Similar alterations of the stratum corneum ceramide profile in atopic dermatitis, psoriasis, and ichthyosis: results from a systematic review and meta-analysis

Rousel, J.; Mergen, C.; Schoones, J.W.; Niemeyer-van der Kolk, T.; Doorn, M.B.A. van; Bouwstra, J.A.; ... ; Rissmann, R.

Similar Alterations of the Stratum Corneum Ceramide Profile in Atopic Dermatitis, Psoriasis, and Ichthyosis: Results from a Systematic Review and Meta-Analysis

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TO THE EDITOR

The intracellular lipid matrix of the stratum corneum is critical for the skin barrier function and consists mainly of cholesterol, fatty acids, and ceramides (Kihara, 2016). Ceramides represent a heterogeneous class of lipids with varying headgroups, carbon chain lengths, and degree of unsaturation (Kawana et al, 2020; Supplementary Figure S2). The composition of the ceramide fraction is altered in atopic dermatitis (AD), psoriasis (PSO), and ichthyosis (ICHT), among other dermatoses (Kihara, 2016). In this study, we aimed to characterize the similarities between the stratum corneum ceramide profile in these indications using a systematic search strategy and meta-analysis.

A search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines for studies that evaluated the stratum corneum ceramide profile and returned 40 articles with 849 patients for AD, 10 articles with 85 patients for PSO, 13 articles with 121 patients for ICHT, and 55 articles with 852 healthy controls (Supplementary Figure S1). From this selection, changes compared with healthy controls were listed in Table 1, and complete ceramide profiles were further visualized by synthesis of a weighted average and relative ceramide profile after extraction of the profiles from articles. Supplemental Materials and Methods provides a more extensive description of the methods, Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart, ceramide classification used, and descriptive review of the observed alterations compiled in Table 1.

As shown in Table 1, all 3 diseases show conclusive decreases in the Cer[NP] abundance and an increased abundances of Cer[NS] with 34 carbons in lesional skin. A conclusive decrease in ceramide carbon chain length was observed in lesional AD and PSO but not always in ICHT. Although increased Cer[NS] and Cer[EOS] abundances are also observed in PSO, AD, and ICHT, these alterations seemed less consistently observed because several articles report no significant change in these abundances compared with controls. Notably, alterations in the nonlesional skin of AD and PSO were much less apparent than in lesional skin of AD and PSO. This is confirmed by the overlap in the weighted average ceramide profile of nonlesional skin and controls as shown in Figure 1. Lesional AD, lesional PSO, and ICHT show an evident decrease in the abundance of Cer[NP] (AD: −6.1 ± 2.3%, PSO: −12.3 ± 1.7%, ICHT: −8.2 ± 4.4%) amounting to percentage reductions in the relative abundance of Cer[NP] of 26% for AD, 52% for PSO, and 35% for ICHT compared with that of controls. Although changes in the Cer[NS] abundances in lesional skin seem smaller as a result of its overall lower abundance, the percentage change is even more drastic (AD: +2.7 ± 4.9% [+37%], PSO: +9.3 ± 0.2% [+127%], ICHT: +7.7 ± 4.9% [+105%]). Similarly, ceraminde AS seems affected in lesional skin, with a 2.2 ± 4.2% (+42%), 11.0 ± 3.2% (+207%), and 6.5 ± 5.2% (+123%) increase for AD, PSO, and ICHT, respectively. The systematic search also returned articles indicating alterations in the ceramide profiles of acne vulgaris, palmoplantar hyperkeratosis, dandruff, pruritus, melasma, scarring, and hypohidrotic ectodermal dysplasia, but the number of articles were low, and these lacked sufficient detail to enable their integration into the table and meta-analysis. However, a comprehensive description has been included with the Supplementary Materials and Methods.

The table and meta-analysis show a high amount of similarity between the lesional skin of different indications. It highlights that ceramide subclass synthesis is skewed and that lipid elongation is impaired in a similar way despite the different immunological background of AD and PSO and extent past the well-defined causative genetic alterations that underly ICHT (Guttman-Yassky and Krueger, 2017; Takeichi et al, 2022). The mechanistic basis for the altered subclass profile remains unclear but might be caused by dysregulated β-glucocerebrosidase and acid-sphingomyelinase, responsible for conversion of sphingomyelins and glucocylceramide into ceramides (Danso et al, 2017). Further downstream, aberrant expression of dihydroceramide desaturase-1 and -2, involved in Cer[xdS] to Cer[xS] or Cer[xP] conversion, might further contribute to the observed alterations (Del Duca et al, 2024; Kihara, 2016). In addition, an altered expression of fatty acid elongases and ceramide synthases involved in ceramide elongation might lead to a decreased ceramide carbon chain length and increased Cer[NS] with 34 carbons (Danso et al, 2017; Ito et al, 2017). Considering the different backgrounds between these diseases but similarities in ceramide profiles, it might be plausible that alterations in

Abbreviations: AD, atopic dermatitis; ICHT, ichthyosis; PSO, psoriasis

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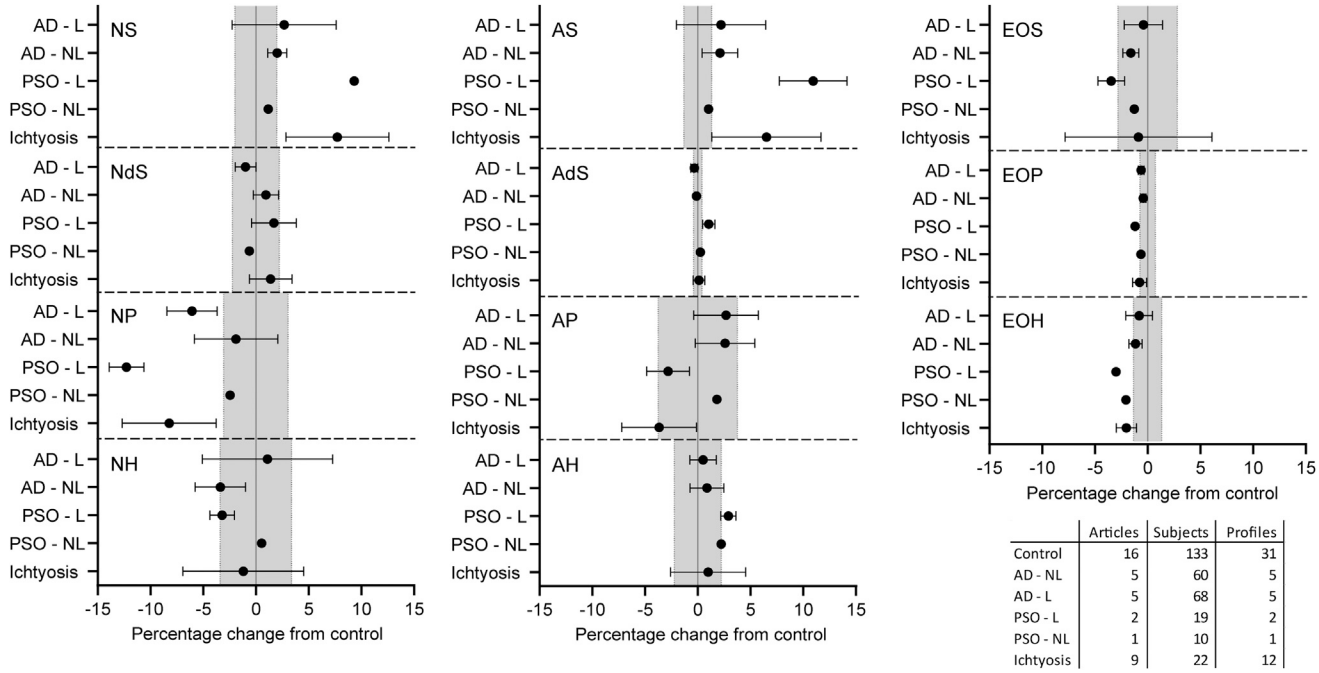
Table 1. Alterations in the Ceramide Profile in Disease, with Increases (↑), Decreases (↓), or No Significant Differences (↔) Indicated Compared with Controls, with the Fraction of Articles Showing Similar Changes Reported

	Articles (n)	Patients (n)	Total Ceramide	[NS]	[NdS]	[NP]	[NH]	[AS]	[AdS]	[AP]	[AH]	[EOS]	[EOdS]	[EOP]	[EOH]	[EOx]	Other	CCL	[NSc34]	muCer	Bound Lipids	Conclusive Evidence ≥3 Sources
Lesional atopic dermatitis	13/29	176/575	4/4 ↓ [1–4]	5/8 ↑ [1, 5–8] 3/8 ↔ [2,4,9]	3/4 ↓ [1,2,4] 1/4 ↔ [9]	5/5 ↓ [1,2,4,8,9]	3/3 ↓ [1,2,4]	4/6 ↑ [1,2,7,8] 2/6 ↔ [4,9]	3/4 ↔ [1,2,9] 1/4 ↓ [4]	2/4 ↔ [1,2] 2/4 ↓ [4,9]	2/3 ↓ [1,4] 1/3 ↔ [2]	8/8 ↓ [1–5, 8–10]	1/2 ↓ [1] 1/2 ↔ [8]	5/5 ↓ [1,2,4,8,9]	4/4 ↓ [1,2,4,8]	2/2 ↓ [1,7]	1/1 [OS] ↓ [9] 1/1 [OP] ↔ [9] 1/1 [OH] ↔ [9] 1/1 [S] ↑ [11] 1/1 [dS] ↑ [11]	10/10 ↓ [1–6, 8,9,12,13]	9/9 ↑ [1, −8,14]	2/2 ↑ [10,14]	1/2 ↔ [10] 1/2 ↓ [15]	↑C34 ↓ Total ↓ [NP] ↓ [EOS] ↓ [EOP] ↓ [EOH] ↓ CCL
Nonlesional atopic dermatitis	17/28	295/529	2/5 ↔ [3,16] 1/5 ↓ [1,17] 1/5 ↑ [18]	7/8 ↔ [2,7,9,16, 18–20] 1/8 ↑ [21]	4/4 ↔ [2,9,20,21]	4/7 ↔ [9,16,21,22] 2/7 ↓ [2,20] 1/7 ↑ [18]	2/4 ↔ [20,22] 2/4 ↓ [2,21]	6/6 ↔ [2,7,9,18,20,21]	4/4 ↔ [2,9,20,21]	7/7 ↔ [2,9,16,18, 20–22]	5/5 ↔ [2,16,18,20,21]	6/12 ↓ [1,5,10,18,21,23] 6/12 ↔ [2,3,9,16,20,22]	1/1 ↔ [20]	3/3 ↔ [2,9,20]	5/6 ↔ [2,16, 20–22] 1/6 ↑ [18]	3/3 ↓ [7,19,20]	1/1 [OS] ↔ [9] 1/1 [OP] ↔ [9] 1/1 [OH] ↔ [9]	5/7 ↓ [8,17,19,21,23] 2/7 ↔ [1,14]	2/2 ↑ [1,19]	1/1 ↑ [10]	3/3 ↔ [10,15,23]	↔ [NdS] ↔ [AS] ↔ [AdS] ↔ [AP] ↔ [AH] ↔ [EOP]
Lesional psoriasis	6/9	57/79	2/3 ↔ [24,25] 1/3 ↓ [26]	4/4 ↑ [24–27]	1/2 ↓ [26] 1/2 ↑ [24]	4/4 ↓ [24–27]	2/3 ↔ [24,27] 1/3 ↓ [26]	3/3 ↑ [24–26]	1/2 ↑ [24] 1/2 ↔ [26]	3/3 ↓ [24–26]	1/2 ↑ [24] 1/2 ↓ [26]	3/4 ↓ [24–26] 1/4 ↑ [28]	2/2 ↔ [24,27]	2/3 ↓ [24,26] 1/3 ↑ [28]	2/3 ↓ [24,26] 1/3 ↑ [28]			6/6 ↓ [12,13,24, 26–28]	2/2 ↑ [24,26]			↑ [NS] ↑ [AS] ↓ [NP] ↓ [AP]
Nonlesional psoriasis	4/5	37/47	2/2 ↔ [16,26]	2/3 ↔ [16,26] 1/3 ↑ [27]	1/1 ↔ [26]	2/3 ↔ [16,26] 1/3 ↓ [27]	1/2 ↓ [26] 1/2 ↔ [27]	1/1 ↔ [26]	1/1 ↔ [26]	2/2 ↔ [16,26]	2/2 ↔ [16,26]	2/3 ↔ [16,26] 1/3 ↑ [28]		1/2 ↔ [26] 1/2 ↑ [28]	2/3 ↔ [16,26] 1/3 ↑ [28]			1/2 ↔ [26] 1/2 ↓ [27]	1/1 ↔ [26]			Inconclusive
Ichthyosis	11/13	38/121	4/5 ↓ [29–32] 1/5 ↔ [33]	7/9 ↑ [30,31, 33–37] 2/9 ↔ [38,39]	6/7 ↔ [30,31,33,35, 36,38] 1/7 ↑ [34]	7/7 ↓ [29–31, 34,35, 37,38]	6/7 ↓ [30,31,34, 36–38] 1/7 ↔ [33]	4/8 ↑ [33–35,37] 4/8 ↔ [30,31,38,39]	3/6 ↔ [31,33,35] 2/6 ↓ [30,38] 1/6 ↑ [34]	3/6 ↓ [30,31,36] 2/6 ↔ [33,35,38] 1/6 ↑ [34]	3/6 ↓ [30,31,34] 3/6 ↔ [33,35,38]	7/9 ↓ [29–31,34, 37–39] 1/9 ↑ [33] 1/9 ↔ [35]	3/5 ↓ [29,34,38] 2/5 ↔ [34,35]	7/8 ↓ [29–31, 33,34,37,38] 1/8 ↔ [35]	7/8 ↓ [29–31, 33,34,36,37] 1/8 ↔ [35]	5/5 ↓ [29,30,34,35, 38]	3/3 [OS] ↑ [30,34,39] 1/1 [OP] ↑ [30] 1/1 [O] ↔ [36]	7/9 ↓ [29–31, 34–36,38] 2/9 ↔ [32,33]	3/3 ↑ [29,31,34]	1/1 ↑ [29]	3/5 ↔ [30,34,38] 2/5 ↓ [33,36,40]	↑C34 ↓ [NP]

Abbreviations: CCL, ceramide chain length; HPTLC, high-performance thin-layer chromatography; muCer, monounsaturated ceramide.

Differences in CCL are defined on the basis of changed average CCL and changes in the abundance of short or long ceramide species. The total subjects and number of articles represent the fraction included in the table of all literature identified through the systematic search. Note that in reference number 4 (Ito et al, 2017), comparison is with nonlesional skin of the same disease. Not all articles in the review have been included in this overview because they lack comparisons with healthy controls (Angelova-Fischer, 2011; Dähnhardt et al, 2021; Ishida et al, 2020; Jungersted et al, 2011; Lee et al, 2021; Oláh et al, 2017; Paslin and Wertz, 2006), present data in wrong format (Chiba et al, 2019; Yokose et al, 2020), or are prospective biomarker studies (Berdyshev et al, 2023; Rinnov et al, 2023; Sho et al, 2022). Please note that studies performed using HPTLC are excluded from the table (Di Nardo et al, 1998; Imokawa et al, 1991; Lavrijsen et al, 1995; Matsumoto et al, 1999; Motta et al, 1994; Paige et al, 1994; Yamamoto et al, 1991). A list of numbered references, as used in this table, is as follows: [1]Boer et al (2020); [2]Ishikawa et al (2010); [3]Kim et al (2023); [4]Ito et al (2017); [5]Berdyshev et al (2022); [6]Berdyshev et al (2018); [7]Danso et al (2017); [8]van Smeden et al (2014a); [9]Chu et al (2023); [10]Boiten et al (2020); [11]Toncic et al (2020); [12]Tawada et al (2014); [13]Pilz et al (2020); [14]Joo et al (2015); [15]Macheleidt et al (2002); [16]Farwanah et al (2005); [17]Kim et al (2017); [18]Bleck et al (1999); [19]Janssens et al (2012); [20]Janssens et al (2011); [21]Emmert et al (2021); [22]Jungersted et al (2010); [23]Berdyshev et al (2021); [24]Uchino et al (2023); [25]Motta et al (1993); [26]Koyano et al (2010); [27]Kim et al (2022); [28]Tyrrell et al (2021); [29]van Smeden et al (2014b); [30]Arai et al (2022); [31]Murase et al (2020); [32]Takeichi et al (2018); [33]Takeichi et al (2020); [34]Yamamoto et al (2021); [35]van Smeden et al (2020); [36]Takeichi et al (2022); [37]Ohno et al (2015); [38]Takahashi et al (2022); [39]Pichery et al (2017); [40]Dick et al (2017). [NSc34] indicates ceramide [NS] species with a total carbon chain length of 34.



	Articles	Subjects	Profiles
Control	16	133	31
AD - NL	5	60	5
AD - L	5	68	5
PSO - L	2	19	2
PSO - NL	1	10	1
Ichtyosis	9	22	12

Figure 1. Forest plot showing the change in the weighted relative ceramide profile in percentages compared with healthy controls, synthesized from articles that report a ceramide profile that contain at least the 11 subclasses presented in this figure. The number of articles, subjects, and profiles included are indicated in the table for each indication. Error bars represent the SD of the weighted mean for diseased skin, and the greay area represents the SD of the weighted mean of the healthy controls. References included per indication are listed in Supplementary Table S1. L denotes lesional, and NL denotes nonlesional. AD, atopic dermatitis; ICHT, ichthyosis; PSO, psoriasis.

the ceramide profile result from aberrant epidermal differentiation instead of primary disease mechanisms such as inflammation or causative mutations. Indeed, epidermal differentiation has been linked to skewing of the Cer[NS] and Cer[NP] synthesis (Yokose et al, 2020). However, the role of inflammation cannot be overlooked in this process and might aggravate or instigate these changes. Indeed, monitoring the effect of anti-inflammatory treatment showed concurrent normalization of the subclass composition and ceramide carbon chain length (Berdyshev et al, 2022).

Of note, the different ceramide profiles integrated in this review are obtained using varying methods for stratum corneum sampling methods, sampling preparation, and liquid chromatography-mass spectrometry. This could have impacted the results because sample preparation and factors such as instrument settings, matrix effects, and internal standards used during liquid chromatography-mass spectrometry analysis can introduce variation (Kawana et al, 2020). This has been partly managed by only including articles that directly contrast disease profiles to controls in Table 1 and by converting all profiles into relative profile before inclusion in Figure 1. Indeed, methodological differences could explain why conflicting reports are present in Table 1 on, for example, the abundance of Cer[AS] in ICHT. Overall, variation seems limited because the control group which is composed of 31 profiles shows an acceptable SD. However, the ceramide profile has shown to vary, among others, between sampling locations and over seasons, which should be considered when matching controls (Ishikawa et al, 2013).

To conclude, with this systematic review and meta-analysis, we show that alterations in the ceramide profile of AD, PSO, and ICHT have a high degree of similarity. These changes are reliably detected in disease and differentiate from controls despite differences in methodology. The ability of the ceramide profile to reflect changes in disease severity upon treatment as shown in AD holds prospect for its use as a disease-monitoring biomarker in PSO and ICHT and might even be applied to other dermatoses provided that the ceramide profile has first been properly characterized.

DATA AVAILABILITY STATEMENT

All data in this review can be retrieved from the original articles as referenced in the (supplementary) reference list.

KEYWORDS

Atopic dermatitis; Barrier; Ceramides; Ichthyosis; Psoriasis

ORCIDs

Jannik Rousel: http://orcid.org/0000-0003-0986-3753
Catherine Mergen: http://orcid.org/0000-0003-2509-6814
Jan W. Schoones: http://orcid.org/0000-0003-1120-4781
Tessa Niemeyer-van der Kolk: http://orcid.org/0000-0002-3221-1609
Martijn B. A. van Doorn: http://orcid.org/0000-0003-1672-7899
Joke A. Bouwstra: http://orcid.org/0000-0002-7123-6868
Jeroen van Smeden: http://orcid.org/0000-0002-2728-2832
Robert Rissmann: http://orcid.org/0000-0002-5867-9090

CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: JR, CM, RR; Data Curation: JR, CM; Formal Analysis: JR, CM; Investigation: JR, CM, JWS; Methodology; JWS, JR, CM; Supervision; RR, JAB, JvS; Writing − Original Draft Preparation: JR, CM; Writing − Review and Editing: RR, JAB, JvS, JR, CM, TN-vdK, MBAvD

Jannik Rousel*[1,2,7], *Catherine Mergen*[2,7], *Jan W. Schoones*[3], *Tessa Niemeyer-van der Kolk*[1], *Martijn B.A. van Doorn*[1,4], *Joke A. Bouwstra*[2], *Jeroen van Smeden*[1,2,5] *and Robert Rissmann*[1,2,6,*] *and Next Generation ImmunoDermatology Consortium

[1]*Centre for Human Drug Research (CHDR), Leiden, The Netherlands;* [2]*Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands;* [3]*Directorate of Research Policy, Leiden University Medical Centre, Leiden, The Netherlands;* [4]*Department of Dermatology, Erasmus Medical Centre, Rotterdam, The Netherlands;* [5]*Department of Clinical Pharmacy and Toxicology, Leiden University Medical Centre, Leiden, The Netherlands; and* [6]*Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands*

[7]*These authors contributed equally to this work.*

[*]*Corresponding author e-mail: rrissmann@chdr.nl*

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2024.02.010.

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Lipid Nanoparticles Efficiently Deliver the Base Editor ABE8e for *COL7A1* Correction in Dystrophic Epidermolysis Bullosa Fibroblasts In Vitro

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TO THE EDITOR

Lipid nanoparticles (LNPs) have been widely approved and used on a global scale for delivery of mRNA. LNPs can package and deliver mRNA-encoding gene editors, including adenine base editors, which convert A•T base pairs to G•C base pairs without double-stranded DNA breaks or donor DNA (Gaudelli et al, 2017). Adenine base editor is a potential treatment approach for the inherited blistering disease dystrophic epidermolysis bullosa (DEB). DEB results from pathogenic variants in *COL7A1*, leading to dysfunctional or absent type VII collagen (C7), a major component of anchoring fibrils that adhere the dermal−epidermal junction , giving stability to skin (Bardhan et al, 2020). There is currently no cure for DEB; however, ∼90% of *COL7A1* variants are single nucleotide variants, with C>T single nucleotide variants accounting for ∼60% of variants (ClinVar database; accessed August 2023). These variants are targetable by adenine base editors; our group and others have demonstrated the utility of adenine base editor in reverting pathogenic variants and restoring C7 expression (Osborn et al, 2020; Sheriff et al, 2022).

Abbreviations: C14, 1,2-Di-((Z)-tetradec-11-enyloxy)-N,N,N trimethylammonium propane chloride; C16, 1,2-Di-((Z)-hexadec-11-enyloxy)-N,N,N trimethylammonium propane iodide; C18, 1,2-Di-((Z)-octadec-9-enyloxy)-N,N,N trimethylammonium propane chloride; C7, type VII collagen; DEB, dystrophic epidermolysis bullosa; DOPE, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine; LFMM, Lipofectamine MessengerMAX; LNP, lipid nanoparticle; sgRNA, single-guide RNA

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