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Original Article

Comparative Effectiveness of 10% Urea Cream and 0.1% Hyaluronic Acid Cream in Diabetic Xerosis: A Prospective Split-Body Clinical Trial

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Running Title: Urea vs Hyaluronic Acid in Diabetic Xerosis

Keywords: diabetes mellitus, hyaluronic acid, skin hydration, urea, xerosis

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Abstract:

Objective: Xerosis cutis is a common dermatological complication in diabetes mellitus and is associated with impaired skin barrier function. This study compared the efficacy of 10% urea cream and 0.1% hyaluronic acid cream in improving skin hydration, reducing transepidermal water loss (TEWL), and alleviating xerosis severity in diabetic patients.

Material and Methods: A prospective split-body clinical trial was conducted in 30 adults with diabetic xerosis. Participants applied 10% urea cream to one lower leg and 0.1% hyaluronic acid cream to the contralateral leg twice daily for 28 days. Skin hydration, TEWL, and xerosis severity were evaluated using Corneometer® CM 825, Tewameter® TM Hex, and the Overall Dry Skin Score, respectively, at baseline, day 14±1, and day 28±1. Statistical analyses were performed using paired tests with ~~a~~ significance set at p-value < 0.05.

Results: At day 28, the increase in skin hydration was significantly greater with urea cream than with hyaluronic acid cream (mean difference: 2.71 arbitrary units; 95% confidence interval: 0.56–4.86; p = 0.015), corresponding to a moderate effect size (Cohen's dz ≈ 0.47), suggesting a clinically meaningful difference.

Conclusion: In patients with diabetic xerosis, ten percent urea cream provided superior enhancement of skin hydration relative to 0.1% hyaluronic acid cream, whereas both formulations showed similar efficacy in improving barrier function and reducing clinical xerosis severity.

Keywords: diabetes mellitus, hyaluronic acid, skin hydration, urea, xerosis

Introduction

Diabetes mellitus continues to represent a significant global health challenge, with an increasing prevalence worldwide. Beyond its well-established systemic complications, diabetes can profoundly affect skin physiology. Cutaneous manifestations are commonly observed in patients with diabetes and are associated with chronic hyperglycemia-induced alterations in microcirculation, immune regulation, and epidermal homeostasis[1,2].

Among the various cutaneous manifestations of diabetes mellitus, xerosis cutis is particularly prevalent, especially in patients with type 2 diabetes. Chronic hyperglycemia

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contributes to impaired epidermal function through disruption of lipid synthesis, abnormal keratinocyte differentiation, and altered filaggrin metabolism. These alterations compromise stratum corneum barrier function and increase transepidermal water loss (TEWL), resulting in clinically dry and fragile skin. Without appropriate treatment, xerosis may progress to fissuring and predispose patients to cutaneous infections[3-5].

Topical moisturizers remain the primary therapeutic approach for managing xerosis cutis. Urea, a key component of the natural moisturizing factor, improves the water-binding capacity of the stratum corneum and may influence epidermal differentiation. Hyaluronic acid, a highly hydrophilic glycosaminoglycan, possesses a strong ability to retain water and maintain skin surface hydration. Although both ingredients are widely used in dermatologic practice, direct comparisons in the specific context of diabetic xerosis remain limited[5,6].

This study directly compared the efficacy of 10% urea cream and 0.1% hyaluronic acid cream in patients with diabetic xerosis. The novelty of this study lies in its head-to-head split-body design, which incorporated objective biophysical assessments, including corneometry and TEWL measurements, together with clinical evaluations, to comprehensively assess the performance of both moisturizers in the same individual.

Material and Methods

This prospective split-body clinical trial included 30 adults aged 18–65 years diagnosed with diabetic xerosis. Participants applied 10% urea cream to the left lower leg and 0.1% hyaluronic acid cream to the right lower leg twice daily for 28 days. Outcome assessors were blinded to treatment allocation, and participants were instructed not to reveal the assigned treatments during clinical assessments.

The primary outcome was the change in skin hydration from baseline to day 28, expressed in arbitrary units (a.u.). Secondary outcomes included transepidermal water loss (TEWL; g/m²/h) and the Overall Dry Skin Score. Data distribution was evaluated using the Shapiro–Wilk test, followed by either a paired t-test or Wilcoxon signed-rank test, as appropriate. Statistical significance was defined as p-value <0.05.

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Results

Study Population

All thirty participants completed the study, with no dropouts reported. The mean participant age was 55.7 ± 8.2 years. The study population comprised 11 males (36.7%) and 19 females (63.3%). No treatment-related adverse effects were observed throughout the study period.

Skin Hydration

No significant differences in baseline hydration were observed between treatment areas. Skin hydration increased over time in both groups; however, treatment with urea cream resulted in a greater improvement at day 28 compared with the hyaluronic acid cream.

Hydration levels at baseline were similar between the lower legs. Progressive increases in skin hydration were observed in both groups throughout the study period. At day 28, the mean hydration values were 61.66 ± 7.14 a.u. on the urea-treated side and 59.30 ± 7.28 a.u. on the hyaluronic acid-treated side.

When treatment responses were directly compared, urea demonstrated a statistically significant benefit over hyaluronic acid cream. The mean paired difference between treatments was 2.71 a.u. (95% confidence interval: 0.56–4.86; p-value = 0.015), with a moderate effect size observed (Cohen's dz ≈ 0.47).

Transepidermal Water Loss

Both treatments significantly reduced transepidermal water loss (TEWL) over the study period, with no statistically significant difference observed between the urea and hyaluronic acid treatments. Although hyaluronic acid demonstrated a numerically greater reduction in TEWL by day 28, the between-treatment difference was not statistically significant (p-value = 0.452).

Xerosis Severity

Clinical xerosis severity improved in both treatment areas over the study period, with comparable outcomes observed between the urea and hyaluronic acid treatments. Assessment using the Overall Dry Skin Score demonstrated improvement in clinical dryness for both groups,

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with no statistically significant difference in the magnitude of improvement between treatments (p-value = 0.651).

Table 1. Baseline demographic characteristics of study participants (mean ± S.D., n = 30)

Table 2. Changes in skin hydration following treatment with 10% urea cream and 0.1% hyaluronic acid cream (a.u., mean ± S.D., n = 30)

Table 3. Changes in transepidermal water loss following treatment with 10% urea cream and 0.1% hyaluronic acid cream (g/m²/h, mean ± S.D., n = 30)

Table 4. Changes in Overall Dry Skin Score following treatment with 10% urea cream and 0.1% hyaluronic acid cream (mean ± S.D., n = 30)

Figure 1. Changes in mean skin hydration (a.u.) from baseline to day 28 following treatment with 10% urea cream and 0.1% hyaluronic acid cream. Data are presented as mean ± standard deviation. Progressive increases in skin hydration were observed in both treatment groups, with a greater improvement demonstrated in the urea-treated area at day 28.

Figure 2. Changes in transepidermal water loss (TEWL) from baseline to day 28 following treatment with 10% urea cream and 0.1% hyaluronic acid cream. Both treatments were associated with a progressive reduction in TEWL throughout the study period.

Figure 3. Changes in Overall Dry Skin Score from baseline to day 28 following treatment with 10% urea cream and 0.1% hyaluronic acid cream. Both treatment groups demonstrated comparable improvement in clinical xerosis severity throughout the study period.

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Discussion

Both topical treatments produced significant improvements in skin hydration, TEWL, and clinical xerosis severity in patients with diabetes mellitus. However, urea treatment resulted in significantly greater enhancement of skin hydration by day 28 compared with hyaluronic acid treatment.

The enhanced hydration observed following urea treatment is consistent with the compound's multifunctional dermatological properties. Urea increases water retention within the stratum corneum as part of the natural moisturizing factor and additionally exerts mild keratolytic

activity at concentrations near 10%. In the context of diabetic skin, characterized by impaired filaggrin metabolism and altered lipid synthesis, these mechanisms may offer distinct therapeutic advantages[4-7].

In contrast, hyaluronic acid primarily exerts its moisturizing effect through its hygroscopic properties, forming a hydrating film on the epidermal surface. Although effective in enhancing superficial skin moisture, its relatively large molecular size may restrict deeper skin penetration unless structurally modified. These mechanisms may explain why both treatments improved hydration, while urea produced a greater magnitude of improvement[6,8].

Although urea demonstrated greater enhancement of skin hydration, reductions in TEWL were comparable between treatments. These findings indicate that both agents may effectively stabilize the epidermal barrier through different mechanistic pathways. Restoration of barrier integrity in diabetic skin is likely mediated by several factors, including normalization of lipid arrangement and improved corneocyte cohesion[4,6].

Clinically, xerosis severity improved in both treatment groups. However, the degree of visible improvement did not completely correspond to the magnitude of changes detected by instrumental measurements. This discrepancy is not unexpected, as clinical scoring systems such as the Overall Dry Skin Score are semi-quantitative and rely on visual and tactile assessment. As such, they may not detect subtle differences between treatments. In contrast, objective biophysical parameters, including skin capacitance and TEWL, provide quantitative evaluation of skin hydration and barrier integrity, enabling detection of subtle physiological changes that may not be readily apparent during routine clinical examination[9,10].

The moderate effect size observed in this study suggests that the statistically significant improvement in hydration is also clinically meaningful. Furthermore, the split-body study design strengthens internal validity by reducing interindividual variability, which is particularly relevant in heterogeneous diabetic populations[11].

Several limitations of this study should be considered. First, treatment adherence was not quantitatively monitored, which may have contributed to variability in treatment exposure. Second, patient-reported outcomes, including pruritus severity and subjective skin comfort, were not

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evaluated, thereby limiting assessment of patient-centered benefits. Third, the 28-day follow-up period may be insufficient to determine the long-term durability of treatment effects. Future studies incorporating extended follow-up periods and patient-reported outcome measures are warranted to provide a more comprehensive evaluation of therapeutic efficacy.

Conclusion

Ten percent urea cream demonstrated superior improvement in skin hydration compared with 0.1% hyaluronic acid cream in patients with diabetic xerosis. Both treatments produced comparable improvements in skin barrier function and clinical xerosis severity without any reported adverse effects.

Acknowledgment

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Conflict of interest

The authors declare that there are no potential conflicts of interest related to this study.

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Table 1. Baseline demographic characteristics of study participants (mean ± S.D., n = 30)

Variable	Value
Age (years)	55.7 ± 8.2
Gender, Male / Female	11 (36.7%) / 19 (63.3%)

Table 2. Changes in skin hydration following treatment with 10% urea cream and 0.1% hyaluronic acid cream (a.u., mean ± S.D., n = 30)

Time Point	Urea 10% (Mean ± S.D.)	HA 0.1% (Mean ± S.D.)
Baseline	20.48 ± 8.63	20.83 ± 8.67
Day 14	43.61 ± 7.51	41.26 ± 7.85
Day 28	61.66 ± 7.14	59.30 ± 7.28

Primary endpoint: Mean paired difference = 2.71 a.u. (95% CI: 0.56–4.86), p-value = 0.015

Table 3. Changes in transepidermal water loss following treatment with 10% urea cream and 0.1% hyaluronic acid cream (g/m²/h, mean ± S.D., n = 30)

Time Point	Urea 10%	HA 0.1%
Baseline	17.10 ± 9.64	17.08 ± 10.68
Day 28	7.49 ± 1.89	7.18 ± 1.94

Between-treatment comparison at day 28: p-value = 0.452

Table 4. Changes in Overall Dry Skin Score following treatment with 10% urea cream and 0.1% hyaluronic acid cream (mean ± S.D., n = 30)

Time Point	Urea 10%	HA 0.1%
Baseline	2.00 ± 0.74	2.07 ± 0.78
Day 28	1.03 ± 0.18	1.07 ± 0.25

Between-treatment comparison at day 28: p-value = 0.651

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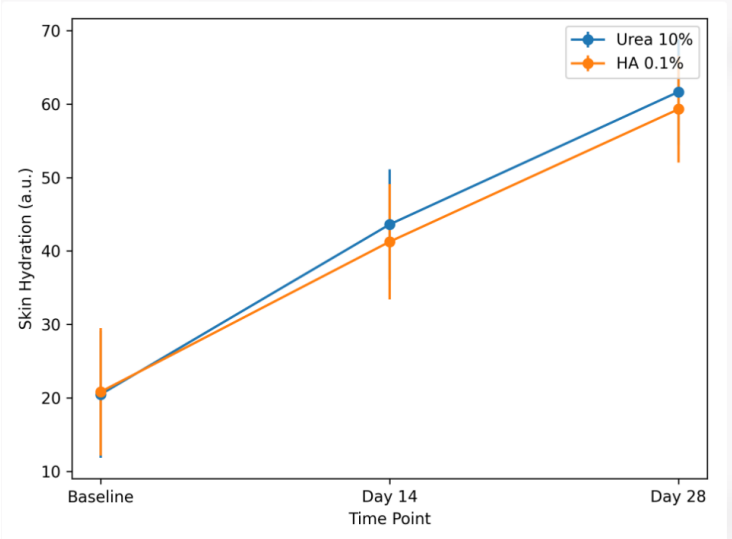


Figure 1. Changes in mean skin hydration (a.u.) from baseline to day 28 following treatment with 10% urea cream and 0.1% hyaluronic acid cream. Data are presented as mean ± standard deviation. Progressive increases in skin hydration were observed in both treatment groups, with greater improvement demonstrated in the urea-treated area at day 28.

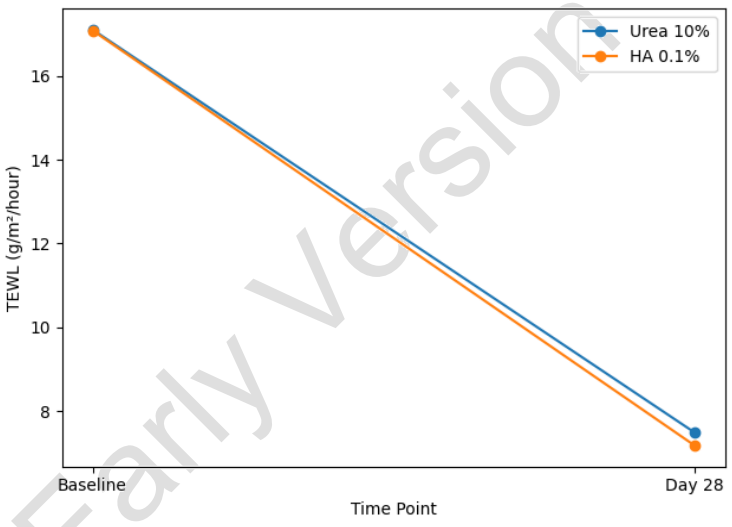


Figure 2. Changes in transepidermal water loss (TEWL) from baseline to day 28 following treatment with 10% urea cream and 0.1% hyaluronic acid cream. Both treatments were associated with a progressive reduction in TEWL throughout the study period.

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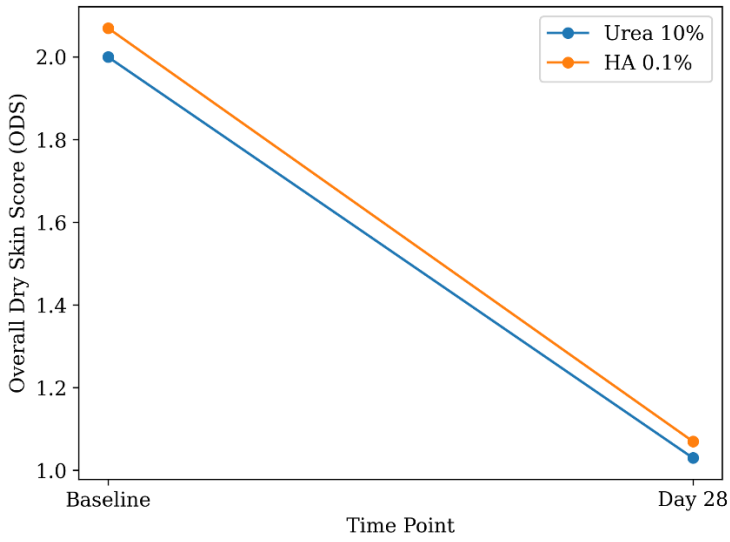


Figure 3. Changes in Overall Dry Skin Score from baseline to day 28 following treatment with 10% urea cream and 0.1% hyaluronic acid cream. Both treatment groups demonstrated comparable improvement in clinical xerosis severity throughout the study period.

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