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Implications of a Diabetic Foot Xerosis Treatment With an Emulsion Containing the Plant-Based Anionic Phospholipids

Thomas Glonek[1], Jack V. Greiner[1], Paula J. Oliver[1], and Terrance L. Baker[2,3,4]

Abstract

Purpose: This study compares and contrasts a skin cream containing plant-based anionic polar phospholipid (APP) technology with a mineral oil hydrocarbon (petrolatum)-based (MHB) skin cream technology in the treatment of skin xerosis (dryness) in diabetic feet. Skin cream with APP technology promotes phospholipid absorption, reparation of intercellular lamellae, and organization of water promoting hydration; whereas skin cream with mineral hydrocarbon-based (MHB) technology principally covers skin, preventing dehydration. **Methods:** Subjects (n = 54) with diagnoses of diabetes mellitus and foot skin dryness were studied using a multicenter, double-blind, masked-study design. An emulsion cream containing 0.05% APP in triglycerides (APP preparation) was compared to MHB skin cream, Eucerin® (MHB preparation) applied topically to skin of the feet. Graded measurements were recorded on 4 efficacy variables including dryness, erythema, fissures, and itching and neurovascular assessments. Implications of the plant-based and mineral-based skin creams in the context of skin xerosis are contrasted. **Results:** APP and MHB preparations were similar in effectiveness and safety. There was no significant difference among any of the 4 efficacy variables ($P < .5$) including neurovascular measurements. The APP preparation is absorbed into the skin, whereas the MHB skin cream leaves detectable residues after each application. **Conclusion:** Although the APP and MHB preparations were not significantly different in effectiveness and safety, distinctively, application of the APP skin cream preparation absorbed into the skin leaving no discernible residue in contrast to the MHB preparation leaving residues potentiating textile damage. Both of these technologies function in the hydration of skin; however, they differ in their modes of action. The plant-based APP preparation functions actively by phospholipid and triglyceride absorption, reparation of skin lamellae, and in the consequent delivery and organization of waters of hydration in skin. The MHB preparation functions passively, hydrating the skin it covers by sealing the skin against dehydration.

Keywords

anionic phospholipids, APP, diabetes mellitus, dry feet, dry skin, mineral oil hydrocarbons, plant-based phospholipids, skin cream, skin xerosis

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Introduction

Dry skin is a common feature of patients with diabetes mellitus. In the United States more than 34 million Americans have diabetes, which is nearly 11% of the U.S. population.[1] Every person with diabetes mellitus has a 15% lifetime risk of developing an ulceration of the foot, a consequence of dry skin. Preventing such morbidity is important given the difficulty in healing ulcerative wounds especially in the context

[1]Clinical Eye Research of Boston, Boston and Winchester, MA, USA
[2]Johns Hopkins Medicine, Baltimore, MD, USA
[3]Sollay Medical Center, Baltimore, MD
[4]Katani Hospital, Katani, Kenya

Corresponding Author:
Thomas Glonek, Clinical Eye Research of Boston, 5 Whittier Place, Ste 102, Boston, MA 02114, USA.
Email: tglonek@rcn.com

of diabetes mellitus.[2] The primary etiologies for foot ulceration are attributed to neuropathy, peripheral arterial disease, and infection, the most frequent precipitating event being minor trauma. Both autonomic neuropathy concurrent with sensory neuropathy are thought to be contributing factors to foot ulcerogenesis. These neuropathies lead to dysfunction of the microvascular blood flow. Dysfunction of the microvascular blood flow contributes to anhidrosis and eventual skin xerosis. This is especially important regarding the skin of the feet, due to its remote and distal location in the body which makes it more vulnerable to multiple disease processes including xerosis. Anhidrosis contributes to dryness of the skin through inadequate hydration, failed delivery of nutrients, as well as the development of inadequate natural oils from sudoriferous glands, one of the 5 skin appendages. Inadequate hydration and failed natural oil production contribute to anhidrosis which may cause cracks or fissures in the skin which can remain recalcitrant to treatment.[2]

A unique feature of anionic (negatively charged) phospholipids is based upon their ability to incorporate directly into damaged lamellar membranes of the skin.[3,4] Phospholipids ordinarily are derived from plant sources. Similarities exist between the restoration of ocular tear film deficiencies[5,6] and restoration of skin intercellular lamellar membranes[3,4,7-9] Historically, treatments for dry eye and dry skin have been based on mineral oil hydrocarbon sources that served to cover the diseased or injured surfaces. The human health impact of mineral oil hydrocarbons[10,11] varies widely from having no adverse effects to potential genotoxic carcinogens. In contrast, the adverse-free plant-based anionic phospholipids demonstrated restoration and strengthening of the tear film,[6,12] and subsequently such chemistry was applied successfully to restoring damaged skin.[3,4] The most common diseases of the integument are dry eye and dry skin.

Daily applications of a moisturizing cream or lotion to the feet ameliorates skin xerosis common to feet in patients with diabetes mellitus. Prevention of dry skin and its associated complications is an important part of diabetic daily foot care.[2,13] As such, daily application of a moisturizing cream or lotion to the feet has become the standard of practice.[14,15] Failure to mitigate complications of untreated skin of diabetic feet can lead to significant morbidity and mortality. Concerns have become evident in the application of moisturizers that include ease of application; moisturizing ability; the presence of residual unabsorbed moisturizer on the treated skin surface; removal of residual moisturizers from foot coverings after previous skin application; soiling of garments, linens, and footwear; additional laundering expenses; and costly replacement of soiled/discolored items, inconvenient features that can lead to patient non-compliance.

It has been well established that with maturation of the skin epidermis there is a disappearance of phospholipids.[16-18] Skin phospholipids have been precisely profiled.[19] Current applications of anionic polar phospholipid (APP) technologies have been used in the treatment of dry eye,[5,6,12] dry skin,[3,4] and the treatment of a recalcitrant foot skin fissure[7] and may offer benefits in the treatment of dry skin in the diabetic foot. For example, as a vehicle for drug delivery, enhanced penetration of the APP skin cream has been demonstrated in a study comparing the permeation rate of 1% hydrocortisone-supplemented APP cream versus 1% hydrocortisone cream alone.[20-22] Permeation rates were facilitated using APP skin cream technology which includes an emulsion using anionic polar phospholipids in a triglyceride base. The properties of this emulsion are particular to the APP skin cream technology. This study presents treatment application implications and assesses whether the APP skin cream was equal to, better than or less effective than a MHB cream for foot skin xerosis as evaluated on graded scales and by users in preference questionnaires.

Our purpose was to compare (1) the effectiveness and performance of a moisturizing non-oily cream formulated with a plant-based 0.5% APP to mineral hydrocarbon-based (MHB) skin cream considered the standard of care for dry skin therapy, and (2) to explain the differences, advantages, and disadvantages of a negatively charged phospholipid plant-based versus mineral hydrocarbon-based skin creams.

Methods

Subjects (n = 54) with diabetes mellitus with dry feet were selected. The effectiveness, performance and safety of APP technology were evaluated by 2 investigators qualified by their training as doctors of podiatric medicine using graded scales and subject preference questionnaires. Since diabetic patients with dry feet are generally in the habit of applying moisturizers to their feet, subject selection was restricted to those that practiced this habit. This 6-week observational study was a double-blind, randomized controlled study to compare the effect of an APP skin cream (APP preparation) used on 1 foot and a market leader, "Eucerin Original Formula" (MHB preparation) on the contra-lateral foot. Feet were photographed at baseline and throughout the course of treatment to document changes in signs of dryness. Questionnaires were used throughout the course of treatment to document symptoms of anhidrosis. At weekly visits, the subject was queried for opinions regarding the self-care treatment, with their comments tabulated.

APP-Containing Cream

The APP composition of the test cream consisted principally of a blend of the natural anionic phosphatides: phosphatidylglycerol, cardiolipin, phosphatidic acid, phosphatidylserine, and phosphatidylinositol, containing less than 10% neutral phospholipid residual, such as phosphatidylcholine and ethanolamine plasmalogens, and no detectable lyso-phospholipids.[3,4] The hydration capacity of

the net negative charged phospholipids, phosphatidylglycerol, phosphatidylserine, and phosphatidylinositol, when arranged in multilayers has been documented.[23] The test preparation was a non-sterile white cream aqueous emulsion containing 0.5% APP in hydrogenated vegetable (triglyceride) oil.

The cream was packaged in white plastic 2-ounce jars labeled "Foot Care Cream 1." The MHB preparation was a non-sterile white cream "Eucerin Original Formula" (Beiersdorf Inc., Norwalk, CT) repackaged from 1 lb jars into the same 2-ounce white plastic jars used as the test preparation. The MHB preparation was labeled "Foot Care Cream 2." The Eucerin Original Formula preparation used remains available to date. In addition to the control numbers on the APP and the MHB preparations, each jar also was labeled as either LEFT or RIGHT designating the foot on which the cream was to be used. The APP and MHB preparations were used in a double-blinded randomized application, where some subjects used the APP preparation on the left foot and others used it on the right foot. The MHB preparation was used on the contra-lateral foot. The APP and MHB preparations had a similar appearance but varied to a degree in fragrance and density so the user might possibly detect differences in the 2 creams. This difference also allowed assessment of preferences (Table l) as well as effectiveness. Although the user might detect differences in the 2 preparations, the subjects were not informed as to which preparation was the APP preparation and which was the MHB preparation, though if any subject had prior experience with Eucerin®, it is possible that the MHB cream might be recognized by the subject.

Subject Selection Criteria

Volunteers with diabetes mellitus with a minimum age of 18 years were recruited from February to March 1997. All patients were under the treatment of a podiatrist for foot care. Inclusion criteria included a confirmed diagnosis of Type I or II diabetes mellitus and having 2 feet even if one or more toes had been amputated. All patients were capable of keeping scheduled biweekly visits, following the prescribed treatment regimen and possessing foot skin with dryness or fissures. Exclusion criteria included pregnancy, foot amputation, lesions where the skin wounds were not closed, ulcers, and inability to be compliant with the treatment application or schedule regimen. Reasons for discontinuation in the study included 2 subjects from site 1 discontinued in the study after the first of the 4 visits. Three subjects from site 2 discontinued, that included 2 subjects with concurrent illnesses/injuries that prevented them from continuing in the protocol to the conclusion of their 6-week treatment. The third subject experienced redness on both feet and legs and discontinued treatment 3 days after the first visit with commencement of treatment. This subject experienced no long-term effects. The condition was rated as mild and only possibly indicative of a positive response to treatment since feet and untreated legs were involved. The condition did not persist after treatment was discontinued.

Study Design

This was a randomized, double-blind autocontrolled study, where diabetic patients served as their own control. Contralateral feet were treated either with the APP preparation or MHB preparation based on the study protocol, right and left designations were randomized such that the APP and MHB preparations remained randomly pre-determined and blinded. Each subject was assigned a test ID number which was maintained throughout the duration of the study. Two test sites were used to evaluate the APP and MHB preparations. Randomized right and left foot designations assured approximately the same number of subjects using the APP preparation versus the random MHB preparations.

Study duration was 6 weeks. During a 1-week washout period subjects abstained from use of other foot care creams; qualifying subjects were given informed consent. Subsequent enrollment of consenting subjects included completion of baseline questionnaire. All tenets of the Declaration of Helsinki for the protection of human subjects in medical research were strictly observed. Each subject was issued 2 jars of skin cream, packaged in identical containers. Subjects were instructed on application method and to perform twice daily skin applications of the preparations using jars marked Left and Right on the left and right foot, respectively. Subjects maintained daily logs for recording time of use and positive or negative observations.

Subjects remained on the same treatment regimen for the duration of the study. Subjects abstained from using other foot care creams or other preparations for the study duration. Study investigators and study coordinators refrained from inspecting jarred creams prior to study conclusion in order to maintain masking. At 2-week intervals, study subjects returned for evaluation and exchange of the unused portions of jars and were issued replacement jars of cream. Daily logs were collected at these visit intervals and new daily logs issued. At each study visit the sole of both feet were photographed separately and together to avoid differences in photographic conditions. Photographs permitted post-study examination, observation, and confirmation.

Each subject was asked to complete an in-house Foot Care Cream Initial Questionnaire prior to beginning the study. A history was taken which included frequency of use of skin cream on the feet, with the clinical history being recorded and including diabetic status, history of neuropathy, vascular disease, skin ulcers, amputation, and renal disease. Baseline information regarding the feet gathered by the clinician included a Diabetic Foot Care Grading System

as described below, which included measurement of dryness, fissures, erythema, itching, and neuropathy risk assessment to include locations of any previous ulcers and sites of amputations; pulse testing to assess vascular status using palpation of the dorsalis pedis and posterior tibial pulses; and sensory perception testing. Neuropathy was assessed using the Semmes-Weinstein monofilament (SWM) test of all subjects and inclusive of only subjects with positive control tests. The positive control was determined using standard monofilament testing for loss of protective sensation in diabetes. At the completion of the study, subjects were given a Foot Care Cream Exit questionnaire.

Treatment Regimen

Skin cream was applied, twice daily, as typical for a moisturizing cream that is applied and hand-rubbed into the skin. Subjects were instructed to clean hands both before and between applications to each foot with disposable towelettes provided. Commonly, preparations are applied with caution between the toes due to the possible adverse effects of promoting sheer, friction, and moisture accumulation and thus, subjects were instructed not to apply cream between the toes. Subjects were instructed to use the creams on the assigned foot, equivalently. No measurement was made of the quantity of the creams used, but unused portions of both creams were collected from the subject at each visit to insure consistency.

Measurements

Measurement scales included user preference and satisfaction internally constructed scales used at commencement of the study and at conclusion of the study. An investigator foot-care-grading scale as described below was used to evaluate dryness, fissures, erythema, and itchiness, at the commencement of the study to establish baseline and thereafter at 2-week intervals. Descriptive statistics were performed related to the demographic and medical history information of the patient populations. Since each patient served as their own control, comparisons among the study populations were unnecessary. A diabetic foot screen for loss of sensation was performed by monofilament testing on both feet of each subject.

Statistical Analysis

Repeated-measures analysis of variance (ANOVA) for the 4 main efficacy endpoints: dryness, erythema, fissures, and itching, were performed. An aggregate severity score among these 4 primary efficacy endpoints was calculated for each subject. A chi-square test of association was performed for monofilament test data at baseline and at the conclusion of the study. Frequency of positive and favorable subject responses and dislikes were computed for each preparation.

Grading Scales

Dryness or skin hydration of the sole of the foot included factors of scaling/flakiness, such that 0 = normal skin hydration or no significant dryness, 1 = mild dryness, minimal skin scaling/flakiness; 2 = moderate dryness, moderate scaling/flakiness; 3 = severe dryness, severe scaling/flakiness. Fissures were measured on the sole of the foot as follows 0 = none; 1 = shallow; 2 = moderate; and 3 = deep. Erythema was measured using colored photographs of the sole of the foot to serve as the standards of the various levels of erythema as follows 0 = none; 1 = mild; 2 = moderate, and 3 = severe. Itching of the sole of the foot subjectively graded by the patient was; 0 = none; 0.5 = intermittent tickling sensation of a small portion of the involved skin; 0 = none; 1 = intermittent tickling sensation of more than a small portion of the involved skin and less than the entire region of the involved skin; 1.5 = an intermittent tickling sensation of the entire region of the involved skin; 2 = a mild continuous itch (can be localized) not requiring rubbing or scratching; 2.5 = a moderate, diffuse, continuous itch with the desire to rub or scratch; 3 = severe continual itch with the desire to scratch or rub the skin; 3.5 = severe continual itch improved with minimal rubbing or scratching; 4 = incapacitating itching requiring rubbing or scratching the skin. Vasculopathic risk assessment included pulse testing for vascular results of the presence or absence of the dorsalis pedis and posterior tibial pulses.

Results

Subjects (n = 54) with a mean age of 70.5 years were enrolled between the 2 sites. This patient population consisted of 35 females (64.8%) and 19 males (35.2%). The subjects were distributed as follows: 50 (92.6%) Caucasian, 3 (5.6%) African-American, and 1 (1.9%) Hispanic.

Forty-three (79.6%) of the subjects had a diagnosis of Type II diabetes mellitus and the remaining 11 (20.4%) had Type I diabetes mellitus. The mean duration of diabetes among reporting subjects was 12.6 years. Diabetes was controlled by diet and/or oral treatment in 31 cases (57.4%) and by subcutaneous insulin in 22 cases (40.7%) of the subjects. One subject used both oral agents and subcutaneous insulin for the control of diabetes. Forty-two subjects reported diseases relevant to this study as follows: neuropathy (23, 54.8%); peripheral vascular disease (26, 61.9%); foot ulcers (9, 21.4%); toe amputation (2, 4.8%); and others (1, 2.3%).

Means for the 4 variables measured at the study visits, baseline, 2, 4, 6 weeks, are presented in Table 1 for the 49

Table 1. Mean Variable Scores for Diabetic Subjects (n = 49) by Treatment Arm [Control (Mineral Hydrocarbon) and Test (Anionic Polar Phospholipid Based) Preparations] and Observation Period.

Variable	Treatment preparation	Baseline	Week 2	Week 4	Week 6
Dryness	Control	1.55*	0.63	0.53	0.45
	Test	1.53	0.76	0.63	0.43
Fissures	Control	0.08	0.02	0.02	0.00
	Test	0.14	0.08	0.04	0.02
Erythema	Control	0.49	0.27	0.24	0.14
	Test	0.49	0.33	0.31	0.14
Itching	Control	0.18	0.06	0.06	0.04
	Test	0.16	0.02	0.02	0.00
Composite	Control	2.31	0.98	0.86	0.63
	Test	2.32	1.18	1.00	0.59

*Two-way Analysis of Variance (ANOVA) with repeated measures on one factor for primary efficacy variables and composite scores.

Table 2. Effects of Treatment Group [Control (Mineral Hydrocarbon Based) and Test (Anionic Polar Phospholipid Based) Preparations] or the Interaction of Treatment Group With Time.

Variable	General model	Treatment group effect	Time effect	Interaction: time × treatment
Dryness	104.39 (0.0001)	0.18 (0.6747)	122.74 (0.0001)	0.74 (0.5286)
Fissures	3.01 (0.0341)	0.86 (0.3573)	6.95 (0.0002)	0.50 (0.6848)
Erythema	17.02 (0.0001)	0.14 (0.7044)	22.72 (0.0001)	0.35 (0.7860)
Itching	5.90 (0.0010)	0.42 (0.5199)	10.94 (0.0001)	0.06 (0.9819)
Composite	85.38 (0.0001)	0.20 (0.6530)	126.56 (0.0001)	0.71 (0.5477)

ANOVA *F*-statistics and *P*-values (in Parentheses). Statistical significance ($P < .05$).

subjects who completed the study. Five subjects had incomplete data, and, thus, their records were excluded from the means analyses. Study results (Table 1) were analyzed using a two-way ANOVA with repeated measures on each factor of the 4 efficacy variables: dryness, fissures, erythema, and itching. In addition, a composite score among the 4 variables was calculated at each time interval. A fifth ANOVA was performed to analyze the results on the composite score. The null hypotheses for these analyses are that the variables do not change with time or between treatment groups. These tests included the 49 subjects with complete data.

In all 5 analyses (including the composite score), a significant effect for time was observed at the .05 level of significance. However, the ANOVA analysis indicated that at the same significance level there was no difference due to the effects of the treatment group or the interaction of the treatment group with time. Table 2 presents the *F*-statistics and *P*-values for these analyses. Post-hoc contrasts found that dryness, fissures, erythema, itching, and composite scores were significantly lower at weeks 2, 4, and 6 as compared to baseline at the .05 level of significance ($P < .05$ for all tests).

Frequency tables between APP and MHB treatment groups and the vasculopathic measurements of the dorsalis pedis and posterior tibial pulses are calculated at each time point. Chi-square statistics were calculated to detect differences in response with continued treatment. There was no difference seen between the APP and MHB treatment groups at the .05 level of significance (Table 3).

Table 3. Pulse Testing: Vascular Testing: Proportion of Subjects With Posterior Tibial (PT) and Dorsalis Pedis (DP) Pulses. Test Cream (Anionic Phospholipid); Control Cream (Mineral Hydrocarbon Based).

Evaluation	Test	Test cream (%)	Control cream (%)
Baseline	PT	21.43	23.47
	DP	26.53	24.49
Week 2	PT	25.51	24.49
	DP	28.57	25.51
Week 4	PT	26.53	25.51
	DP	28.57	26.53
Week 6	PT	23.47	23.47
	DP	29.59	26.55

In order to monitor neuropathic changes in monofilament test scores were assessed inclusive of all subjects and inclusive of only subjects with positive control tests (Table 4). The positive control was determined using standard monofilament testing for loss of protective sensation in diabetes. In both cases, subjects with missing data were excluded.

Table 4. Mean Monofilament Test Scores for Each Group (Subjects n = 49). Control (Mineral Hydrocarbon Based) Treatment Preparation; Test (Anionic Phospholipid) Treatment Preparation.

Analyses	Treatment preparation	Baseline	Week 2	Week 4	Week 6
All subjects	Control	2.33	2.29	2.44	2.29
	Test	2.33	2.31	2.44	2.25
Positive control	Control	2.67	2.72	2.83	2.67
	Test	2.52	2.68	2.83	2.52

Table 5. Mean Scores for Test Site 1 (Subjects, n = 27). Control (Mineral Hydrocarbon Based) Treatment Preparation; Test (Anionic Phospholipid) Treatment Preparation.

Test	Treatment preparation	Baseline	Week 2	Week 4	Week 6
Dryness	Control	1.59	0.63	0.56	0.48
	Test	1.52	0.56	0.52	0.41
Fissures	Control	0	0	0	0
	Test	0.07	0.04	0	0
Erythema	Control	0.41	0.19	0.26	0.15
	Test	0.41	0.19	0.26	0.15
Itching	Control	0.07	0	0	0
	Test	0.07	0	0	0
Aggregate	Control	2.07	0.81	0.81	0.63
	Test	2.07	0.78	0.78	0.56

Ninety-three feet were assessed in the first test (all subjects) and 73 assessed in the second test. The ANOVA with repeated measures was performed to assess this parameter of neuropathy. The null hypothesis for these analyses is that neuropathy did not change over time and/or between treatment groups.

When all subjects with complete data sets were included, the overall observation was not significant at the .05 level of significance ($F = 2.58$, $P = .06$) between APP and MHB groups, although it is approaching significance. However, when the model was restricted to only subjects who had a positive control response, the overall observation became significant at the .05 level (.0173). A significant time-effect was seen ($P = .0118$), but the treatment group and time-effect remained non-significant ($P = .7203$ and .8730, respectively). Post-hoc tests showed that the 4-week monofilament test score differed from the baseline score for both treatment groups ($P = .0023$), but that the week 2 ($P = .1362$) and week 6 ($P = .8571$) scores were not significantly different (Table 4).

Possible effects between sites 1 and 2 were assessed by calculating the mean scores for the 4 variables and the composite score and by comparing these scores over time. Tables 5 and 6 present the mean scores for site 1 (n = 27) and site 2 (n = 22) respectively. Excluded were subjects with incomplete data. A possible association between response and APP and MHB groups is seen in site 2, where scores appear to decrease earlier in feet treated with the MHB preparation versus those treated with the APP preparation. A lower score represents an improvement in the subjects' condition. In site 2, a two-way ANOVA test with repeated measures was conducted for each variable. The results of such testing reveal significance with time. The F-statistic reveals the largest of any of the group effects in the analysis ($F = 1.6$) and this may indicate a possible association which can only be clarified by examining a larger study cohort.

An assessment of the subjects' prior treatment history as an indicator of treatment success in this study was conducted. Patients were grouped by whether they had undergone prior treatment of their dry foot condition. Table 7 presents the mean variable levels observed during this study with no significant differences.

The exit questionnaire responses in the category of "likes" demonstrated that 35 of 56 (63%) of subjects using the plant-based APP preparation reflected a positive experience; whereas, 23 of 56 (41%) using the mineral hydrocarbon-based preparation had a positive experience (Supplemental Table S1), a >20% difference. Evaluation of "dislikes" revealed positive responses were essentially the same among the APP treated subjects (13 of 56 [23%]) and MHB treated subjects (12 of 56 [21%]).

Discussion

Over a 6-week study period, the results, whether pooled or unpooled, demonstrated that the data from both study sites, obtained using either the plant-based anionic phospholipid preparation or the mineral hydrocarbon-based preparation

Table 6. Mean Scores for Test Site 2 (Subjects, n = 22). Control (Mineral Hydrocarbon Based) Treatment Preparation; Test (Anionic Phospholipid) Treatment Preparation.

Test	Treatment procedure	Baseline	Week 2	Week 4	Week 6
Dryness	Control	1.50	0.64	0.50	0.41
	Test	1.55	1.00	0.77	0.45
Fissures	Control	0.18	0.05	0.05	0
	Test	0.23	0.14	0.09	0.05
Erythema	Control	0.59	0.36	0.23	0.14
	Test	0.59	0.50	0.36	0.14
Itching	Control	0.32	0.14	0.14	0.09
	Test	0.27	0.05	0.05	0
Composite	Control	2.59	1.18	0.91	0.64
	Test	2.64	1.68	1.27	0.64

Table 7. Skin Treatment History. Control (Mineral Hydrocarbon Based) Treatment Preparation; Test (Anionic Phospholipid) Treatment Preparation.

History	Treatment preparation	Variable	Baseline	Week 2	Week 4	Week 6
No prior treatment	Control	Dryness	1.45	0.55	0.42	0.31
		Fissures	0.05	0.00	0.00	0.00
		Erythema	0.40	0.35	0.21	0.11
		Itching	0.40	0.11	0.11	0.11
	Test	Dryness	1.50	0.65	0.42	0.26
		Fissures	0.10	0.00	0.00	0.00
		Erythema	0.40	0.45	0.37	0.11
		Itching	0.35	0.05	0.00	0.00
Previously treated	Control	Dryness	1.67	0.70	0.60	0.52
		Fissures	0.09	0.03	0.03	0.00
		Erythema	0.48	0.17	0.20	0.14
		Itching	0.03	0.00	0.03	0.00
	Test	Dryness	1.61	0.83	0.73	0.52
		Fissures	0.15	0.13	0.07	0.03
		Erythema	0.48	0.17	0.20	0.14
		Itching	0.06	0.00	0.03	0.00

skin creams, were equally safe and effective in reducing dryness, fissures, erythema, and itching. When analyzed by study site, a difference appeared where the MHB preparation indicated a potential improved response earlier in treatment; however, this response was not statistically significant.

Considering that dryness can result in or from damage to the skin's lamellar system,[24] the sensation of dryness and its consequent itching sensation may induce skin rubbing with eventual elicitation of an inflammatory response.[25] This inflammatory response is manifested as erythema and possibly painful neuropathy. In the present study there was no improvement in the monofilament test which was designed to test neuropathy; however, there was a trend toward improvement at the 4-week time point, though at 6 weeks, this trend returned to baseline. In this small patient population, there was no quantifiable neuropathic pain over time or between treatment groups. Vasculopathic assessment conducted via examination of peripheral pulses demonstrated no difference between the distal pedal or posterior tibial pulses between the treatment groups.

The exit questionnaires provided for subjective feedback of subject comments (Supplemental Table S1). Personal preference regarding the texture of the cream is evident and may play a role in the subject's assessment of the cream's effectiveness. Review of the exit questionnaire comments revealed the number of "dislikes" were essentially the same among APP and MHB treatment groups. However, overall, subjects using the APP preparation reported a more positive experience in contrast to subjects using the MHB preparation.

The APP preparation has 2 main components each of which contributes to its function to increase skin hydration; the APP component and the preparation base comprised of triglycerides.[3,4] The unique biochemical and biophysical properties of the APP preparation support the concept that the plant-based skin cream actively increases hydration via multiple functional mechanisms in contrast to the MHB

skin preparation which passively increases hydration by preventing dehydration. The properties of APP's chemical structure appear to explain mechanisms for how APP molecules can act as humectants that hydrate viable skin tissues via 3 mechanisms that employ their polarity: (1) facilitates permeation of the epidermis accompanied by water,[20-22] (2) ability to repair the skin's lamellar system formed by phospholipid bilayers,[26-28] and (3) organizing the waters of hydration into a structured (ice-like) configuration.

The first mechanism for increasing skin hydration using APP skin cream technology is the enhancement and improvement of tissue permeability.[20-22] Hydrated anionic polar phospholipids are drawn into the skin by a hydrophilic dynamic interactive attraction between polar headgroups and water[29] in the skin, and as such, the APP component permeates into the epidermis due to charged polarity. The APP preparation permeation also occurs with the accompanying polar triglycerides comprising the preparation base. This charged polarity in both the APP and the triglyceride components is an attracting force causing penetration of the epidermis. This permeation allows both the phospholipids and glycerides to be available for the eventual repair of the bilayer structure of intercellular lamellae within the stratum corneum.[3,4] Further, the starch-like portions of skin glycoproteins and glycolipids are highly hygroscopic. As repairs progress, this hygroscopic property results in attraction and chaperoning of additional water molecules into the skin and organization of these water molecules into an ice-like structure, leading to increased skin hydration.

Since the incorporation of phospholipids into the multilamellar structures of intercellular bilayers containing interstitial water-of-hydration[23] has important implications for maintaining the hydration of the epithelium, the second mechanism for increasing skin hydration using APP skin cream technology includes charged phospholipids and triglycerides. These molecules possess a unique chemistry that results in the formation of a bilayer polar lipid film when in contact with water. This phenomenon of bilayer formation in the presence of water is similar to the plasma membrane bilayer of living cells, which also involves a substantial fraction of negatively charged phospholipid molecules. The negatively charged APP molecules supplement the glycoprotein and glycolipid bilayers within the lamellar strata of the epithelium, providing repair. This occurs when one or more polar terminus groups and one or more nonpolar terminus groups on phospholipids form their characteristic bilayer. The APP with negative charges at their polar head groups are water-seeking. The polar and nonpolar terminus groups are separated from each other by a spacer segment, the doubly esterified glycerol backbone residue of the phospholipid molecules.[20-22] Due to electrostatic forces, this bilayer component forms an organized, aligned lamellar structure within the intercellular space between epidermal cells of the stratum corneum. Each adjacent bilayer is separated by a layer of water.[20-22] The formation of the lamellar structure is a process that allows repair of defects or holes in the lamellar strata that results from skin damage and concurrent loss of the natural polar lipid components. With these defects or holes in the lamellar structure there is a loss of the organization of water which results in dehydration. The overall effect of the availability of anionic phospholipids and triglycerides is replenishment of the bilayer lamellae. This naturally occurs in healthy skin. The anionic phospholipids and polar glycerides repair hydrophilic spaces by filling the gaps or vacancies created in the damaged lamellae. This process occurs regardless of the nature of the damage. The charged polar heads of the APP molecules provide a surface via their thermodynamic driving force for organization of water.[29]

Since the APP preparation also contains neutral polar lipids (triglycerides) in its base composition, these neutral lipids form an aligned interstitial layer containing water between the interior non-polar groups of the bilayer. As such, these neutral polar lipids provide greater lubricity between skin epithelial corneocytes. It is believed that the outermost layers of the intercellular lamellae bond to adjacent epithelial cells by hydrogen bonding. As a consequence, even the triglyceride composition of the APP preparation serves an important role in restoring layers of interstitial water.

This hydrogen bonding provides the third mechanism of increasing skin hydration by increasing stability to the entire lamellar structure. This results in an associated organization of water in an ice-like fashion leading to increased moisturizing of the skin.[21,22] Water maintains the barrier function of the stratum corneum.[30] Water imparts skin suppleness, elasticity, plasticity, flexibility, and softness.[31]

All 3 of the above mechanisms rely on active participation of the polarity of the molecules in the APP preparation and assist in the prevention of further transepidermal water loss, rehydration, and function of the multiple natural systems of the body that compliment the repair of injury due to dry skin.[3,4]

In contrast to the APP-based preparations, MHB preparations uniquely address the problem of passively hydrating damaged dry skin by covering or cloaking the skin like a physical band-aid. MHB preparations are enriched in materials where the attraction to the skin is a hydrophobic encounter with proteins, oils and fats preventing interaction with the skin surface. This covering limits further dehydration of the skin while reducing further injury such as occurs from friction, shear, excessive moisture, or pressure. These MHB preparations, primarily derived from petrolatum oils, function as passive barriers in contrast to the active participation of the components of the APP preparations discussed above. The barrier or covering of the MHB preparations remain on the skin surface but are not absorbed into the skin, and thus, leave a residue. Even though the present study demonstrates that there is no difference in signs and

symptoms with treatments using the APP technology or Eucerin®, a market leader using MHB technology, there is a distinct difference in that the skin cream with APP technology is visibly absorbed into the skin, whereas Eucerin is not. Consequently, unlike MHB preparations, the APP preparation leaves no detectable residue that is apt to result in soiled garments, bedding linens, or foot coverings.

An additional consideration is that mineral hydrocarbons can damage textile materials through the process of creep, where migration of a MHB preparation can occur covering adjacent surfaces, for example, garments or footwear. Creep can result in soiling footwear including the lining of a leather shoe or other absorbable shoe linings, for example, elastics, cottons, and polyesters.

In addition to the influence of epidermal hydration on the friction of skin against textiles,[32] garments or footwear contaminated by the mineral-hydrocarbons-containing preparations can be irreversibly damaged and discolored by residues. These residues consisting of hydrocarbon particles often become bound to the cloth or fabric of garments when exposed to hot water (conventional laundering) or even pressed in the case of bed-sheet linens. This binding of residues makes removal difficult, even with dry cleaning. The use of APP preparations avoids such difficulty. Many moisturizing products containing mineral hydrocarbons applied to the skin are characterized by retained surface residues.[33] Most patients will have concerns about these unabsorbed hydrophobic mineral hydrocarbon residues that are retained on the skin surface, whereas moisturizers with APP technology have been shown to be absorbable[20] and when applied are without visibly detectable residues.

Both concepts of creep and irreversible binding of mineral hydrocarbons are deleterious, and with time, mineral hydrocarbons are increasingly difficult to remove. Removal of these mineral hydrocarbons may be attempted with strong detergents or hypochlorite (bleach) to reduce staining; however, damage to textiles might be unavoidable. Thus, although the same or equivalent skin treatment results as described in the present study may be accomplished with the MHB preparation, there can be significant consequences. Alternatively, use of an APP preparation minimizes these unforeseeable complications with mineral hydrocarbons which include decreased ease of application; added time-duration of application; difficulty in removal of residual product between applications; staining/soiling of textile materials. As such, APP preparations, in contrast to use of MHB preparations, have multiple advantages.

The limitations of this study include sample size which precludes investigation of multiple demographics, degree of glycemia, and the study being of relatively brief duration.

In conclusion, this study demonstrated equivalency in effectiveness of 2 topical technologically different creams for skin hydration in the treatment of dry skin disease in patients with diabetes mellitus. These hydrating skin cream preparations were derived from plant-based anionic phospholipids and triglycerides and mineral hydrocarbon-based technologies. In dry skin diseases the preservation and restoration of hydration is paramount. Although treatment with both creams appear to result in equivalent hydration of the skin tissue, they have strikingly and fundamentally different modes of action. The results of this study showing therapeutic equivalency in signs and symptoms provided a unique opportunity to consider the differences in the mode of action for each technology. The more common MHB technology passively preserves skin integrity by prevention of further water loss by covering or cloaking the skin surface, which reduces water loss preventing further dehydration. This promotes passive hydration of the skin by preventing dehydration. The disadvantages of the MHB preparation include (1) no active healing, healing is accomplished passively, and (2) leaving a residue on the skin surface that can soil textiles and require repeated residue removal that may result in recurrent damage to the newly healed epithelial surface. Although similar therapeutic outcomes are reported in this study, the plant-based APP preparation employs active mechanisms of repair and water replenishment to rehydrate skin. As discussed, the APP preparation has clear advantages over the MHB preparation including: (1) active absorption by permeation of anionic phospholipid and triglyceride molecules, (2) chaperoning chemically associated water molecules into the epithelium, and (3) reparation of the skin bilayer lamellae comprised of phospholipids, triglycerides, and water.

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ORCID iD

Jack V. Greiner https://orcid.org/0000-0003-1659-1020

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