Efficacy of topical Urea, arginine and carnosine (Ureadin Rx DB ISDIN) in the treatment of severe xerosis of the feet in Type II Diabetic patients.

A randomized, assessor-blinded controlled trial vs. standard glycerol-based emollient cream.

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Abstract

Background: Xerosis is a common skin disorder frequently observed in diabetic patients. An effective hydration of foot skin in diabetics is a relevant preventive strategy in order to maintain an healthy foot. Urea is considered an effective hydrating and emollient topical product.

Study aim: The aim of the present study was to evaluate the efficacy of topical urea 10% with arginine and carnosine (Ureadin Rx DB, ISDIN Spain) in comparison with glycerol-based emollient topical product (Dexeryl, Pierre Fabre), in Type II diabetic patients.

Patients and Methods: We assessed the effect of urea 10% lotion (UL) containing also arginine and carnosine on skin hydration in a randomized, evaluator-blinded comparative study in 40 type II diabetic patients, aged 40-75 years, treated with UL or the comparator for 28 days with a twice-daily application. The principal outcomes were the Dryness Area Severity Index (DASI) Score and the Visual Analogue Score (VAS) for skin dryness evaluated at baseline and at the end of study period by an investigator unaware of treatment allocation.

Results: UL induced significantly greater hydration than the glycerol-based emollient cream with a 89% reduction in DASI score (from 1.6 to 0.2; p < 0.001) in comparison with baseline values. After 4 weeks, compared with the control group, DASI score in UL treated group was significantly lower (0.2 vs. 1.0; p=0.048). VAS score significantly increased in both groups during treatment. VAS score at the end of treatment period was significantly higher in UL group in comparison with the control group (9.8 vs. 8.2; p=0.05).

Conclusion: application of urea 10% lotion increases skin hydration and alleviates the condition of skin dryness in Type II diabetic patients in comparison with a control glycerol-based emollient product.

Key Words: Skin xerosis, diabetes, urea, controlled trial.
Introduction and Background:

Cutaneous complications are common in diabetes, with approximately 30% of patients experiencing some skin involvement during the course of their illness and these may also be an early indicator of undiagnosed diabetes. In particular xerosis is a common skin disorder frequently observed in diabetic patients. An effective hydration of foot skin in diabetics is a relevant preventive strategy in order to maintain a healthy foot. Emollients and moisturizers topical products are efficacious in repairing the epidermal barrier function and in correcting xerosis. However few studies have been conducted in diabetic patients assessing wheter this treatment can help correct alterations in functional and mechanical properties of diabetic skin. Urea is considered an effective hydrating and emollient topical product. Recent experimental data performed in human keratinocytes suggest that urea is not a simple emollient compound but it is able to improve cell differentiation increasing gene expression of transglutaminase, filaggrin, aquaporin, and loricrin, therefore improving keratinocytes differentiation. Arginine is an important substrate for Nitric Oxide formation. In diabetic skin a deficit in NO production as been demonstrated. This reduction could be due to an enhanced arginine consumption linked to high arginase enzymatic activity. Carnosine is able to interfere with advanced glycosilated endproducts formation. This action has been also demonstrated for urea. Recently a topical product containing urea 10%, arginine and carnosine has been developed (Ureadin Rx DB, Isdin Spain). This formulation, from a theoretical point of view, is an interesting topical product with a composition particularly suitable for the specific treatment of the xerotic skin in diabetic patients. However so far not controlled clinical data are available particular with a head-to-head comparison design with standard topical emollient treatment.

Study aim

The aim of the present study was to evaluate the efficacy of topical urea (Ureadin Rx DB, ISDIN) in comparison with glycerol-based emollient topical product (Dexeryl, Pierre Fabre), in the treatment of xerotic skin in Type II diabetic patients.
Research Design, Patients and Methods

The present study was a mono-center prospective, parallel group, randomised, assessor-blinded trial. Randomisation list with a 1:1 ratio and with a block of 4 was generated by the mean of statistical software (G-Power). Study trial was registered in the Dutch Trials Register (trial number 3328). Local Institutional Review Board approved the study protocol. Study was performed between March 2011 and February 2012. Patients were enrolled in the trial after their written informed consent according to the Declaration of Helsinki. We assessed the effect of urea 10% lotion (UL) arginine and carnosine on skin hydration in 40 type II diabetic patients, aged 40-75 years, treated with UL or the comparator (EC) for 28 days with a twice-daily application regimen. The principal outcomes were the Dryness Area Severity Index (DASI) Score, according to Seerup et al, and the Visual Analogue Score (VAS) for skin dryness evaluated at baseline and at the end of study period by an investigator unaware of treatment allocation (GF). The DASI score evaluates dry skin assessing with a 5 point Likert scale ranging from 0=no dryness to 4=severe dryness. Secondary endpoint was the patient-assessed itch sensation according to Hagermak. Statistical analyses were performed using SPSS statistical software (ver 13.0). Data were expressed as mean (SD). All P values were two-sided. The trial was designed as a superiority trial. The power calculation assumed a difference between the two treatments in the DASI score at week 4 of at least 1.1 points with an effect size of 0.6. This assumption provided 90% power at an alpha level of .05 (two-tailed test) for a sample size of at least 40 evaluable patients in total. Sample size calculation was performed using G*Power program Ver.3.03 (Kiel, Germany). Two-tailed Mann-Whitney (unpaired) and Wilcoxon (paired) tests were applied to compare treatments and to compare baseline levels with values at the end of study period. The analysis was based on the intention-to-treat principle and involved all patients who were randomly assigned to the treatments. A P value >0.05 was considered statistically significant. Inclusion criteria were an history of Type 2 Diabetes mellitus of at least 6 years. Main exclusion criteria were: insulin-dependent diabetes mellitus, an history of clinical peripheral disease, a positive history of ulcer of the lower limb.
Results

A total of 78 patients were screened for inclusion in the study. A total of 40 patients, fulfilling inclusion and exclusion criteria were enrolled: 20 were randomised to UL and 20 to EC group. Table 1 shows the patients characteristics at baseline. Main characteristics at randomisation were similar in the two groups even if there was a trend in patients randomised to UL regarding age and duration of diabetes. All patients concluded the 4-week treatment period. Figure 1 shows the study flowchart. UL lotion induced significantly greater hydration than the glycerol-based emollient cream with a 89% reduction in DASI score (from 1.7 to 0.2; p < 0.001) in comparison with baseline values. After 4 weeks, compared with the control group, DASI score in UL treated group was significantly lower (0.2 vs. 1.0; p=0.048). (Figure 2). VAS score significantly increased in both groups during treatment. VAS score at the end of treatment period was significantly higher in UL group in comparison with the control group (9.8 vs. 8.2; p=0.05) (Figure 3). Itching score (IS) at baseline were 8.5 in UL and 9.3 in EC group. At week 4, IS increased significantly (P=0.05) in UL to 9.9 in comparison to baseline. In EC group IS was 9.7 at week 4. No differences were observed in the two groups at week 4.

Conclusion

Diabetes mellitus induces many pathophysiologic changes in the skin\textsuperscript{15}. Xerosis (with prevalence higher than 40%) with pruritus and scleroderma-like skin changes are the most commonly observed cutaneous manifestations of this common disease\textsuperscript{16}. In 238 subjects with insulin-dependent diabetes mellitus Yosipovitch et al\textsuperscript{17} found that ichthyosiform skin changes were the most common and prevalent skin alteration observed in 48% of the evaluated sample. Diabetes also induces increase in the dermis of advanced glycosylation end products (AGEs), which may be responsible for some skin changes in persons with elevated blood sugars\textsuperscript{18}. Xerosis (with prevalence higher than 40%) with pruritus and scleroderma-like skin changes are the most commonly observed cutaneous manifestations of this
common disease. Urea and carnosine could favourably interfere with formation and accumulation of advanced glycated endproducts. Arginine supplementation improve microcirculation in diabetes. UL is a topical product containing urea 10%, arginine and carnosine. Our study has shown that application of urea 10% associated with arginine and carnosine lotion increases skin hydration and alleviates the condition of skin dryness in Type II diabetic patients in comparison with a control glycerol-based emollient product. Some limitations should be considered in evaluating our results. First this study was not double-blind. The main difficulty in performing a double-blind trial in this setting was linked to the different formulations of the study products (lotion versus a cream). Therefore we decided to perform an assessor-blinded evaluation of the primary endpoint of the study. A second limitation of our study is that we have evaluated as primary endpoint a subjective clinical assessment parameters (DASI score and the VAS) instead of an instrumental objective variable. However the main therapeutic goal of emollient treatment in diabetes is to obtain an increase in hydration of the skin clinically evaluable. Further studies are necessary to evaluate if the treatment with this topical product could be associated with improvement in microcirculation and/or modification of skin structure in diabetes.

Acknowledgement.

The study was funded by independent non profit source. Study drugs were supplied by Isdin Italy. No potential conflicts of interest relevant to this paper were reported. AF and GF had the original study idea. MM helped regarding study design, protocol definition, data collection and analysis.
### Table

Patients characteristics at randomization, mean (SD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>UL group (n=20)</th>
<th>EC group (n=20)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>10/10</td>
<td>6/14</td>
<td>ns</td>
</tr>
<tr>
<td>Age, years</td>
<td>66(7)</td>
<td>58(8)</td>
<td>ns</td>
</tr>
<tr>
<td>History of Diabetes, years</td>
<td>14 (6)</td>
<td>9(3)</td>
<td>ns</td>
</tr>
<tr>
<td>Serum glucose mg/100 mL</td>
<td>153 (40)</td>
<td>153 (21)</td>
<td>ns</td>
</tr>
<tr>
<td>DASI</td>
<td>1.7 (0.8)</td>
<td>1.9(0.5)</td>
<td>ns</td>
</tr>
<tr>
<td>VAS skin xerosis</td>
<td>6.1 (1.4)</td>
<td>7.3 (1.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Itching score (from 0 to 10)</td>
<td>8.5</td>
<td>9.3</td>
<td>ns</td>
</tr>
</tbody>
</table>
**Figure 1**

*Legend: Evolution of DASI score from baseline at week 2 and week 4 in UL treated patients and EC treated group.*

P< 0.001; Wilcoxon test; UL group baseline vs. week 4.

P< 0.001; Wilcoxon test; UL group baseline vs. week 2.

P=0.048 Mann-Whitney test; UL vs. EC at week 4.
Figure 2

Legend: Evolution of VAS score for skin xerosis from baseline at week 2 and week 4 in UL treated patients and EC treated group.

P=0.05; Mann Whitney test; UL vs. EC at week 4.
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Figure 2

Legend: Evolution of VAS score for skin xerosis from baseline at week 2 and week 4 in UL treated patients and EC treated group.

P=0.05; Mann Whitney test; UL vs. EC at week 4.

![VAS score of skin xerosis](chart.png)