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Topical supplementation with physiological lipids rebalances the stratum corneum ceramide profile and strengthens skin barrier function in adults predisposed to atopic dermatitis

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Abstract

Background People with atopic dermatitis (AD) suffer from dry, itchy skin with reduced skin barrier function that leaves it prone to irritant and allergen penetration. Alterations in the composition and structure of the stratum corneum (SC) lipid lamellae underpin this increase in permeability. A wide range of emollients is used to ameliorate the skin of patients with AD, but the majority have unclear effects on the lipid lamellae and barrier function.

Objectives To compare the effects of a multivesicular emulsion containing physiological lipids and glycerine (MVE + GL) with a commonly prescribed oil-in-water emulsion containing glycerine without physiological lipids (O/W + G).

Methods A double-blind intraparticipant-controlled study was undertaken in adults with a history of eczema. Participants applied MVE + GL to one forearm and lower leg and O/W + G to contralateral sites twice daily for 28 days. Skin properties were assessed before and after treatment. A detailed lipidomic profile was generated from SC samples, alongside *in vivo* attenuated total reflectance Fourier transform infrared spectroscopic analysis of its molecular composition.

Results Fifty-eight people were included in the study [mean (SD) age 46 (21) years]. At sites treated with MVE + GL skin barrier integrity improved significantly [mean (SD) transepidermal water loss after 20 skin tape strips ($TEWL_{20}$) 38.02 (18.64) g m^{-2} h^{-1} pretreatment vs. 29.79 (13.47) g m^{-2} h^{-1} post-treatment; $P < 0.001$], whereas O/W + G had no effect [35.6 (18.39) g m^{-2} h^{-1} vs. 37.4 (16.69) g m^{-2} h^{-1}]. Concordantly, skin sensitivity to sodium lauryl sulfate (SLS) was significantly reduced by MVE + GL treatment [mean (SD) post-SLS TEWL 35.58 (15.43) g m^{-2} h^{-1} pretreatment vs. 29.54 (11.64) g m^{-2} h^{-1} post-treatment ($P < 0.001$); erythema was also reduced]. Skin moisture increased more rapidly at sites treated with MVE + GL vs. O/W + G, leading to a more rapid reduction in visual skin dryness. Over 1600 lipid species were detected in the SC. Ceramide species NP (non-hydroxy-phytosphingosine) and AP (α-hydroxy-phytosphingosine) with 18-carbon sphingoid bases, both ingredients of the MVE + GL, increased significantly by 24% and 19%, respectively, following MVE + GL treatment. In contrast, changes of 9% for NP(18) and 6% for AP(18) were not statistically significant at sites treated with O/W + G. Increased abundance of NP(18) species relative to NdS (non-hydroxy-dihydrosphingosine) species was related to improvements in skin barrier integrity.

Conclusions While the glycerine-containing emollient reduced skin dryness, it had no impact on barrier function. In contrast, MVE + GL improved the physical integrity of the barrier and reduced the sensitivity of the skin.

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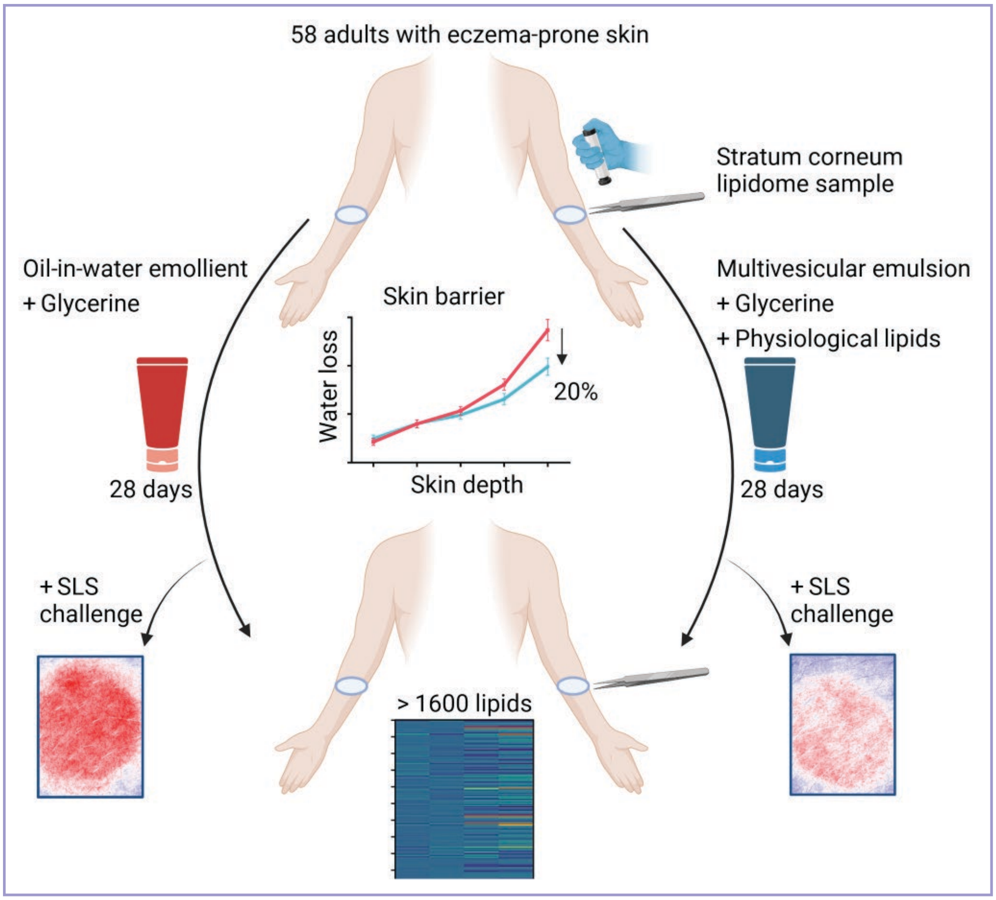
Graphical Abstract



Lay summary

Eczema is the most common chronic skin condition. It affects 1% to 10% of adults in Europe. The upper layers of our skin form a barrier that keeps water in our bodies and stops irritants from getting in. This skin barrier is made of cells called ‘corneocytes’. These are surrounded by a tough protein envelope and embedded in a network of ‘fatty’ molecules (called ‘lipids’). The composition of these fatty molecules is altered in the skin of people with eczema. The skin does not function effectively as a barrier as more water is lost, and irritants can more easily penetrate the deeper skin layers. Moisturizing creams are an effective treatment for eczema, but it is unclear which are most appropriate to use.

This study was carried out in the UK. We aimed to find out if a cream containing lipids found in skin could improve the skin’s ability to act as a barrier. We compared this cream to one without these lipids. We asked 58 people with eczema to apply these creams separately on their forearms for a month and measured how the skin responded. We found that skin treated with the cream containing skin-identical lipids lost less water. It was also more resistant to physical damage and was less sensitive to irritation than before treatment. In contrast, the cream without lipids did not improve the skin barrier. Both creams improved dryness, but quicker results were found for the cream containing the lipids found in skin.

Our findings suggest that the addition of skin-identical lipids to moisturizing creams is a promising way of improving skin barrier function.

What is already known about this topic?

- Some emollients used to treat atopic dermatitis (AD) have little or no positive effect on the function of the skin barrier.
- The lipid profile of the stratum corneum (SC) differs in people with AD compared with the profile in healthy skin.
- Use of emollients can alter the arrangement of lipids in the skin barrier.
- Emollients containing physiological lipids have been used to treat AD, but whether the lipid composition is changed by treatment is unknown.

What does this study add?

- Glycerol as an emollient additive is insufficient to improve skin barrier function in eczema-prone individuals.
- The ceramide composition of the skin barrier is altered by emollient application.
- Changes in ceramide composition are identified which associate with improvements in skin barrier function.
- The carbon length of a ceramide's sphingoid base appears to determine its impact on skin barrier function.
- The abundance of non-hydroxy-dihydrosphingosine (NdS) ceramides negatively correlates with skin barrier function.

What is the translational message?

- Where skin sensitivity and skin barrier impairment are an issue, emollients must do more than resolve clinical signs of dryness.
- Topical supplementation with essential physiological lipids is an effective strategy to repair SC lipid matrices and leads to improved skin barrier function.
- The success of lipid supplementation depends on how applied lipid mixtures change the balance of ceramides in the skin at the species level.

In atopic dermatitis (AD), reduced function of the skin as a barrier leads to excessive water loss from, and increased irritant entry into, the viable skin layers. The barrier function of skin resides in the stratum corneum (SC), a structure composed of multiple layers of corneocytes embedded in a lipid-rich matrix called the lipid lamellae.[1] The major components of these lamellae are ceramides, cholesterol and fatty acids. Altered ceramide profiles in patients with AD,[2] and evidence from *in vitro* modelling of lipid mixtures,[3–5] suggest that the ceramide profile of the skin is an important determinant of skin barrier function. Ceramides are composed of a sphingoid base (SB) linked through an amide bond to a fatty acid (the acyl chain). Over 1000 different ceramide species have been identified in the human SC.[6] Attempts to describe the functional implications of this variability are an ongoing focus of research.

In AD, consistent use of some emollients can increase the time between flares and reduce the requirement for topical corticosteroid use.[7,8] However, the effectiveness of emollients varies. Clear evidence to support the use of particular formulations or ingredients remains an unmet need. There is evidence that use of emollients enriched with physiological lipids can improve barrier function and clinical outcomes.[9,10] However, it remains unclear how emollient use affects the lipid profile of the SC.

In this study, we compared an oil-in-water emollient with glycerine (O/W+G) to a multivesicular emulsion with physiological lipids and glycerine (MVE+GL). The aim was to determine the effects of these formulations on the skin barrier and the SC lipidome.

Patients and methods

Study design

This was an interventional intraparticipant-controlled right/left randomized double-blind cohort study in adults with dry skin and a self-reported history of eczema, comparing the effects of twice-daily application of MVE+GL with O/W+G for 4 weeks. Skin condition was assessed at baseline, day 2, day 14 and at the end of treatment (EoT).

The study targeted recruitment of 58 participants in 3 cohorts of approximately equal size based on age (age groups: 18–39 years; 40–59 years; ≥60 years). The target for completion was 48 participants with 82% power to detect a difference of 6 g m^{-2} h^{-1} in transepidermal water loss (TEWL) after induced irritation (the primary outcome).

Intervention

Participants undertook a 7-day washout from leave-on topical products at the test sites on the volar forearm and the outer surface of the lower leg before baseline assessments. Application of O/W+G [Cetraben® (containing glycerine); Thornton & Ross, Huddersfield UK] and MVE+GL [CeraVe® (containing glycerine, capric triglyceride, ceramides NP, AP and EOP, phytosphingosine and cholesterol); L'Oréal, Clichy, France] started after these assessments. Participants were trained in the application of two fingertip units of emollient to each treatment area in accordance with the randomization schedule.

Outcomes

The primary outcome was the difference in TEWL between test sites after sodium lauryl sulfate (SLS)-induced irritation. Secondary outcomes included erythema following SLS exposure, skin barrier integrity measured with TEWL and skin tape-stripping (STS), barrier cohesion based on protein collection by STS, moisturization assessed by visual scoring and hydration (capacitance). Comparisons were made between test sites and the effect of each emollient vs. baseline. Exploratory outcomes included molecular composition of the SC using attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) and STS, and mass spectroscopy of STS samples. Further detail is provided in Appendix S1 (see Supporting Information).

Statistical analysis

All data were analysed using Prism 10 (GraphPad, La Jolla, CA, USA). The significance threshold for the biophysical and ATR-FTIR analyses was $P<0.05$. Results are presented as mean (SD) in the text, unless otherwise indicated.

Results

Fifty-eight adults with a self-reported history of eczema were recruited and began treatment between April 2022 and March 2023 (Figure S1, Table S1; see Supporting Information). Participants used the study emollients twice daily on separate test areas on opposite sides of the body for 28 (4) days. Similar amounts of each treatment were used: 3.66 (0.86) g daily of O/W+G and 4.04 (0.92) g daily of MVE+GL.

TEWL, an important measure of permeability barrier function, was within the expected range at baseline and was unaltered by treatment (Figure 1). STS removes cell layers from the SC leading to an increase in TEWL, a measure of skin barrier integrity. Before treatment there was no difference between test sites in TEWL following 20 STS ($TEWL_{20}$) or the amount of protein removed. At EoT, skin barrier integrity/cohesion was similar at sites treated with O/W+G [$TEWL_{20}$ 35.65 (18.40) g m^{-2} h^{-1} before vs. 37.38 (16.69) g m^{-2} h^{-1} after treatment ($P=0.47$), a difference of +5%; protein removed was 347.99 (110.18) μg cm^{-2} before vs. 328.95 (108.58) μg cm^{-2} after treatment ($P=0.18$)]. At sites treated with MVE+GL, barrier condition was improved with a reduction in the amount of protein removed vs. baseline [353.57 (101.43) μg cm^{-2} before vs. 282.85 (114.21) μg cm^{-2} after treatment; $P<0.001$] and there was a 22% reduction in $TEWL_{20}$ [38.02 (18.64) g m^{-2} h^{-1} before vs. 29.79 (13.47) g m^{-2} h^{-1} after treatment; $P<0.001$]. The centre of gravity (COG) of the lipid peak (approximately 2850 cm^{-1}) in an ATR-FTIR mid-infrared spectrum of the skin indicates the chain conformation of the SC lipids,[11] with a higher position indicating an increase in conformational disordering associated with reduced barrier function.[3,12] Treatment with O/W+G significantly increased the COG of the lipid peak, whereas treatment with MVE+GL had no effect.

Next, we examined whether the skin's response to irritant exposure was affected by treatment. SLS was applied to the skin for 24 h under occlusion and the resulting inflammation assessed by quantifying erythema and TEWL. At baseline, there was a clear erythematous response to SLS at > 95% of the test sites (median score 1, mild erythema). Erythema index (EI) increased from 38.77 (0.59) to 50.60

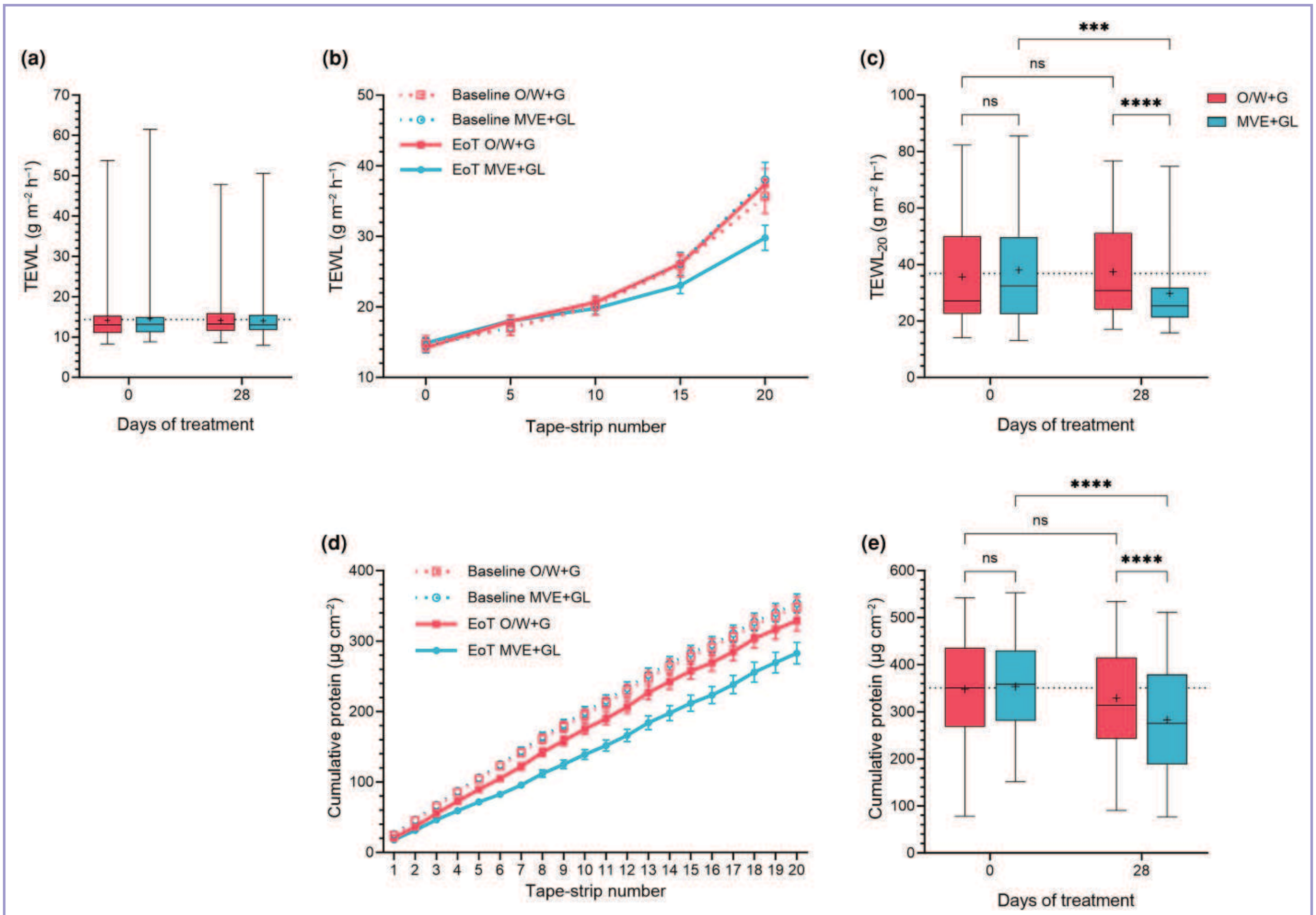


Figure 1 Skin barrier integrity and cohesion are affected by emollient treatment. (a) Basal transepidermal water loss (TEWL) on the forearm at baseline and at end of treatment (EoT). Mixed-effects analysis revealed no significant effect of treatment or difference between treatments. (b) TEWL and (d) protein removed at increasing depths through the stratum corneum (SC) and after skin tape-stripping (STS) (c, e) at baseline and EoT. Dotted line in (a), (c) and (e) indicates the day 0 mean. Line graphs in (b) and (d) show the mean (SEM). Boxes represent the interquartile range, whiskers show the range, median is indicated as a horizontal line and '+' denotes the mean. MVE+GL, multivesicular emulsion with physiological lipids and glycerine; ns, not significant (i.e. $P>0.05$); O/W+G, oil-in-water emollient with glycerine. ***$P<0.001$, ****$P<0.0001$ (Fisher's post-test following mixed-effects analysis).

(0.25) arbitrary units (AU) and TEWL increased from 13.42 (0.25) to 35.36 (0.31) g m^{-2} h^{-1} (areas combined). Following treatment, the skin's response to SLS was unchanged at sites treated with O/W+G (Figure 2). In contrast, sensitivity to SLS was reduced at sites treated with MVE+GL vs. baseline; more sites had no or barely perceptible erythema than moderate or strong erythema (Table S2; see Supporting Information). EI was reduced [47.30 (8.53) vs. 50.77 (8.90) AU; $P=0.002$] and TEWL was lower [29.54 (11.64) vs. 35.58 (15.43) g m^{-2} h^{-1}; $P<0.001$]. At EoT, average TEWL after SLS exposure was 5.04 g m^{-2} h^{-1} lower at sites treated with MVE+GL vs. O/W+G ($P<0.001$).

At baseline, all participants had visible dryness on the lower leg [median score 2; scaling, slight roughness (Table S3; see Supporting Information)]. Hydration measured using the capacitance method indicated very dry skin [25.37 (0.07) AU, both areas]. Skin moisturization improved with both treatments; median skin dryness decreased to 1 (faint scaling/roughness) at sites treated with O/W+G and to 0.5 at sites treated with MVE+GL after 2 days of treatment. Most sites had no dryness by day 14 (Table S4; see Supporting Information). SC hydration increased concordantly: sites treated with MVE+GL were more hydrated than sites treated with O/W+G after 2 days [O/W+G 31.70 (10.14) vs. MVE+GL 33.32 (9.16) AU; $P=0.02$] and 14 days [O/W+G 35.64 (8.51) vs. MVE+GL 37.53 (8.57) AU; $P=0.003$] of treatment. Both sites had similar levels of hydration at EoT ($P>0.99$; Figure 3). To directly measure the amount of water in the SC, ATR-FTIR spectroscopy with STS was used. FTIR measurements are normalized to protein, inferred from the amide peak. Both treatments increased SC water levels: sites treated with MVE+GL exhibited 25% more water across the SC than sites treated with O/W+G at EoT (Fisher's $P<0.001$; Figure 4 d). ATR-FTIR spectroscopy was also used to determine the amount of glycerine through quantification of hydroxyl groups of polyols. Polyols increased from baseline with both treatments [at EoT: O/W+G 0.73 (0.11) vs. MVE+GL 0.87 (0.20) AU; $P<0.001$]. Polyol abundance was significantly associated with skin barrier integrity ($TEWL_{20}$: $r=-0.51$) and hydration (capacitance: $r=0.45$).

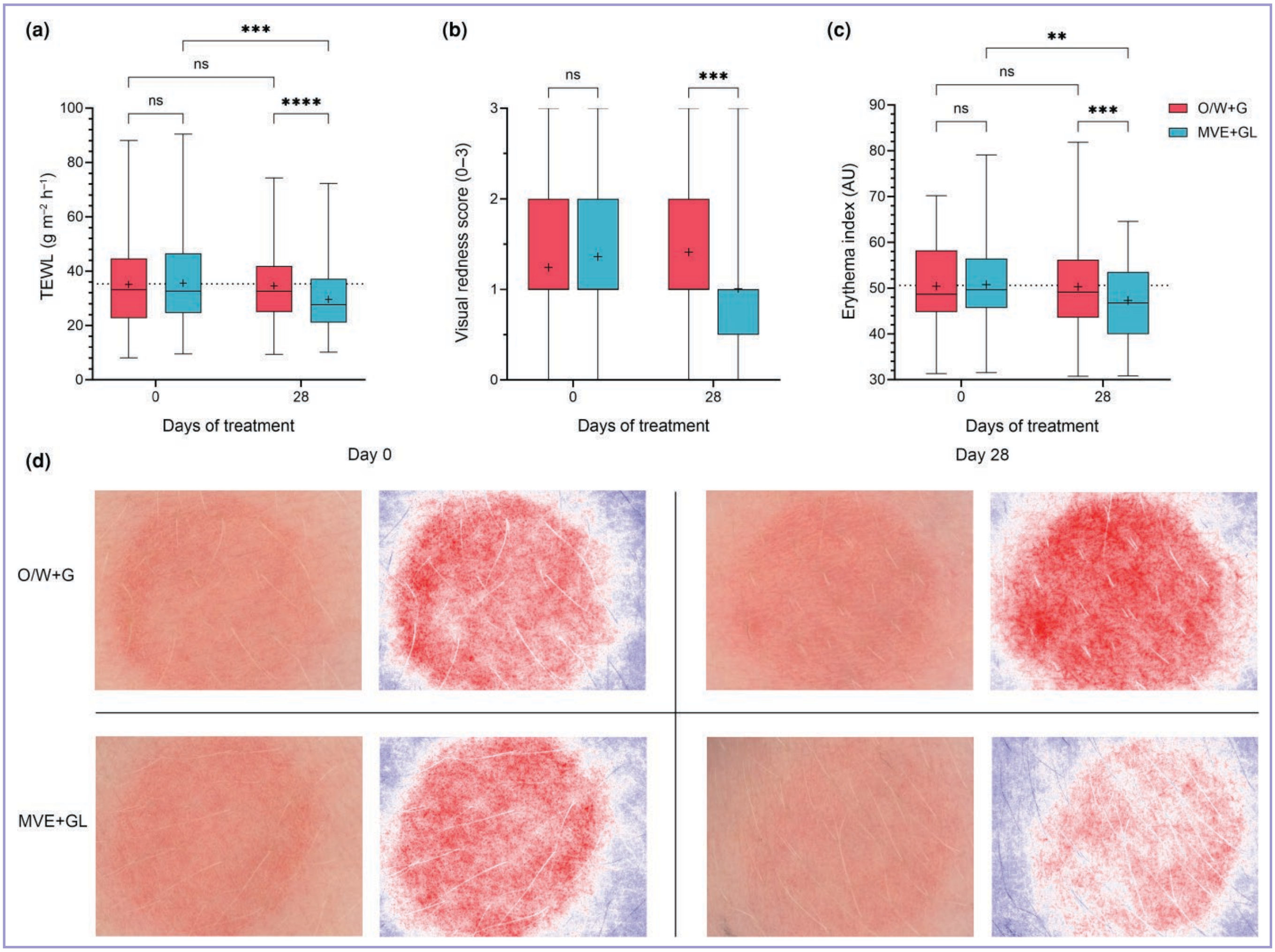


Figure 2 Skin irritation following exposure to sodium lauryl sulfate (SLS) is affected by emollient treatment. (a) Transepidermal water loss (TEWL), (b) visual redness score and (c) erythema index on the forearm 24 h after SLS exposure, at baseline and at end of treatment. (d) Representative images of erythema: rendered panels show erythema index scoring. Boxes represent the interquartile range, whiskers show the range, median is indicated as a horizontal line and '+' denotes the mean. AU, arbitrary unit; MVE+GL, multivesicular emulsion with physiological lipids and glycerine; ns, not significant (i.e. $P>0.05$); O/W+G, oil-in-water emollient with glycerine. $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ [(a, c) Fisher's test following mixed-effects analysis; (b) Wilcoxon signed rank test].

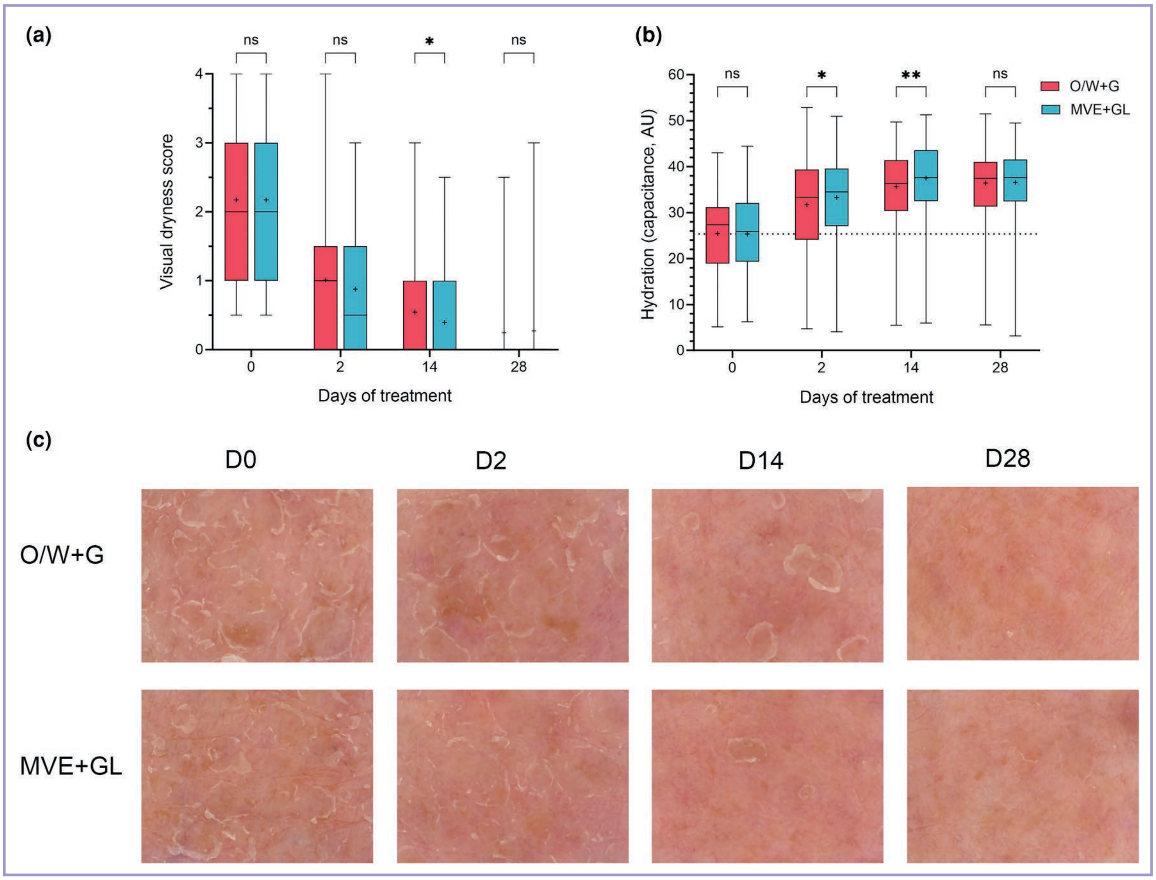


Figure 3 Skin moisturization is affected by emollient treatment. (a) Visual dryness scores, (b) hydration and (c) representative images of the lower leg at baseline and throughout treatment. In (b), mixed-effects analysis identified significant effects of treatment and a difference between treatments; however, post-test comparisons were made between treatments only. Boxes represent the interquartile range, whiskers show the range, median is indicated as a horizontal line and '+' denotes the mean. The dotted line indicates the day 0 mean. AU, arbitrary unit; D, day; MVE + GL, multivesicular emulsion with physiological lipids and glycerine; ns, not significant (i.e. $P > 0.05$); O/W + G, oil-in-water emollient with glycerine. *$P < 0.05$, **$P < 0.01$ [results of multiple (a) Wilcoxon tests and (b) Sidak's post-test].

Finally, we undertook MS-based profiling of SC ceramides, cholesterol and glycerides obtained from STS in tandem with ATR-FTIR spectroscopy at baseline and EoT. Total lipids, including physiological and nonphysiological lipids (based on CH_2 groups), were increased from baseline by 49% following O/W + G and by 54% following MVE + GL treatment (Figure 4 g), whereas lipid esters predominantly from physiological lipids, including triglycerides (included in MVE + GL), were only increased after MVE + GL treatment [49% ($P = 0.008$); Figure 4 h]. Total lipids and lipid esters were associated with skin dryness ($r = -0.46$ and $r = -0.34$, respectively). In the five lipid groups analysed by MS, the proportion of ceramides relative to total measured lipids increased with emollient use (Figure 5 a); however, this change was not reflected when normalized to protein (Figure S2; see Supporting Information). Analysis of the ceramides by subclass revealed few changes in response to treatment [Figure 5 b, c (relative to lipid class); Figure S2b, c (normalized to protein)]. Stratification of ceramides by their constituent chain lengths revealed striking treatment effects on the relative abundance of ceramides with 18-carbon SBs, and 18- and 24-carbon acyl chains. Regarding the 18-carbon SBs, MVE + GL treatment increased the relative abundance of six of eight subclasses [AH(18) 12%, AP(18) 19%, AS(18) 27%, NP(18) 24%, NS(18) 16%, NdS(18) 18% (Figure 5 h), five of which were consistent with significant changes normalized to protein (Figure S2 d)]; O/W + G increased the levels of three of eight subclasses [AS(18) 14%, NS(18) 11%, NdS(18) 18%, where only AS was significantly elevated when normalized to protein]. NP(18), AP(18) and AS(18) ceramides were significantly more abundant at sites treated with MVE + GL compared with O/W + G (relative to lipid class or normalized to protein). We observed a trend for lower $TEWL_{20}$ (improved skin integrity) in skin with increasing proportions of ceramides with shorter SBs [< 20 carbons; Figure 5 e, Figure S3 (see Supporting Information)]. A relative increase in the proportion of 18-carbon SB ceramides within most subclasses was associated with better skin barrier integrity. We did not find a relationship between acyl or total chain length and skin barrier integrity in this analysis [Figure 5 g; Figure S4 (see Supporting Information)].

Of the 1633 molecular species detected, 364 were present in > 70% of samples in one of the treatment groups. We compared the abundance of these species before and after treatment. A similar number of species significantly changed in abundance with both treatments (O/W + G, $n = 87$; MVE + GL, $n = 83$), including 52 identical

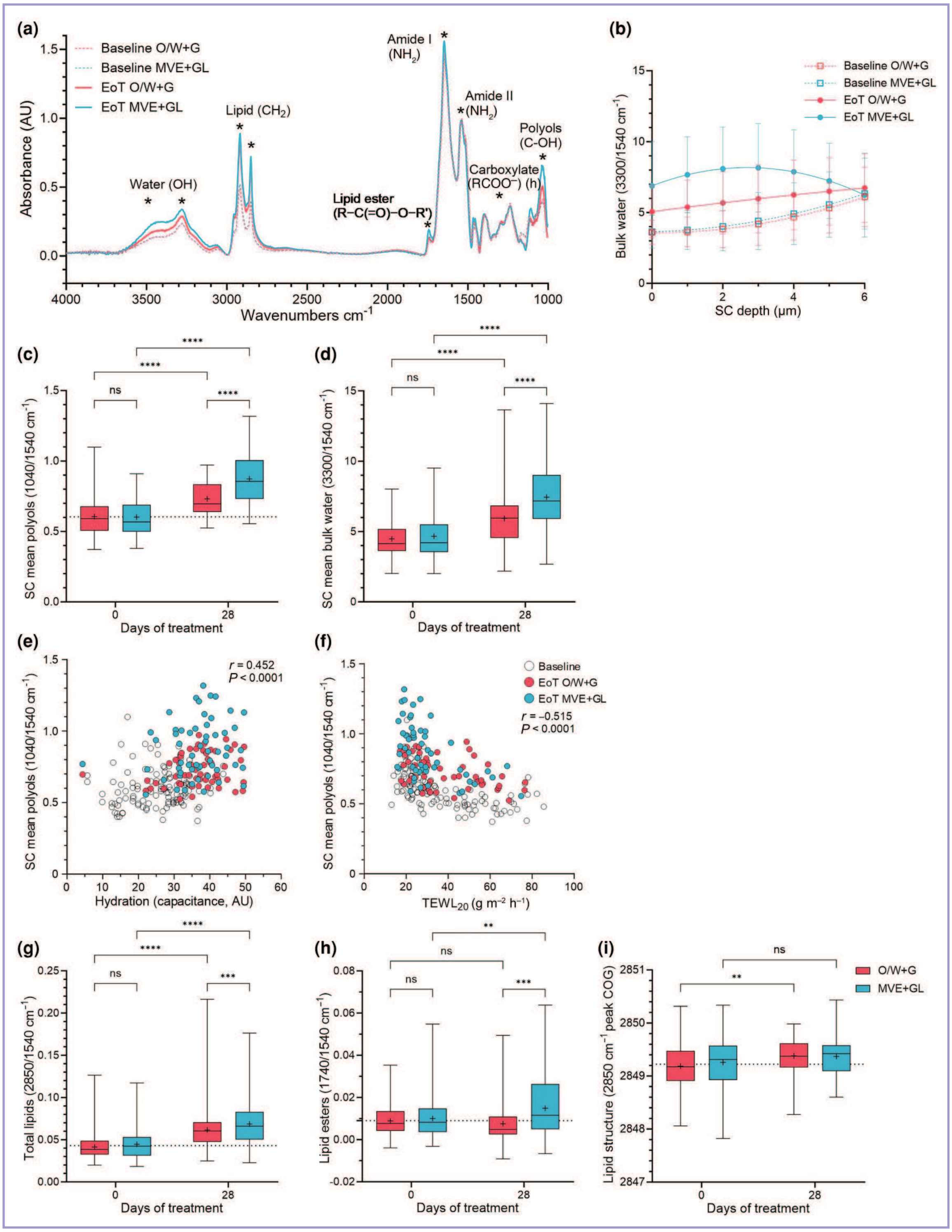


Figure 4 Emollient treatment affects the molecular profile of the stratum corneum (SC). (a) Average mid-infrared spectrum collected using an attenuated total reflectance Fourier transform infrared spectrometer from the skin surface of the forearm. (b) Interpolated water values from 0 to 6 μm within the SC constructed using measurements collected after 5, 10, 15 and 20 tape strips. SC (c) polyols (glycerine) and (d) water. (e) Correlation between polyol (glycerine) abundance and hydration, and (f) barrier integrity. (g) Total lipid, (h) lipid esters and (i) lipid structure. Quantification from absorbance peak area (mean value 0–6 μm) normalized to amide II-associated peak (c, d, g, h) and (i) peak position. AU, arbitrary units; COG, centre of gravity; EoT, end of treatment; MVE + GL, multivesicular emulsion with physiological lipids and glycerine; ns, not significant (i.e. $P > 0.05$); O/W + G, oil-in-water emollient with glycerine. $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$ (Fisher's test following mixed-effects analysis).

species. Significant changes of twofold or greater were only observed after MVE + GL treatment (Figure 6). Apart from the NdS species, these ceramides were identified in < 50% samples at baseline but in far higher numbers of samples after treatment with MVE + GL. We looked for associations between lipid species abundance and

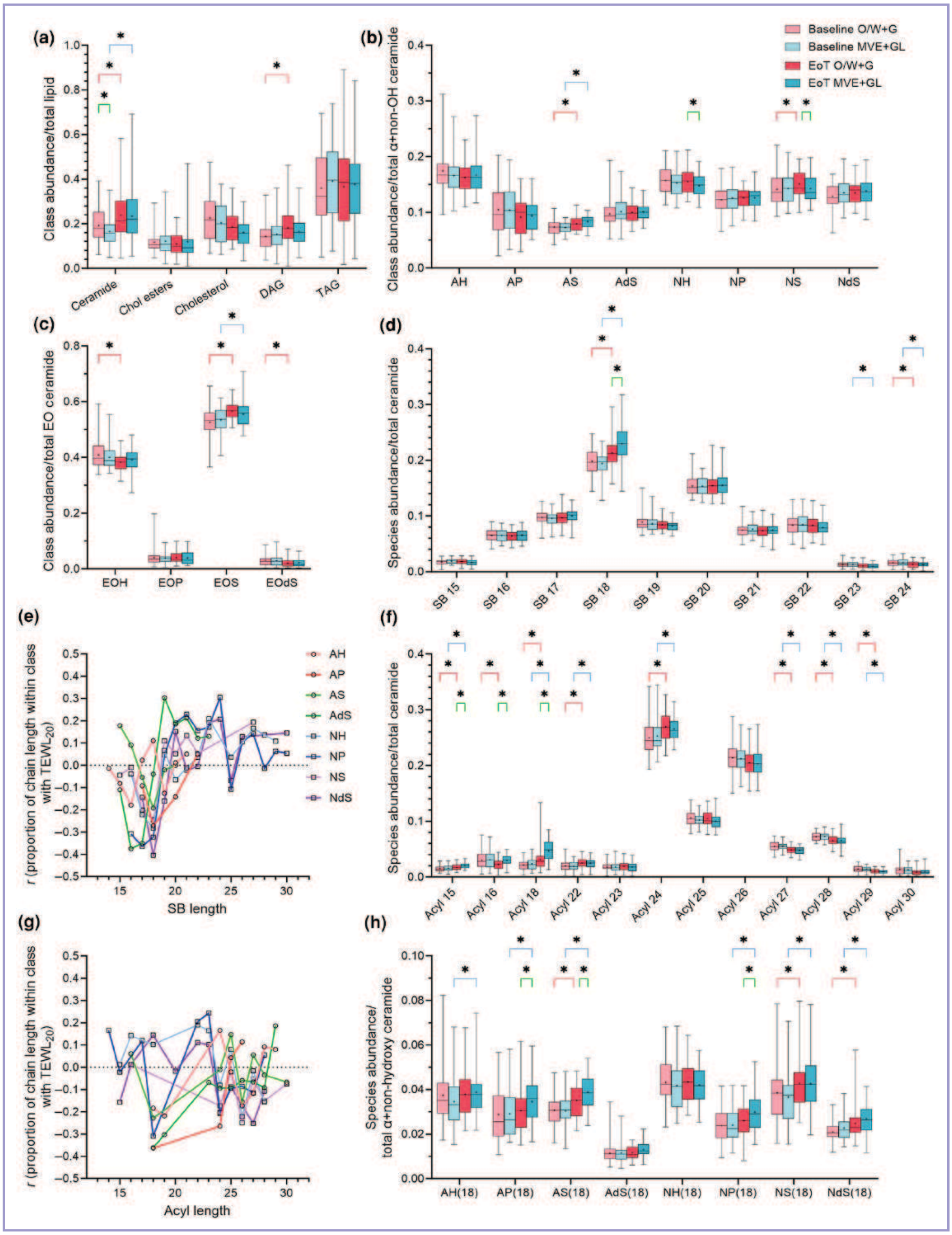


Figure 5 Change in the composition of stratum corneum (SC) lipids in response to emollient treatment: mass spectrometry analysis. Relative abundance of (a) major lipid groups, (b, c) ceramide subclasses and (h) α-hydroxy/non-hydroxy ceramides with an 18-carbon sphingoid base (SB) combined with any acyl chain (16–32 carbons). Distribution of α-hydroxy/non-hydroxy ceramides by (d) SB chain length, combined with any acyl chain (13–35 carbons), and (f) acyl chain length, combined with any SB (14–42 carbons). Only subclasses representing > 1% of α-hydroxy/non-hydroxy ceramides are presented. (e, g) Correlation between the abundance of ceramide by chain length and barrier function. Mixed-effects analysis was used to assess differences between baseline and end of treatment (EoT) and between treatments, with control of the false discovery rate ($Q = 0.01$); only comparisons where $q < Q$ are plotted (indicated by an asterisk). Green lines indicate treatment comparisons, red lines indicate timepoint comparisons for oil-in-water emollient with glycerine (O/W + G) and blue lines indicate timepoint comparisons for multivesicular emulsion with physiological lipids and glycerine (MVE + GL). Boxes represent the interquartile range, whiskers show the range, median is indicated as a horizontal line and '+' denotes the mean. AdS, α-hydroxy-dihydrosphingosine; AH, α-hydroxy-6-hydroxysphingosine; AP, α-hydroxy-phytosphingosine; AS, α-hydroxy-sphingosine; DAG, diacylglycerol; EO, ester-linked-ω-hydroxy ceramide; EOdS, ω-hydroxy-dihydrosphingosine; EOH, ω-hydroxy-6-hydroxysphingosine; EOP, ω-hydroxy-phytosphingosine; EOS, ω-hydroxy-sphingosine; NdS, non-hydroxy-dihydrosphingosine; NH, non-hydroxy-6-hydroxysphingosine; NP; non-hydroxy-phytosphingosine; NS, non-hydroxy-sphingosine; TAG, triacylglycerol; $TEWL_{20}$, transepidermal water loss after 20 tape strips.

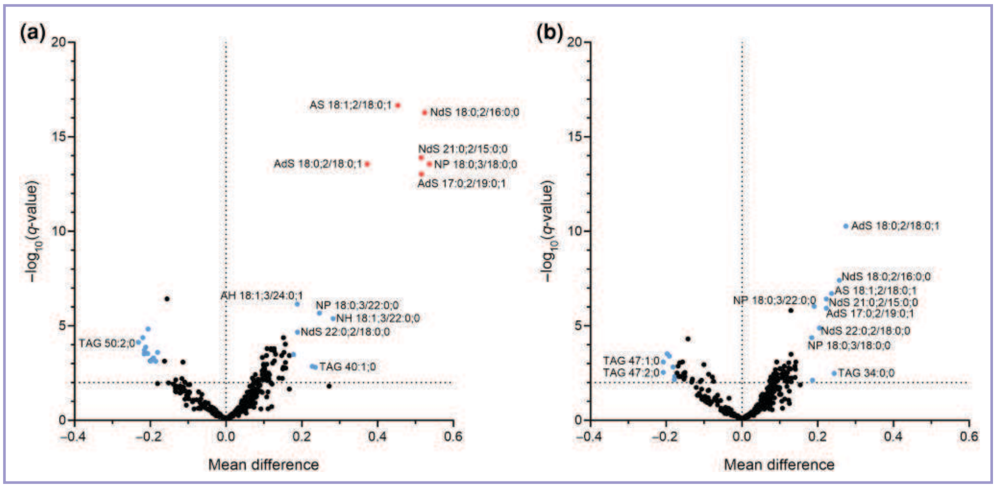


Figure 6 The abundance of lipid species within the stratum corneum changes in response to emollient treatment. Difference in molecular species abundance ($\log_{10}$ pmol mg^{-1} protein) vs. baseline following treatment with (a) multivesicular emulsion with physiological lipids and glycerine (MVE+GL) and (b) oil-in-water emollient with glycerine (O/W+G). Species were included for analysis when detected in >70% of samples in at least one cohort. Differences were assessed using multiple *t*-tests, with control of the false discovery rate (Q=0.01). Red points represent species more than 2-fold abundant following treatment, blue points species with more than 1.5-fold change. AdS, α-hydroxy-dihydrosphingosine; AH, α-hydroxy-6-hydroxysphingosine; AS, α-hydroxy-sphingosine; NdS, non-hydroxy-dihydrosphingosine; NH, non-hydroxy-6-hydroxysphingosine; NP; non-hydroxy-phytosphingosine; TAG, triacylglycerol.

$TEWL_{20}$. Table 1 provides the top 10 associations (these were all negative; high species abundance associated with better barrier integrity) and change in species abundance with treatment. Notably, six of the species were NH ceramides. Four of the species were increased more than twofold in response to treatment with MVE+GL. As the relative balance of ceramide species appears to be an important determinant of barrier function,[13,14] we determined the abundance of these four species relative to total NdS ceramides [an increase in NdS ceramides associated with worsening barrier integrity in this population (Williams *et al.*, submitted); Figure S4 a]. Increased abundance of these species relative to NdS was associated with improved barrier integrity, reduced skin sensitivity and greater SC hydration [r=−0.447, r=−0.294 and r=0.437 for NP18:0:3/18:0:0 relative to NdS, respectively (Figure S5; see Supporting Information)].

Discussion

In this study, the effects of two humectant-containing emollients, with and without physiological lipids, were compared in people with dry, eczema-prone skin. Over a 28-day treatment period, both emollients increased skin hydration and improved clinical signs of dryness. The onset of effects was more rapid with the multivesicular emulsion containing glycerine and physiological lipids (MVE+GL) and the water content of the SC was higher (25%). Only MVE+GL was associated with an improvement in the integrity of the skin barrier, and a reduction in sensitivity to the common household irritant SLS (TEWL reduced by 17%). Both treatments appeared to affect the composition of the SC lipidome. The proportion of AP(18) and NP(18) ceramides in the SC, both ingredients of MVE+GL, were increased by 19% and 24%, respectively, following MVE+GL treatment. The relative

Table 1 Changes in the abundance of lipid species correlated with differences in biophysical and functional properties of the skin

Species	Correlation (r),[a] $TEWL_{20}$	O/W+G EoT – BL[b]	FC[c]	$-\text{Log}_{10}$ q-value	Discovery (q<Q)	MVE+GL EoT – BL[b]	FC[c]	$-\text{Log}_{10}$ q-value	Discovery (q<Q)	Species/NdS correlation (r)[a] $TEWL_{20}$
AdS 18:0;2/18:0;1	−0.479	0.27	**1.86**	**10.27**	**Yes**	0.37	**2.34**	**13.56**	**Yes**	−0.510
NH 20:1;3/27:0;0	−0.410	0.035	1.08	0.44	No	0.11	**1.29**	**2.11**	**Yes**	−0.490
NH 18:1;3/27:0;0	−0.374	0.086	1.22	1.19	No	0.044	1.11	0.70	No	−0.496
NH 17:1;3/26:0;0	−0.364	−0.015	0.97	0.25	No	0.016	1.04	0.34	No	−0.516
NH 25:1;3/24:0;0	−0.354	−0.042	0.91	0.66	No	0.071	1.18	1.42	No	−0.500
AdS 17:0;2/19:0;1	−0.349	0.22	**1.66**	**5.93**	**Yes**	0.52	**3.31**	**13.03**	**Yes**	−0.435
NH 18:1;3/25:0;0	−0.342	−0.0014	1.00	0.11	No	0.022	1.05	0.37	No	−0.505
NP 18:0;3/18:0;0	−0.331	0.18	**1.51**	**4.37**	**Yes**	0.54	**3.47**	**13.56**	**Yes**	−0.447
NH 17:1;3/28:0;0	−0.325	−0.016	0.96	0.22	No	0.1	**1.26**	**2.64**	**Yes**	−0.567
AS 18:1;2/18:0;1	−0.313	0.24	**1.74**	**6.71**	**Yes**	0.45	**2.82**	**16.66**	**Yes**	−0.406

Bold text indicates a significant fold change. AdS, α-hydroxy dihydrosphingosine; AS, α-hydroxy-sphingosine; BL, baseline; EoT, end of treatment; FC, fold change; MVE+GL, multivesicular emulsion with physiological lipids and glycerine; NdS, non-hydroxy ceramide dihydrosphingosine; NH, non-hydroxy-6-hydroxysphingosine; NP, non-hydroxy-phytosphingosine; O/W+G, oil-in-water emollient with glycerine; $TEWL_{20}$, transepidermal water loss after 20 tape strips. [a]Spearman correlation; [b]$\log_{10}$ pmol mg^{-1}; [c]$10^{(\text{EoT – baseline})}$.

abundance of ceramide species associated with improved skin barrier integrity increased more with MVE + GL than with O/W + G, suggesting a role for lipid supplementation in the observed treatment effects.

Previously we compared the effects of MVE + GL with a simple oil-in-water (O/W) emollient without humectants.[12] The O/W emollient did not impart clinically relevant improvements in skin moisturization. The addition of glycerine to the O/W emulsion used in this study appeared to increase the efficacy in reducing skin dryness and improving hydration. The effects of glycerine on skin barrier function are unclear. Here, we have shown that although SC glycerine levels are positively associated with improvements in skin barrier integrity and moisturization, regular use of an O/W emulsion with glycerine (i.e. O/W + G) did not have an observable effect on skin barrier function. The results support evidence that not all emollients have a positive effect on the skin barrier.[15–18] The condition of the skin barrier is a key aspect of AD pathophysiology; skin barrier deficit is likely to be a key driver of disease initiation,[19,20] and the extent of its dysfunction is associated with disease severity.[21,22] Neither emollient altered basal TEWL. As the assessments were carried out on uninvolved skin there is less scope for improvements in TEWL; furthermore, a positive clinical impact of an emollient is not always accompanied by reductions in TEWL.[7] Improvements in the integrity/cohesiveness of the barrier with MVE + GL treatment accompanied by decreased sensitivity to SLS supports the conclusion that skin barrier function is enhanced.[23] In agreement with evidence that basal TEWL alone may be insufficient to fully characterize barrier function.[24] Detergents can bind and denature SC proteins, disrupt SC lipid lamellae and can increase the dissociation of SC corneocytes.[25,26] Use of MVE + GL may stabilize the structure of the lipid lamellae and corneodesmosomes and/or restrict penetration and protein binding of SLS.[27] An anti-inflammatory mechanism reducing sensitivity to irritant cannot be excluded. Changes to the SC lipidome with treatment may contribute to the observed changes in barrier function.

We characterized the SC lipidome in nonlesional eczema-prone skin before and after emollient use. Both emollients increased total SC lipids and the relative abundance of SC ceramides. However, not all lipids are beneficial to skin function and the balance of applied lipids is key to determining skin barrier effects.[28]

Lipid abundance changes of twofold or more were only observed following MVE + GL treatment. Both lipid supplementation by the emollient and changes to endogenous ceramide metabolism may have contributed to these changes. The activity of key enzymes in ceramide synthesis, such as β-glucocerebrosidase and acid sphingomyelinase, are affected by SC pH and water content.[29,30] Therefore, hydrating the skin may boost its ceramide-generating capacity. The incorporation of physiological lipids in the MVE + GL formulation also provided an additional source of metabolites. These metabolites may regulate biosynthetic pathways to increase ceramide synthesis, and ceramides themselves can act as signalling molecules.[31] For example, ceramides can activate receptors in the peroxisome proliferator-activated receptor pathway.[32,33] At the subclass level, both emollients increased the relative abundance of AS (α-hydroxy-sphingosine), but only O/W + G increased NS (non-hydroxy-sphingosine) ceramides. EOS (ω-hydroxy-sphingosine) ceramides, which are crucial to the lamellar phase structure and are preferentially bound to the cornified envelope,[34,35] were increased with both emollients relative to other EO (ester-linked-ω-hydroxy) ceramides. Earlier studies have highlighted increases in AS and NS species and decreases in EOS species in AD-affected vs. unaffected and healthy skin, and have associated these ceramides with skin barrier deficit.[2,29,36,37] However, changes to AS and NS abundance are not consistently reported in affected skin,[38–42] and detailed analysis implicates more nuanced changes within each subclass.[13,23,40,42] Total ceramide chain length also appears important, with short-chain ceramides (34 total carbons) associated with AD severity and poor skin barrier function.[2,37,43] While many of these studies did not explore the contribution of acyl and SB length, very short acyl chains appear to be detrimental.[44] We did not observe an association between total ceramide chain length and barrier function in this cohort.

Our data suggest that the length of the SB (range 14–30 carbons) plays a role in skin barrier function, with a length of 18 carbons being the optimum for a strong barrier in most subclasses. A significant difference in the abundance of AP (α-hydroxy-phytosphingosine), AS and NP (non-hydroxy-phytosphingosine) species with 18-carbon SBs was observed with MVE + GL treatment compared with O/W + G. Given that AP and NP are ingredients of MVE + GL, it suggests that they are successfully delivered to the SC.

At the species level, a marked increase in the abundance of six species associated with improved skin barrier function was identified in response to MVE + GL treatment. These belonged to the AdS (α-hydroxy-dihydrosphingosine), NH (non-hydroxy-6-hydroxysphingosine), NP and AS subclasses. Previous studies have identified a relationship between high levels of NP relative to NS (non-hydroxy-sphingosine) species and improved skin barrier function.[14,40] We observed negative impacts on barrier properties with greater proportions of NdS (non-hydroxy-dihydrosphingosine) species (although the length distribution of the SB and acyl chains remained an important modifier of this effect). In particular, declining NH levels relative to NdS were associated with increased skin dryness and loss of skin barrier integrity (Williams *et al.*, submitted). Rinnov *et al.* also revealed a relationship between SB chain length and the risk of infants developing AD.[13] *In vitro* modelling of lipid membranes has demonstrated that ceramide structure influences barrier behaviour. Membranes assembled with NdS ceramides had reduced structural organization, higher water loss and increased permeability to small molecules vs. models formed with other ceramide species.[3,45] Taken together, our data suggest a shift away from NdS species (predominantly with long SB and short acyl chains) toward AdS, NH, NP and AS species, driven by MVE + GL treatment, leads to improved skin barrier function.

Lipid groups such as free fatty acids, sphingomyelins and protein-bound ceramides were not included in this analysis. The lipid analysis was exploratory in nature; nevertheless, evidence has been presented for a link between changes in SC ceramide profile with treatment and barrier function. A strength of this study was the broad adult age range, but a paediatric cohort was not included. All participants had a propensity for eczema; there is no reference for 'healthy' skin due to a focus on an at-risk population in need of barrier restoration. The complexity of ceramide chemistry in the SC is emphasized. The effect of lipid-based treatments on the overall balance of ceramide species is important and so the findings of this work will not be generalizable to other ceramide-based therapies.

This study combined biophysical assessments of skin function with the identification of SC lipid changes at the species level, to evaluate the impact of emollient use on eczema-prone skin. Surprisingly, standard O/W emollient therapy (with glycerine) had no benefit to skin barrier function, despite indications that glycerine levels (and some ceramides) were increased in the SC. Marked changes to the SC lipidome associated with skin barrier strengthening, and a reduced response to irritant challenge, were observed using the MVE+GL. Maintaining a healthy skin barrier and avoiding exposure to irritants, are accepted strategies for managing AD.[46] In practice, avoidance of common irritants is challenging. Therefore, barrier-strengthening emollients with physiological lipids and glycerine offer benefits over and above emollients containing glycerine only.

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Conflicts of interests

S.G.D. has received fees for giving lectures and/or attending advisory boards and research funding from Almirall, Astellas Pharma, Bayer Dermatology, Hyphens, LEO Pharma, L'Oréal, MSD, Pfizer, Rohto Pharma, Sanofi and Stiefel-GSK. M.J.C. has been/is a clinical trial investigator for the following organizations: Atopix, Galapagos, Hyphens, Johnson & Johnson, Kymab, LEO Pharma, L'Oréal/La Roche Posay, Novartis, Pfizer, Regeneron and Sanofi-Genzyme. He is an advisory board member, consultant and/or invited lecturer for the following organizations: AbbVie, Amlar, Astellas, Atopix, Boots, Dermavant, Galapagos, Galderma, Hyphens, Johnson & Johnson, Kymab, LEO Pharma, L'Oréal/La Roche Posay, Menlo, Novartis, Oxagen, Pfizer, Procter & Gamble, Reckitt Benckiser, Regeneron and Sanofi-Genzyme. The other authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement

The University of Sheffield Research Ethics Committee approved the study, under project reference 044518. The study was performed in accordance with the Declaration of Helsinki 1964 and its later amendments

Patient consent

Informed consent to participate in the study was obtained from all participants. Written patient consent for publication was obtained.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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ACR 50, ≥50% response in the American College of Rheumatology criteria; **AS**, ankylosing spondylitis; **CRP**, C-reactive protein; **DMARD**, disease-modifying antirheumatic drug; **HS**, hidradenitis suppurativa; **IGA**, Investigator's Global Assessment; **(m)NRI**, (modified) non-responder imputation; **MRI**, magnetic resonance imaging; **nr-axSpA**, non-radiographic axial spondyloarthritis; **NSAID**, non-steroidal anti-inflammatory drug; **PASI 75/90/100**, ≥75/90/100% improvement from baseline in Psoriasis Area and Severity Index; **PsA**, psoriatic arthritis; **PsD**, psoriatic disease; **PsO**, psoriasis; **TNFi-IR**, tumour necrosis factor-α inhibitor – inadequate responder; **TRAE**, treatment-related adverse event.

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