme</b>	Larger flakes covering almost the entire skin surface in the examination field	Gross irregularity and major disturbance of skin marking and definite stiffening	Advanced redness in entire examination field (redness of cracks not included)	Dominated by deep cracks

**Table 1.** Signs and symptoms of skin dryness assessed in the Specific Symptom Sum Score (SRRC) system developed by the European Group on Efficacy Measurement of Cosmetics and other Topical Products (EEMCO).<sup>25</sup>

Community pharmacists are likely to be first-line healthcare professionals in the assessment of dry skin. However, community pharmacists are not necessarily experienced in evaluating xerosis and recommending a moisturising product based on a non-invasive dermatological evaluation.<sup>26</sup> Against this background, Korean researchers conducted a study to validate clinical scoring systems for assessment of dry skin in pharmacies.<sup>26</sup> Scoring systems developed by the European Group on Efficacy Measurement of Cosmetics and other Topical Products (EEMCO) for the characterisation of xerosis and efficacy substantiation of moisturising products were validated by evaluating scoring differences between pharmacists and a dermatologist.<sup>26</sup> The scoring systems included a visual scale, Overall Dry Skin Score (ODS), and Specific Symptom Sum Score (SRRC) system (Table 1).<sup>25</sup> The results of the study were based on 387 patients with dry skin who were evaluated at 157 community pharmacies on day 0 and day 28. They demonstrated that the EEMCO-developed visual scale, ODS, and SRRC could be used to evaluate dry skin in pharmacies with moderate to substantial reliability.<sup>26</sup> Interestingly, the study also demonstrated the benefits of moisturisation, with all parameters of skin dryness assessed (scaling, roughness, redness, cracks/fissures) being significantly improved by daily moisturiser use as assessed by the community pharmacists and dermatologist.<sup>26</sup>

## Treatment

The terms moisturisers and emollients are often used interchangeably despite their differences. In simple terms, moisturisers add moisture to the skin by their humectant effect. These agents draw water into the stratum corneum. Emollients soften the skin by their occlusive effect. They provide an oily layer to dry skin thus slowing water loss from the stratum corneum.

Along with simple general measures, moisturisers and emollients are the mainstay of treatment for straight-forward cases of xerosis and should be used as adjunctive therapy in more complex clinical cases.<sup>27</sup> They can be categorised in four main types (Table 2), although it should be noted that not all moisturisers and emollients are the same and not all are intended to be therapeutic.<sup>27</sup>

TYPE	CHARACTERISTICS	OBSERVATIONS	INGREDIENTS
<b>Emollient dominant</b>	Typically used for 'normal' skin; make the skin feel soft and smooth; designed to maintain skin condition; not designed to repair damaged skin or have long-term effects on the skin	Although usually labeled as lotions or body moisturisers, the goal of many of these products is to provide fragrance and soften the skin rather than to provide skin-moisturising effects	Oils, lipids, and their derivatives (e.g. stearic, linoleic, oleic, and lauric acids; cetearyl alcohol; mineral oil; lanolin)
<b>Humectant-based, light duty</b>	Suitable for 'normal' skin, maintenance of skin condition, and daily use; generally oil-in-water emulsions	Provide hydrating effects to the skin via humectants that attract and bind water from the deep epidermis and environment to impart hydrating benefits; absorb more quickly than occlusive formulations and therefore are more aesthetically pleasing, promoting patient compliance	Glycerin, sorbitol, urea, sodium lactate, lactic acid, carnitine, sodium PCA, arginine hydrochloride, serine, alanine, histidine, citrulline, lysine, sodium chloride, glycogen, mannitol, sucrose, glutamic acid, threonine
<b>Occlusive protective</b>	Typically used on dry and/or damaged skin; formulation types include ointments and often are water-in-oil lotion or cream emulsions; provide an occlusive barrier that reduces transepidermal water loss and protects irritated inflamed skin from external irritants to promote moisture retention and allow barrier repair	Because of their occlusive nature, they are sometimes less aesthetically pleasing than oil-in-water emulsions, which can impact compliance; effective in improving the ashen powdery appearance of dry skin	Skin-protectant actives (e.g. petrolatum, dimethicone, lanolin, mineral oil); occlusive hydrophobic ingredients (e.g. olive oil, soybean oil, beeswax, jojoba oil)
<b>Therapeutic</b>	Formulated to treat xerosis and diseased skin conditions with a xerotic component, generally contain a balance of occlusives for barrier support, emollients to soften and smooth skin, and humectants to provide water to the stratum corneum	Better-constructed moisturisers due to their balanced composition of multifunctional ingredients that protect, hydrate, and support endogenous barrier repair processes	Emollients, occlusives, humectants/NMF, ceramides

**Table 2.** Comparison of the characteristics, features and ingredients of the four major types of moisturiser/emollient.<sup>27</sup> Abbreviations: PCA = pyrrolidone carboxylic acid; NMF = natural moisturizing factor.



Moisturisers and emollients influence the water concentration gradient in the stratum corneum via two main effects:<sup>16</sup>

1. Humectant effect: Restoring, retaining or increasing moisture content within the stratum corneum allowing the addition of water from the dermis or from the applied product itself.
2. Occlusive effect: Coating of the skin surface reduces TEWL and facilitates accumulation of moisture within the stratum corneum.

These modes of action are often combined in the same product, although there exist exceptions including petrolatum and floating (spreading) bath oils, which are considered to work only by forming a semi-occlusive layer on the stratum corneum.<sup>16</sup>

By binding water to the stratum corneum, moisturisers improve skin surface hydration, which has been consistently demonstrated to improve the epidermal barrier function and to reduce the scaling, redness, and fissures associated with xerosis.<sup>26,28-31</sup> However, fewer studies have specifically assessed the effects of moisturisers and emollients in the treatment of xerosis in patients with diabetes mellitus.

In a non-comparative study, an emollient containing urea 5% combined with occlusive and humectant agents was applied to one leg and one arm of 40 patients with type 1 or type 2 diabetes mellitus twice daily for four weeks.<sup>15</sup> One month's treatment with the emollient produced a significant increase in skin hydration versus untreated skin (15.5 vs 3.9 arbitrary units [AU]), which was associated with a significantly greater reduction in desquamation index (-2.2 vs 0.2 AU) and TEWL (1.24 vs 2.06 g/hr/m<sup>2</sup>). The increase in skin hydration was supported by a significant improvement in dry skin as assessed by a dermatologist (from 6.95 to 0.93cm) and patients (6.58 to 1.03cm) using a 10cm visual analogue scale, with patients also perceiving an improvement in pruritus (from 2.0 to 0.1cm).<sup>15</sup>

Two randomised double-blind studies have evaluated the benefits of moisturisation on xerosis of the feet in diabetes mellitus patients.<sup>30,32</sup>

The first of these studies compared the efficacy of a moisturiser containing 10% urea and 4% lactic acid with its emulsion-base vehicle (control) in the treatment of 40 patients with diabetes mellitus who had moderate-to-severe xerosis of both feet.<sup>30</sup> Using a nine-point Xerosis Assessment Scale, feet treated with the moisturiser twice daily for 4 weeks demonstrated significantly greater reduction in mean xerosis grading (-2.94) than feet treated with the control (-1.79), and the difference remained statistically significant two weeks after discontinuation of the moisturiser.<sup>30</sup>

Also of note, urea cream (especially at 40% strength) has been demonstrated to be keratolytic and help to treat calluses of the feet.<sup>33</sup> Urea-based formulations can also enhance the penetration of other topical agents applied to thickened, keratotic, scaly skin.<sup>15</sup>

In the second of the two randomised double-blind studies that assessed the effects of moisturisation on xerosis of the feet in diabetes mellitus patients, an emollient consisting of a 2.5% chitin-glucan formulation applied once daily for three weeks was compared with placebo in 30 menopausal women with type 1 or type 2 diabetes mellitus who had xerosis of the feet.<sup>32</sup> Electrometric assessments demonstrated significantly increased moisturisation of the stratum corneum of the feet during the treatment phase and a 2-week non-treatment follow-up phase.<sup>32</sup>

Furthermore, it should not be forgotten that tight control of diabetes mellitus itself, i.e. rigid glycaemic control, reduces the risk of vasculopathy, neuropathy and nephropathy. Hence, it is likely that anti-diabetic therapy will reduce or prevent the skin manifestations of diabetes mellitus.<sup>17</sup>

## SKIN MANAGEMENT 1:

### Key Advice for Diabetes Patients

1. Reduce the frequency of bathing or showering to every second or third day, unless physically active. Sponge body folds daily.
2. Take short (5-10min) baths or showers with warm (not hot) water.
3. Use mild cleansers that are alcohol-free. Note that soaps are detergents that remove NMF and hydrating lipids from the stratum corneum.
4. Diluted water-dispersible oils can be used in the shower or bath as a soap.
5. Gently pat (rather than rub) the skin dry.
6. The right moisturiser for the patient is the one they will use regularly, so it is often a case of 'trial and error'.
7. Apply moisturiser to warm, damp skin, i.e. within 5min of getting out of the bath/shower.
8. Moisturiser should be applied liberally – it takes 30g of moisturiser to coat the entire average 70kg body.
9. Rub in downward strokes, in the direction of hairs.
10. Moisturise the skin daily, repeat frequently throughout the day as often as necessary.
11. Use of a greasier moisturiser (known as ointment) may be necessary in winter or very low humidity environments.
12. Hairy or sweaty people may prefer lighter preparations (e.g. creams or lotions), especially during summer.
13. Pay attention to high-risk areas, i.e. lower limbs, heels and feet.
14. Avoid accumulation of moisturiser in toe-web spaces – maceration may facilitate development of tinea pedis or bacterial infection.

## SKIN MANAGEMENT 2:

### Key Advice for Diabetes Patients

1. General skin care measures are paramount to the maintenance of skin integrity
2. Reduce time spent in air-conditioned rooms.
3. Apply sunscreen (SPF30+) every morning and 20min before going outdoors.
4. Reduce solar damage by staying out of the sun between the peak UV radiation times of 10am to 3pm. Use an app such as the 'SunSmart UV Alert' to check the UV index.
5. Wear smooth fabrics that allow the skin to breathe, such as cotton, silk, or fine merino wool.
6. Seek early medical attention for any abrasion, blister, rash, etc.
7. Weight loss will have a positive effect on plantar keratoderma and cracked heels
8. Supportive and protective footwear is essential to prevent friction point development.
9. Identify, remove or address other factors, e.g. oral medications such as statins.

## Prevention of Diabetic Foot Disease

Diabetic foot disease is a serious chronic complication of diabetes mellitus that is associated with an increased risk of infection and ulceration, which can lead to amputation. The economic burden of diabetic foot disease is considerable.<sup>34,35</sup> In the UK, for example, the cost of diabetic foot care was estimated at £580 million in 2010-11.<sup>35</sup> The risk of lower limb amputation is 20-fold higher in patients with diabetes mellitus compared with non-diabetes patients.<sup>36</sup> Hence, prevention and treatment strategies targeting diabetic foot disease are likely to be cost effective and potentially cost saving.<sup>37</sup>

When severe, xerosis of the soles of the feet, with scaling, cracking and fissures, can facilitate the development of diabetic foot disease.<sup>30,38,39</sup> Callus formation, which results from excessive pressure and friction, can precede necrosis and the breakdown of the soft tissue over the bony prominences of the feet. This contributes to the development of diabetic foot disease, with diabetic foot ulcers typically being surrounded by a ring of callus.<sup>12,38</sup> Prevention of xerosis and callus formation is therefore an important intervention that should help to reduce the risk of diabetic foot disease.<sup>12,38</sup>

Critical in the prevention of diabetic foot disease is tight glycaemic control to minimise the risk of peripheral microvascular disease and peripheral neuropathy, which are major contributing factors in the development of diabetic foot disease.<sup>38</sup> For example, having demonstrated a correlation between deep fissures and diabetic microangiopathy, a group of German researchers concluded that control of blood supply should be effective for preventing deep fissures prone to ulceration.<sup>39</sup>

Also important in the prevention of diabetic foot disease are routine examination of the feet, pressure point relief, minimisation of callus formation, and prevention of xerosis.<sup>12,38</sup> A strategy involving the use of emollients and keratolytic-enriched formulations should be beneficial in preventing and treating dry skin and calluses of the feet, and hence help to reduce the risk of the diabetic foot disease.<sup>16</sup>

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### EXPERT COMMENTARY – *Hon. Associate Professor Marius Rademaker*

Diabetes affects over 350 million people worldwide and this is expected to increase to half a billion by the year 2030. Whilst we know that diabetes can have profound negative effects on the kidneys, retina and peripheral nerves, amongst other tissues, skin involvement is often under-recognised. As many as two-thirds of patients may develop skin complications from their diabetes. These can range from minor itch and dry skin (xerosis), to diabetic dermopathy, necrobiosis lipodica and scleredema adultorum. What is often not appreciated is the significant accelerating effect that diabetes has on the cutaneous (photo-) ageing process.

Whilst the exact pathogenic mechanisms for each skin complication remains unclear, we appreciate that hyperglycaemia itself results in epidermal dehydration. This coupled with a change in skin pH, a decrease in antimicrobial peptides (resulting in impaired innate immune response), delayed wound healing, and accumulation of advanced glycation end products (AGEs), results in an increased risk of xerosis and skin infections. Unfortunately, poorly controlled glucose levels induce both macro- and microangiopathy, as well as damage to peripheral nerves, further exacerbating cutaneous injury.

Ideally, tight glucose control (and weight reduction in type 2 diabetes mellitus), from the time of diagnosis, will reduce the cutaneous complications, with new HbA1c targets of <48 mmol/mol (6.5%). However, this is a difficult target to achieve, so skin care will remain a vital component of diabetes care. The early adoption of good skin care, with regular use of appropriate moisturisers and emollients, sunscreens and specific complication-directed therapies, is essential. Early referral to a dermatology team should be considered to minimise irreversible skin damage.

### EXPERT COMMENTARY – *Dr Patricia Lowe*

Poor skin integrity is an early sign of poor glycaemic control in the diabetic patient. This review article serves as a timely reminder for all medical and allied health professionals involved in the care of diabetic patients to check the integrity of their patients' skin, particularly in high risk areas such as the lower limbs and feet.

Intervention at an early stage is critical. Just as health professionals advise general (non-prescription) measures for other disorders, e.g. hypertension, we are uniquely placed to reinforce the message about maintaining skin integrity to diabetic patients. These simple general and specific measures are outlined in the text and highlights boxes of this review. Being proactive rather than reactive will only help to reduce the burden of diabetic skin disease in the long run, especially those of the foot.

If left untreated, xerotic skin becomes pruritic causing significant symptomatic distress to patients. The skin also becomes more sensitive to external elements and a vicious cycle begins, wherein poor skin integrity leads to entry of infective agents such as bacteria (cellulitis) or dermatophyte fungi (tinea), which further reduces barrier function, along with reduced ability to care for the skin if the patient's activities of daily living are compromised.

Although a chronic condition, xerosis tends to wax and wane, so patients may subconsciously reduce compliance with skin care especially during warmer months. It is essential to remind your patient that general skin care measures are a vital part of their daily diabetic routine.

Xerosis is not the only skin issue these diabetic patients experience. Thus, a full cutaneous examination for skin cancers and other diabetic related dermatoses should be performed by the Dermatologist.

## Take-Home Messages

- Dry skin is a common skin condition in people with diabetes mellitus, especially dry skin of the feet with the heels being particularly affected.
- Dry skin can lead to cracks and fissures that can lead to low-grade inflammation.
- Cracks and fissures are associated with an increased risk of infection and foot ulceration (diabetic foot disease), which can eventually lead to amputation.
- Regular and correct application of appropriate moisturisers and emollients can be effective in improving xerosis.
- As an adjunct to tight glycaemic control, regular use of moisturisers and emollients may help to reduce the risk of diabetic foot disease.

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