Evaluation of the moisturizer Pédimed® in the foot care of diabetic patients

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Abstract

Aim. – Xerosis is one of the most common abnormalities observed in the diabetic foot, promoting ulceration through the development of fissures and hyperkeratosis. Its treatment is therefore paramount and must be implemented early on. The objective of this study was to assess the moisturizing properties of Pédimed® cream in the treatment of foot xerosis in diabetic patients.

Methods. – In this randomized double-blind study, Pédimed® and its placebo were randomly allocated to the right/left foot of each patient (one active/one control side). Products were applied twice daily for 4 weeks. Xerosis was assessed using the clinical Xerosis Assessment Scale (XAS), corneometry (skin hydration measurement) and D-Squame® (scale sample analysis) after 14 (D14) and 28 (D28) days of treatment.

Results. – Twenty-four men and 30 women, aged 57.0 ± 12.7 years, with type 1 or type 2 diabetes and moderate-to-severe foot xerosis were included. A dramatic decrease in XAS score that was more marked with Pédimed® than with placebo was observed from D14 (38.1% vs 20.9%, P < 0.0001), reaching 61.9% vs 34.9% at D28 (P < 0.0001). The number of feet with fissures was greatly reduced with Pédimed® compared with placebo at both D14 (11.1% vs 22.2%, P = 0.031) and D28 (5.6% vs 18.5%, P = 0.039). Skin hydration increased by 48.9% with Pédimed® vs 31.7% with placebo at D14 (P = 0.0002), reaching 57.3% vs 36.5% at D28 (P < 0.0001). All D-Squame® parameters showed greater improvement with Pédimed®. Product tolerability was excellent.

Conclusion. – Validated clinical and paraclinical tools demonstrated the efficacy of Pédimed® in improving xerosis and reducing fissures of the feet in diabetic patients.

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Keywords: Diabetes; Foot lesions; Xerosis; Dry skin; Emollient

Résumé

Évaluation de l’émollient Pédimed® dans la prise en charge du pied du diabétique.

Objectif. – La xérose est l’une des anomalies les plus fréquentes du pied diabétique, favorisant le développement de fissures et d’hyperkératose et ainsi la survenue d’ulcérations. L’objectif de cette étude était d’évaluer les propriétés emollientes de la crème Pédimed® dans la xérose du pied de patients diabétiques.

Méthodes. – Dans cette étude randomisée en double-insu, Pédimed® et son placebo ont été aléatoirement attribués au pied droit/gauche de chaque patient (un côté actif/témoin), pour application biquotidienne pendant quatre semaines. La xérose a été évaluée grâce au score clinique XAS, par cornéométrie (mesure de l’hydratation cutanée) et par D-Squame® (analyse de squames) après 14 (j14) et 28 (j28) jours de traitement.

Résultats. – Vingt-quatre hommes et 30 femmes (57,0 ± 12,7 ans), présentant une xérose des pieds modérée à sévère ont été inclus. La réduction du score XAS a été plus importante avec Pédimed® qu’avec placebo, dès j14 (38,1% contre 20,9%, P < 0,0001), atteignant 61,9% contre 34,9% à j28 (P < 0,0001). Les pieds présentant des fissures étaient moins nombreux avec Pédimed® qu’avec placebo à j14 (11,1% contre 22,2%; P = 0,031) et à j28 (5,6% contre 18,5%; P = 0,039). L’hydratation cutanée a augmenté de 48,9% avec Pédimed® contre 31,7% avec placebo à j14 (P = 0,0002), atteignant 57,3% contre 36,5% à j28 (P < 0,0001). Tous les paramètres D-Squame® ont été plus améliorés avec Pédimed®. La tolérance au produit a été excellente.

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1. Introduction

Diabetic foot is characterized by abnormalities and neuropathy-related issues that increase the risk of chronic ulcers. While chronic sensorimotor diabetic peripheral neuropathy can cause a progressive loss of protective sensations and foot deformities, autonomic neuropathy is considered to play a major role in promoting anhidrosis, hyperkeratosis and callus formation in weight-bearing areas due to sudomotor dysfunction [1]. All these abnormalities predispose patients to foot ulceration, as emphasized by the International Working Group on the Diabetic Foot [2]. Moreover, xerosis has a weakening effect on the stratum corneum (superficial skin layer) that may lead to cracks and fissures [3] and, subsequently, to foot infections [4]. After assessing the risk factors for ulceration in diabetic patients, Litzelman et al. [5] noted that 82.1% of diabetic patients also suffered from xerosis, combined or not with fissures or cracks. As a result, preventing ulceration is paramount, as more than 2% of these patients will develop new foot ulcers each year after an initial episode [6].

Simple measures, including the treatment of dry skin and fissures, are effective in preventing foot ulcers [7–9]. The management of dry or fissured skin is based on the application of a topical moisturizer as soon as xerosis is detected [10]. The aim is to improve cell hydration so as to restore skin softness and elasticity [11].

Moisturizing creams are generally based on glycerine, paraffin, urea and lactic acid. By forming a lipid layer on the skin surface (occlusive action), glycerine and paraffin help to improve skin barrier function and prevent dehydration, thus reducing transepidermal water loss. On the other hand, glycerine, urea and lactic acid are part of the so-called ‘natural moisturizing factor’, a group of water-soluble substances responsible for maintaining water within the keratinized epidermal layers of the skin [11]. The properties of urea are concentration-dependent, with moisturizing effects at 5%, desquamation action at 20% and keratolytic action at 40% [12]. Lactic acid is a hygroscopic water-soluble compound characterized by its high water-capturing ability and excellent substantivity on cutaneous proteins, enabling long-lasting efficacy. The properties of these constituents, together with their complementary action (namely, mechanical barrier function and skin hydration) form the basis of their benefits in the treatment of xerosis [11,13]. Several studies have focused on the efficacy of moisturizers in a variety of dry skin conditions [14–17], but only one assessed their impact on the feet of diabetic patients [18]. In that study, Pham et al. demonstrated the efficacy of a cream containing 10% urea and 4% lactic acid in the treatment of xerosis of the feet.

The aim of the present study was to assess both the efficacy and safety of Pédimed®, a moisturizer specifically designed for the treatment of xerosis of the feet in diabetic patients.

2. Methods

The present randomized, double-blind, placebo-controlled study was conducted at the European Skin Research Centre at Hôtel-Dieu in Toulouse, France. The objective was to compare the moisturizing properties of Pédimed® with those of a placebo. Each patient served as his/her own control. Pédimed® and the placebo were randomly allocated to either the right or left foot of each patient (resulting in one active and one control foot). The study was performed in accordance with the principles of the Helsinki Declaration and the applicable local regulations, and was approved by the local Independent Ethics Committee. Written informed consent was obtained from each patient enrolled in the study before any procedures were carried out.

2.1. Patients

Patients enrolled in the study were men and women, aged between 18 and 75 years, with type 1 or type 2 diabetes and moderate-to-severe xerosis (xerosis assessment scale (XAS) score ≥ 3 to ≤ 7) on both feet (XAS score differences of ≤ 1 between feet), who had not used any topical moisturizers or keratolytic agents on their feet for at least 2 weeks. The main exclusion criteria were: foot lesions (ulcer, skin infection), excluding benign fissures; severe hyperkeratosis (requiring chiropody treatment); peripheral arterial disease diagnosed by the absence of the two peripheral pulses (dorsalis pedis and tibialis posterior) and/or a transcutaneous partial pressure of oxygen (TcpO2) less than 25 mmHg in the supine position; major static disorders affecting the feet (particularly unilateral or bilateral amputation); and hyperkeratotic disease not related to diabetes (namely, atopic dermatitis, ichthyosis, psoriasis and haemodialysis).

2.2. Study products

The test product was Pédimed® (Pierre Fabre Médicament, Boulogne, France), a white-coloured cream containing 10% glycerine, 5% urea, 1% lactic acid (moisturizing agents) and 8% paraffin (occlusive agent) in an emulsion base. The placebo was an emulsion base with none of the active ingredients, and was otherwise identical to Pédimed® in terms of colour, odour and texture. Patients were asked to apply Pédimed® and the placebo themselves to their right/left feet (randomly assigned) after thorough washing (with A-Derma® soap) and drying. A pea-sized amount of each product was applied in a thin layer to the entire foot, including the sock area, every morning and evening for 28
of skin capacitance) on the upper surface of the foot [19].

Xerosis was also assessed using biometrology methods. The Xerosis Assessment Scale and overall clinical cutaneous score in the studied diabetic patients.

### Assessment of xerosis

<table>
<thead>
<tr>
<th>Assessment of xerosis</th>
<th>XAS</th>
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<tbody>
<tr>
<td>Normal skin</td>
<td>0</td>
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<tr>
<td>Few minute flakes</td>
<td>1</td>
</tr>
<tr>
<td>Many undifferentiated skin flakes</td>
<td>2</td>
</tr>
<tr>
<td>Some polygonal scales</td>
<td>3</td>
</tr>
<tr>
<td>Moderate number of polygonal scales</td>
<td>4</td>
</tr>
<tr>
<td>Large number of polygonal scales</td>
<td>5</td>
</tr>
<tr>
<td>Fissuring between scales</td>
<td>6</td>
</tr>
<tr>
<td>Moderate deep fissuring between scales</td>
<td>7</td>
</tr>
<tr>
<td>Deep fissuring</td>
<td>8</td>
</tr>
<tr>
<td>Xerosis assessment scale /8</td>
<td></td>
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</tbody>
</table>

### Sensation on palpation

<table>
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<tr>
<td>Supple skin</td>
<td>0</td>
</tr>
<tr>
<td>Stiff skin</td>
<td>1</td>
</tr>
<tr>
<td>Rough skin</td>
<td>2</td>
</tr>
</tbody>
</table>

### Assessment of keratosis (thickness of corneal layer)

<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>No hyperkeratosis</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkeratosis not severe</td>
<td>1</td>
</tr>
<tr>
<td>Severe hyperkeratosis (requiring chiropody treatment)</td>
<td>2</td>
</tr>
<tr>
<td>Overall clinical cutaneous score /12</td>
<td></td>
</tr>
</tbody>
</table>

### Results

Sixty-three patients were screened for this study and 55 (87.3%) were included. Four patients failed to meet the criteria for xerosis—two had psoriasis and two women were not using the appropriate contraceptive methods. Of the 55 patients included, 54 completed the study and were included in the analyses. One patient was excluded before the study started because he was within the exclusion period of another trial, a criterion stipulated by the French National Volunteer Database.

The demographic characteristics of the study population are shown in Table 2. Type 1 diabetes had been progressing for 28.7 ± 14.1 years and type 2 diabetes for 13.8 ± 9.2 years. Body mass index (BMI) was lower in type 1 (30.3 kg/m²) than in type 2 (23.6 kg/m²) diabetics, which is consistent with the pathophysiological link found between overweight and type 2 diabetes through insulin resistance. In terms of compliance, 96.3% of patients reported a number of product applications greater or equal to 80% the scheduled number, with no differences between the two feet. The mean amount of product used was within the predefined range (70–130%) of the recommended amount in 53.7% and 55.6% of the feet treated with Pédimed® and placebo, respectively. All patients (except two) with compliance ranging from 0 to 10. Safety was assessed by noting all observed local, regional and systemic adverse events. Compliance was estimated by means of a diary in which patients recorded the twice-daily applications, and also by weighing the tubes of product at D14 and D28.

### Statistical analysis

Statistical analyses were performed on the full patient dataset according to an intention-to-treat approach. Quantitative parameters were compared using the Wilcoxon signed rank test when data displayed a symmetrical distribution, or with the sign test when this was not the case. Qualitative parameters were compared using the McNemar exact test. Safety analyses were descriptive.

All analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC, USA). All tests were two-tailed, with a level of significance set at 5%.

### 3. Results

The Xerosis Assessment Scale and overall clinical cutaneous score in the studied diabetic patients.

#### Assesment criteria

The assessment criteria were determined at baseline (D0), and after 14 (D14) and 28 days (D28) of treatment. Xerosis was assessed clinically using both the XAS and the overall clinical cutaneous score (OCCS). The XAS, described elsewhere by Pham et al. [18], is a nine-point scale (0–8) that assesses the amount and size of skin flakes, scales and fissures (Table 1). This classification system is a useful tool to assess the impact of a moisturizing cream. The OCCS is a 15-point score, calculated as the sum of the XAS score plus skin roughness and the presence of hyperkeratosis (Table 1). In addition, the number of feet affected by xerosis, hyperkeratosis and fissures were determined by physical examination. All clinical assessments were performed by the same investigator in a given study patient.

Xerosis was also assessed using biometrology methods. The hydration index was determined by corneometry (measurement of skin capacitance) on the upper surface of the foot [19]. Scaling was assessed by scale sample analysis from computerized images using the D-Squame® method [20]. The parameters studied were the heterogeneity, thickness, optical density and surface area of the scales.

Patients’ assessments of the products in terms of efficacy and pleasantness of use were carried out using a visual analogue scale.
As shown in Fig. 1A, there was a dramatic decrease in XAS score as early as D14: 38.1% in the Pédimed® group vs 20.9% in the placebo group, with a more marked effect with Pédimed® ($P < 0.0001$). At D28, this decrease reached 61.9% with Pédimed® and 34.9% with placebo ($P < 0.0001$). These results were confirmed by the OCCS findings (Fig. 1B). Indeed, whereas the baseline score was about 6.0 ± 1.9 in both groups, there was a significant decrease from D14, which was more marked with Pédimed® than with the placebo (38.3% vs 23.3%, $P < 0.0001$), and further enhanced at D28 (63.3% vs 36.7%, $P < 0.0001$).

Clinical assessment of hyperkeratosis and fissures on the feet revealed no significant differences between the groups at baseline. Hyperkeratosis decreased throughout the duration of treatment, with no significant differences between the groups (Fig. 2). In addition, the feet affected by fissures were significantly more improved by Pédimed® compared with the placebo after 14 days of treatment (11.1% vs 22.2%, $P = 0.031$), a difference that was sustained until the end of treatment at D28 (5.6% vs 18.5%, $P = 0.039$).

As shown in Fig. 3, the hydration index measured by corneometry increased between D0 and D14 by 48.9% with
Pédimed® vs 31.7% with the placebo ($P = 0.0002$). This increase was even more marked at D28, reaching 57.3% with Pédimed® vs 36.5% with the placebo ($P < 0.0001$). Also, all D-Squame® parameters showed greater improvement with Pédimed® than with the placebo after 14 days of treatment. However, at D28, only scale thickness and the heterogeneity index remained significantly more improved with Pédimed® than with the placebo (Fig. 4).

As for product safety, four patients reported a total of five adverse events. Their causal relationship with the study product was excluded in four cases (bullous dermatitis, sciatica, pyrexia, shoulder surgery) and was non-assessable for one event (mild burning sensation). No cases of contact allergy were reported.

### 4. Discussion

The aim of the present study was to demonstrate both the efficacy and safety of Pédimed® in the treatment of foot xerosis in diabetic patients. Each patient served as his/her own control (Pédimed® or the placebo being randomly assigned to the right/left foot). The study population was similar to the national sample that was representative of the French diabetic patients included in the ENTRED (Echantillon National Témoin Représentatif des Personnes Diabétiques) study [21] in terms of demographic characteristics, medical history for diabetes and co-morbidities.

Xerosis was assessed using validated clinical and paraclinical tools such as the XAS [18], corneometry [19] and D-Squame® [20]. At baseline, no differences were seen between the feet randomized to Pédimed® or the placebo, regardless of the test parameters. Pédimed® was shown to significantly reduce diabetic foot xerosis compared with the placebo as early as D14. This superiority was subsequently growing until the end of study (Fig. 1). Pédimed® also demonstrated a greater potential to reduce hyperkeratosis and fissures.

In the present study, the degree of improvement in XAS scores achieved after 14 and 28 days of treatment was greater than that observed by Pham et al. in 2002 [18], although the patients in our study had less severe xerosis at baseline. To address this issue, additional analyses were performed to take into account the severity of xerosis at baseline (data not shown). These showed that the efficacy of Pédimed® was positively correlated with baseline xerosis severity, and that this efficacy was sustained even the presence of hyperkeratosis of the feet.

One limitation of the present study was its short period of treatment assessment. However, given the type of product (a moisturizer), no reduction in product efficacy related to duration of use is likely. This was supported by the stability of the intergroup difference in XAS score observed over time: 43.8%
at D14 and 42.3% at D28. Another point was the absence of any difference in the number of applications and amount of product used between the periods D0–D14 and D14–D28, suggesting that compliance would be satisfactory in the long term.

To explore the pathophysiological pathways leading to clinical changes, biometrology measurements were performed. The hydration index assessed by corneometry increased with both products, but significantly more with Pédimed® compared with the placebo whatever the time point considered, thereby attesting to the better moisturizing properties of Pédimed®. Furthermore, Pédimed® demonstrated significantly better control of desquamation (assessed by the D-Squame® method) compared with the placebo after 14 days of use as regards surface area, thickness, optical density and the heterogeneity index of scales. After 28 days of treatment, the difference between the two groups remained significant only for scale thickness and the heterogeneity index. This was probably due to the hydrating effect of the excipients contained in the placebo, an effect that is well known and frequently observed in studies conducted in the field of topical products. However, an effect of the daily foot care, including foot soaping and washing by the patients, cannot be excluded.

Regarding the overall assessment of patients, both products were considered similar in terms of efficacy after 14 days of use (6.0 vs 5.4, P = 0.334); however, after 28 days, Pédimed® was adjudged as better than the placebo (7.0 vs 5.8, P = 0.015). Pleasantness of use was found to be identical, regardless of the time point (P = 0.774 at D14 and P = 0.743 at D28). This suggests that patients were unable to distinguish between the two test products in terms of formulation, which supports the validity of the blinded study method and reinforces the results as regards efficacy.

Finally, clinical and paraclinical validated tools allowed the efficacy of Pédimed® cream to be demonstrated by both improving xerosis and reducing fissures on the feet of diabetic patients. The product also proved to have excellent tolerability.

In the context of preventing foot ulcers in diabetic patients, it is essential to control all abnormalities, especially xerosis, to reduce the development of cracks and fissures [8–10]. Daily applications of a moisturizing cream are easy to perform and reinforce the frequency of foot self-examination, one of the five cornerstones proposed by the International Working Group on the Diabetic Foot consensus guidelines [2]. Improved skin hydration reduces the recurrence of hyperkeratosis and also plays a role in preventing the onset of ulcers [7,11].

In conclusion, the present study highlighted the usefulness of Pédimed® cream for treating the skin disorders that are frequently seen affecting the feet of diabetic patients and may, thus, help to prevent further complications, such as ulceration.

Conflict of interest statement

E.G., A.R. and A.D. are employees of Pierre Fabre Laboratories. J.M. has been a member of the Advisory Board, has served as a principal investigator, and has received fees for medical presentations from Pierre Fabre Laboratories. F.C.P. has served as an investigator.

References