

REVIEW ARTICLE

Clinical significance of the water retention and barrier function-improving capabilities of ceramide-containing formulations: A qualitative review

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Funding Information

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Abstract

A decrease in the ceramide content of the stratum corneum is known to cause dry and barrier-disrupted skin. In this literature review, the clinical usefulness of preparations containing natural or synthetic ceramides for water retention and barrier functions was evaluated. The PubMed, Cochrane Library, and Iqaku Chuo Zasshi databases were searched using keywords such as “ceramide”, “skincare products”, “barrier + hydration + moisture + skin”, and “randomized trial”. All database searches were conducted in February 2019. Forty-one reports were selected based on the following criterion: comparative control studies that evaluated the effects of ceramide-containing formulations based on statistical evidence. Among the 41 reports, 12 were selected using the patient, intervention, comparison, and outcome approach. These 12 reports showed that external ceramide-containing preparations can improve dry skin and barrier function in patients with atopic dermatitis. However, a double-blinded comparative study with a large sample size is warranted for appropriate clinical use.

KEYWORDS

atopic dermatitis, ceramides, dry skin, intercellular lipid of stratum corneum, skin barrier

1 | INTRODUCTION

The skin, which covers the entirety of the human body, is the largest organ, and it fulfills a variety of functions and roles critical to homeostasis, including the following: (i) water retention in the body; (ii) thermoregulation; (iii) prevention of irritation and invasion of external microorganisms and foreign substances; and (iv) function as a sensory organ. Regarding the third barrier function, there are three important factors, namely filaggrin, tight junction, and stratum corneum lipids. Recent studies showed the important role of filaggrin gene mutation in barrier dysfunction of atopic dermatitis.¹ Although

tight junction of the upper epidermis is a critical structure for skin barrier function,² the association with skin diseases is not yet fully elucidated and a possible role in barrier dysfunction of atopic dermatitis is suggested.³

The outermost layer of the skin, the stratum corneum, is responsible for maintaining the barrier function of the skin, which is particularly important for preserving a constant internal environment.⁴ The stratum corneum is composed of 10–15 layers of corneocytes separated by lipid layers and has been described as having a “brick and mortar” structure.⁵ The intercellular lipids of the stratum corneum that make up these lipid layers form an amphipathic extracellular lipid

[Correction added on 15 October 2021 after first online publication: The Funding Information was added to the article]

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matrix, which retains bound water, performs a moisturizing function, and maintains the strong bond between corneocytes. This lipid matrix acts as a barrier that prevents water loss from the epidermis and invasion of the body by external foreign substances.^{6,7} The components of intercellular lipids are ceramides, cholesterol, and cholesterol esters.⁸ Ceramides, which constitute approximately 50% of these lipids (by weight), are sphingolipids consisting of sphingosine bases bound to fatty acids via amide linkages. There are 12 subclasses of ceramides, categorized by the types of constituent sphingosines and fatty acids.⁹

Treatment with an organic solvent to reduce its intercellular lipids of the stratum corneum has been shown to result in dry skin and reduced barrier function.¹⁰ Additionally, a decrease in ceramide levels has been observed in the stratum corneum of patients with atopic dermatitis, and this decrease is considered to be a factor in the dry skin and decreased barrier function seen in atopic dermatitis.¹¹ To maintain and repair the skin barrier, it is important to reduce the aggravating factors. However, external supplementation of the lipid content, such as with ceramides, should be considered. Moisturizers that contain "blocking" ingredients such as petrolatum and lanolin prevent water loss by covering the surface of the skin.¹² Furthermore, the skin barrier function and water retention capacity of the stratum corneum are improved by moisturizers containing natural or synthetic ceramides.¹³

In this study, in an effort to understand the clinical applications of synthetic ceramide or ceramide-containing formulations, we reviewed both domestic and international literature to evaluate whether ceramide-containing formulations are beneficial for improving skin dryness and barrier function.

2 | METHODS

2.1 | Literature search

The PubMed, Cochrane Library, and Igaku Chuo Zasshi (Ichushi) databases were searched using keywords such as "ceramide," "skincare products," "barrier + hydration + moisture + skin", and "randomized trial." All database searches were conducted in February 2019.

2.2 | Literature selection

In the first round of screening, we examined the titles and abstracts of all retrieved papers (regardless of language) and selected studies concerned with the external application of ceramide-containing formulations to moisturize and improve the barrier function of human skin. Studies on the application of ceramide-containing formulations to the skin of non-human animals, p.o. administration of ceramides, mechanisms of ceramide lipid metabolism, or basic studies of designer drugs (e.g., for cancer therapies) were excluded. Furthermore, duplicate results (i.e., retrieval of the same paper from multiple databases) were excluded. In the second round of screening, the full texts of selected papers were read; letters and non-systematic reviews were excluded; and clinical or epidemiological studies that fit the evaluation objectives of this study were selected (Figure 1).

2.3 | Critical examination

In the first stage of the review process, we evaluated each research report. The evidence level of each study was ranked according to its

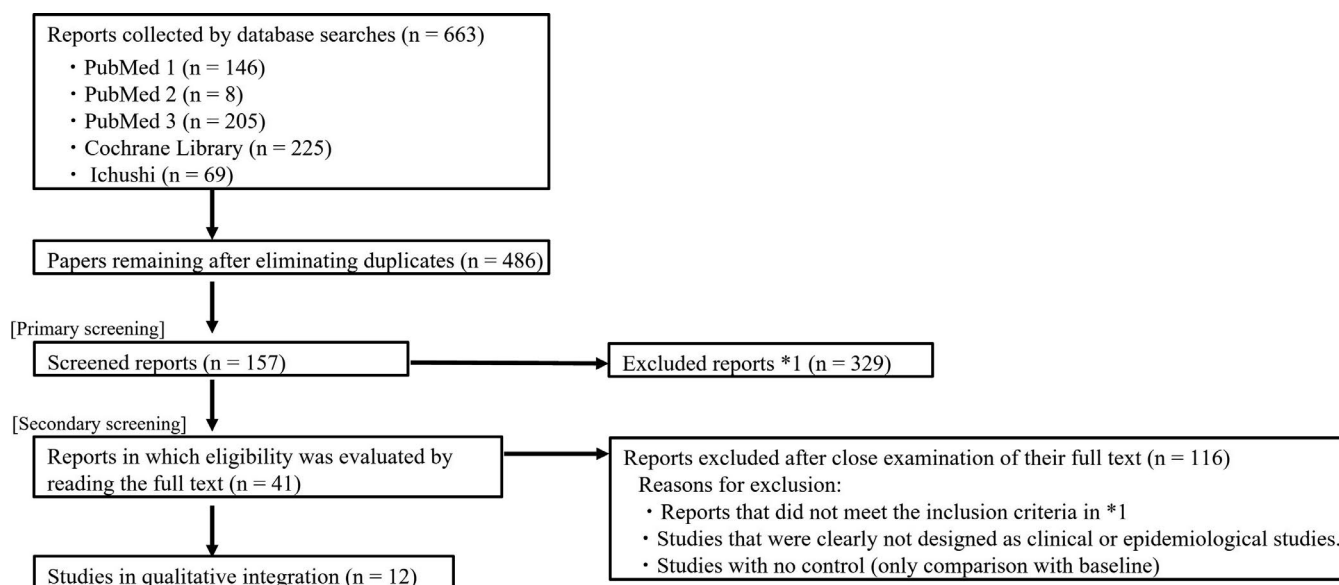


FIGURE 1 Literature search flowchart. Date from literature search. PubMed 1: 18 February 2019; PubMed 2: 18 February 2019; PubMed 3: 18 February 2019; Cochrane Library: 18 February 2019; Ichushi: 18 February 2019. *1 Reports not meeting the following inclusion criteria based on titles and abstracts were excluded: English-language or Japanese reports on skin care effects (improvement of skin conditions) using a ceramide-containing preparation. Exclusion criteria: research on drug development, including studies using non-human skin, oral administration (functional foods and medical products), lipid metabolism, and cancer treatment

TABLE 1 Forty-one reports obtained through the second round of screening

Ref. number	Authors	Year	Skin disease/condition	LOE
13	Spada <i>et al.</i>	2018	Normal skin/sensitive skin	2
17	Marseglia <i>et al.</i>	2014	Atopic dermatitis	2
18	Draelos	2011	Atopic dermatitis	2
19	Frankel <i>et al.</i>	2011	Atopic dermatitis	3
20	Sugarman <i>et al.</i>	2009	Atopic dermatitis	2
21	Miller <i>et al.</i>	2011	Atopic dermatitis	2
22	Draelos	2008	Eczema	2
23	Berardesca <i>et al.</i>	2001	Atopic dermatitis, irritation contact dermatitis, allergic contact dermatitis	2
24	Sugiura <i>et al.</i>	2006	Atopic dermatitis	3
25	Kircik	2014	Atopic dermatitis	3
26	Wananukul <i>et al.</i>	2013	Atopic dermatitis	2
27	Yamagishi <i>et al.</i>	2011	Atopic dermatitis	3
28	Hata <i>et al.</i>	2002	Atopic dermatitis	3
29	Mizutani <i>et al.</i>	2001	Atopic dermatitis	2
30	Koppes <i>et al.</i>	2016	Atopic dermatitis	2
31	Lee <i>et al.</i>	2003	Atopic dermatitis	2
32	Nakamura <i>et al.</i>	1999	Atopic dermatitis	3
33	Ma <i>et al.</i>	2017	Atopic dermatitis	2
34	Matsumoto <i>et al.</i>	2007	Atopic dermatitis	3
35	Weber <i>et al.</i>	2012	Sebum deficiency	2
36	Morganti <i>et al.</i>	1999	Mild dry skin	2
37	Daehnhardt <i>et al.</i>	2016	Sebum deficiency	2
38	Machado <i>et al.</i>	2007	Sebum deficiency	3
39	Nojiri <i>et al.</i>	2018	Sebum deficiency	2
40	Liu <i>et al.</i>	2015	Psoriasis	2
41	Kiyohara <i>et al.</i>	2014	Health-care workers (hand irritation caused by repeated hand washing)	2
42	Lodén <i>et al.</i>	2000	Healthy skin of healthy people or skin treated with tape stripping/sodium lauryl sulfate	2
43	Kucharekova <i>et al.</i>	2002	Healthy skin of healthy people or skin treated with tape stripping/sodium lauryl sulfate	3
44	Huang <i>et al.</i>	2008	Healthy skin treated with sodium lauryl sulfate	3
45	De Paepe <i>et al.</i>	2002	Healthy skin treated with sodium lauryl sulfate or acetone	2
46	De Paepe <i>et al.</i>	2000	Healthy skin treated with sodium lauryl sulfate	2
47	Shinohara <i>et al.</i>	2014	Hand-foot skin reaction (induced by sorafenib)	2
48	Tsuboi <i>et al.</i>	2006	Health-care workers (hand irritation caused by repeated hand washing)	3
49	Ishikawa <i>et al.</i>	2003	Pressure ulcers	3
50	Hao <i>et al.</i>	2015	Pressure ulcer	3
51	Cannizzaro <i>et al.</i>	2018	Irritated skin (side-effect of oral isotretinoin)	2
52	Okuda <i>et al.</i>	2002	Healthy skin of healthy people	3
53	Byun <i>et al.</i>	2012	Healthy people (skin damage due to UV exposure)	2
54	Sugita <i>et al.</i>	2009	Healthy women (age-related wrinkles on the outer corners of the eyes, nasolabial folds)	2
55	Berger <i>et al.</i>	2018	Ostomy skin (skin protectant)	4
56	Colwell <i>et al.</i>	2018	Ostomy skin (skin protectant)	2

Abbreviations: LOE, Oxford Centre for Evidence-Based Medicine level of evidence; UV, ultraviolet.

TABLE 2 PICO for reports selected via the second round of screening

Ref. no.	Research design	LOE	Patient (P)		Intervention (I)
			Target illness	Cases (sex, age)	
17	Open-label RCT (evaluator blinded)	2	Atopic dermatitis (mild-to-moderate)	107 cases (59 males/48 females, 5.9 years old) 1. Ceramide-containing cream: 72 cases (36 males/36 females), 6 ± 6 years old 2. Control cream: 35 cases (23 males/12 females), 5.8 ± 5 years old	Ceramide-containing cream Dosage: applied 2 times daily Period: 6 weeks
18	Double-blind RCT (body partitioned)	2	Atopic dermatitis (mild-to-moderate)	20 cases (20 females, ≥18 years old) 1. Ceramide-containing cream 2. Hyaluronic acid-containing emollient cream	Ceramide-containing cream Dosage: applied 2 times daily Period: 4 weeks (one of either the left or right leg or arm)
21	Open-label RCT (evaluator blinded)	2	Atopic dermatitis (mild-to-moderate)	39 cases (2–17 years old) 1. Ceramide-containing cream 2. Glycyrrhetic acid-containing cream 3. Moisturizer (commercial product)	Ceramide-containing cream Dosage: applied 3 times daily Period: 3 weeks
20	Open-label RCT	2	Atopic dermatitis (moderate-to-severe)	121 cases (48 males/73 females) 1. Ceramide-containing cream: 59 cases (22 males/37 females, 8.2 years old) 2. Fluticasone-containing cream: 62 cases (26 males/36 females, 7 years old)	Ceramide-containing cream Dosage: applied 3 times daily Period: 4 weeks
25	Double-blind RCT (body partitioned)	2	Atopic dermatitis (mild-to-moderate)	55 cases (27 males/28 females, 37.5 months old) 1. Ceramide-containing moisturizer 2. Hydrocortisone-containing moisturizer	Ceramide-containing moisturizer Dosage: applied 2 times daily Period: 8 weeks
30	Double-blind RCT (body partitioned)	2	Atopic dermatitis (mild-to-moderate)	95 cases (35 males/60 females, 21–51 years old) 1. Ceramide + Mg-containing cream hydrocortisone: 48 cases (16 males/32 females, 28.5 years old) 2. Ceramide + Mg-containing cream moisturizer: 47 cases (19 males/28 females, 25.0 years old)	Ceramide + Mg-containing cream Dosage: applied 2 times daily Period: 6 weeks (left or right side)
31	Open-label randomized cross-over trial	2	Atopic dermatitis	27 cases (16 males/11 females, 4.4 years old) 1. Ceramide-containing cream 2. Moisturizer (commercial product)	Ceramide-containing cream Dosage: applied 2 times daily Period: 4 weeks
33	Double-blind RCT	2	Atopic dermatitis (mild-to-moderate)	64 cases (27 males/37 females) 1. Ceramide-containing moisturizer + ceramide cleanser: 32 cases (13 males/19 females, 5.5 ± 2.9 years old) 2. Ceramide cleanser: 32 cases (14 male cases/18 female cases, 5.3 ± 2.4 years old)	Ceramide-containing moisturizer Dosage: applied 2 times daily Ceramide cleanser Dosage: applied 1 time daily Period: 12 weeks
36	Double-blind RCT	2	Sebum deficiency	40 cases (40 females, 23–35 years old) 1. Ceramide-containing cream 2. Placebo (base cream only)	Ceramide-containing cream Dosage: applied 2 times daily Period: 12 weeks

Comparator (C)	Outcome (O)		Species of ceramide or pseudo-ceramide
	Indices	Results	
Control cream Dosage: applied to affected area 2 times daily Period: 6 weeks	1. Eczema Severity Score (ESS) 2. Investigator General Assessment (IGA) 3. Tolerance score	ESS over the 6-week period was significantly lower in the group using ceramide-containing cream than in the control group. Both groups exhibited good tolerance.	Ceramide 3
Hyaluronic acid-containing emollient cream Dosage: applied 2 times daily Period: 4 weeks (one of either the left or right leg or arm)	1. Severity of eczema, erythema, scales, lichenification, abrasions, pruritus, stinging, burning sensation 2. Skin findings	Both groups showed significant improvement in all clinical signs and symptoms. However, hyaluronic acid foam significantly improved eczema severity by 2 weeks, while ceramide-containing cream did not.	Not mentioned
Glycyrhretinic acid-containing cream moisturizer (commercial product) Dosage: applied 3 times daily Period: 3 weeks	1. Investigator General Assessment (IGA) 2. Affected surface area (relative to BSA) 3. Investigator General Assessment of Improvement (IGAI) 4. Eczema index (EASI) 5. Itch severity (VAS)	No difference in efficacy was observed among the three groups. The moisturizer (commercial product) was cost-effective.	Synthetic ceramide
Fluticasone-containing cream Dosage: applied 2 times daily Period: 4 weeks	1. Severity (SCORAD) 2. Itching score 3. Sleep habits score 4. Patient/family evaluation score 5. IGA	There was no difference in the improvement in itching, sleep habits, and patient/family scores, but fluticasone-containing cream showed early improvement in SCORAD and IGA.	Not mentioned
Hydrocortisone-containing moisturizer Dosage: applied 2 times daily Period: 8 weeks	1. Severity (SCORAD) 2. Transepidermal water loss	The severity was similar with both agents, but the suppression of transepidermal water loss was superior with the ceramide-containing moisturizer.	Not mentioned
Hydrocortisone moisturizer Dosage: applied 2 times daily Period: 6 weeks (left or right side)	1. SCORAD 2. Transepidermal water loss, skin hydration, pH, and natural moisturizing factors	The ceramide-containing cream had the same degree of improvement as hydrocortisone and was significantly superior to the moisturizer. The ceramide-containing cream was superior to the hydrocortisone and moisturizer in improving skin hydration.	Ceramide 1, 3, 6II
Moisturizer (commercial product) Dosage: applied 2 times daily Period: 4 weeks	Efficacy (change in SCORAD score)	Both treatments resulted in improvements, but moisturizers showed better results than the ceramide-containing cream.	Pseudo-ceramide
Ceramide cleanser Dosage: applied 1 time daily Period: 12 weeks	1. Time since relapse 2. IGA 3. PRO	The moisturizer + cleanser therapy delayed the time to recurrence by ~2 months, and the recurrence rate after 12 weeks was low, resulting in high patient satisfaction.	Ceramide precursor
Placebo Dosage: applied 2 times daily Period: 12 weeks	1. Skin surface lipids 2. Stratum corneum water content 3. DAH score (degree of skin dryness)	The ceramide-containing cream maintained the skin structure and significantly improved both skin surface lipids and skin hydration.	Ceramide 6

(Continues)

TABLE 2 (Continued)

Ref. no.	Research design	LOE	Patient (P)		Intervention (I)
			Target illness	Cases (sex, age)	
37	Double-blind RCT	2	Sebum deficiency (xerosis)	12 cases (3 males/9 females, 32–58 years old) Ceramide-containing cream Placebo (base cream only)	Ceramide-containing cream Dosage: applied 2 times daily Period: 4 weeks
39	Double-blind RCT	2	Sebum deficiency (xerosis)	39 cases (39 females) 1. Ceramide-containing cream 2. Placebo (base cream only)	Ceramide-containing cream Dosage: applied at least 2 times daily Period: 4 weeks
47	Open-label RCT	2	Hand-foot skin reaction	33 cases (26 males/7 females) 1. Ceramide-containing hydrocolloid dressing: 17 cases (14 males/3 females, 65 ± 10 years old) 2. Urea-containing cream: 16 cases (12 males/4 females, 68 ± 7 years old)	Ceramide-containing dressing Dosage: changed every 2–3 days Period: 4 weeks

Note: The reports had an LOE ≥ 2 and evaluated the moisturizing/barrier function-improving effects of ceramide-containing formulations. Abbreviations: BSA, percent of body surface area of atopic dermatitis; EASI, Eczema Area and Severity Index; HFSR, hand-foot skin reaction; LOE, Oxford Centre for Evidence-Based Medicine level of evidence; PICO, patient, intervention, comparison, and outcome; PRO, patient-reported outcome; RCT, randomized controlled trial; SCORAD, Severity Scoring for Atopic Dermatitis; VAS, visual analog scale.

research design, and the content of each study was organized into the patient, intervention, comparison, and outcome (PICO) format.¹⁴ Furthermore, research designs were ranked according to existing evidence level systems (Oxford Centre for Evidence-Based Medicine 2011 levels of evidence, LOE): meta-analyses and systematic reviews were ranked as LOE 1; randomized controlled trials (RCT), LOE 2; non-RCT, LOE 3; cohort and case-control studies, LOE 4; and case collections, LOE 5.¹⁵

In the second stage of the review process, we used the grading of recommendations assessment, development, and evaluation (GRADE) system, which is on its way to becoming the global standard for evidence-based medicine evaluations.¹⁶ In cases where it was possible to integrate findings from multiple similar studies, we evaluated the overall evidence level of these studies after integration (as quantitative systematic reviews or meta-analyses).

3 | RESULTS

The results obtained from PubMed, Cochrane Library, and Ichushi are shown in Figure 1. A total of 663 reports were extracted. After eliminating duplicates across databases, 486 papers remained. After the first round of screening of these 486 papers, 157 remained. Finally, after the second round of screening, 41 papers were found to discuss the moisturizing and barrier improvement effects of the application of ceramide-containing formulations on human skin (Table 1).^{13,17–56} PICO and effect-index similarity analyses were performed for these 41 papers.

3.1 | Critical examination

To examine the possibility of conducting a quantitative meta-analysis, we attempted to compare studies with common subjects and interventions.

First, let us consider studies that evaluated ceramide-containing formulations in the context of atopic dermatitis. One report detailed a 28-day evaluation of young children with moderate-to-severe atopic dermatitis, in which the efficacy of ceramide-containing formulations was equivalent to that of topical steroids (control group).²⁰ Another report detailing a 21-day evaluation of the same formulation in young children with mild-to-moderate atopic dermatitis found no significant difference in the efficacy between the ceramide-containing formulation and a petrolatum; however, the petroleum was more cost-effective.²¹ We believe that the difference in the severity of atopic dermatitis of targeted patients, their age, and trial period are all reasons for the same product receiving different evaluations in these two reports. However, even if ceramide-containing formulations did not perform significantly differently from petroleum when skin symptoms were comparatively mild, ceramide-containing formulations exhibited the same effect as topical steroids when symptoms were more severe. This suggests that in addition to their moisturizing and barrier function-improving effects, ceramide-containing formulations possess anti-inflammatory properties.

In other similar studies, even when the same ceramide-containing formulations were used, differences in skin condition (patient, P), trial duration (intervention, I), and comparison product (comparison, C) led to a variety of observed effects (outcome, O). Thus, we determined that it would be difficult to implement our planned second-stage critical examination, the quantitative meta-analysis recommended by

Comparator (C)	Outcome (O)		Species of ceramide or pseudo-ceramide
	Indices	Results	
Placebo Dosage: applied 2 times daily Period: 4 weeks	1. Transepidermal water loss 2. Stratum corneum water content 3. Skin structure, morphology 4. Skin lipids	Reconstitution of stratum corneum lipids was seen.	Ceramide 3
Placebo Dosage: applied at least 2 times daily Period: 4 weeks	1. Skin thickness 2. Skin reaction trial 3. Transepidermal water loss 4. Stratum corneum ceramide content	Skin irritation improved quickly with ceramide-containing cream, accompanied by a significant increase in keratin ceramide levels.	Pseudo-ceramide
Urea-containing cream Dosage: apply 2–3 times a day Period: 4 weeks	Percentage of patients with HFSR worsening from grade 1 to grade 2/3 over a period of time	The ceramide-containing dressing suppressed worsening on the sole of the foot, but there was no difference in the symptoms on both arms.	Not mentioned

the GRADE system. Therefore, we returned to the first stage of our critical evaluation process and decided to limit ourselves to collecting target papers, selecting papers with representative evidence, and conducting a qualitative meta-analysis. Our selection criteria were as follows: (i) controlled studies (LOE ≥ 2 as categorized by the aforementioned research design-based system); and (ii) studies that used statistical methodologies to investigate the moisturizing and/or barrier function-improving effects of ceramide-containing formulations.

3.2 | Qualitative meta-analysis

From among the 41 reports discussing the moisturizing and barrier function-improving effects of ceramide-containing formulations, we searched for comparative RCT (which have a high LOE) that targeted patients with skin barrier function disorders. After excluding studies that used skin irritation models in healthy individuals, we found 12 reports that targeted skin illnesses. The breakdown of these studies is as follows: atopic dermatitis, eight reports; xerosis, three reports; and hand-foot skin reaction, one report.

An overview of these 12 papers, which we used to evaluate the effects of ceramide-containing formulations, is given in Table 2^{17,18,20,21,25,30,31,33,36,37,39,47} Most studies on atopic dermatitis targeted mild-to-moderate illness, and ceramide-containing formulations were shown to improve skin function, such as by improving water content and inhibiting transepidermal water loss. Outlines of several representative examples from these reports are provided below.

Marseglia *et al.*¹⁷ targeted patients with mild-to-moderate atopic dermatitis. They compared 72 cases in which a ceramide-containing cream was used (mean age, 6 years) with 35 cases in which a cream base was used (mean age, 5.8 years). They observed an obvious

improvement in symptoms among patients who used the ceramide-containing cream and concluded that the cream was effective for treating mild-to-moderate atopic dermatitis.

Sugarman *et al.*²⁰ targeted patients with moderate-to-severe atopic dermatitis. They compared 59 cases in which a ceramide-containing cream was used (mean age, 8.2 years) with 62 cases in which topical steroids (fluticasone cream) were used (mean age, 7.0 years). Both treatments improved the severity Scoring for Atopic Dermatitis (SCORAD) and pruritus as well as sleep scores, and the degree of improvement was equivalent.

Wanankul *et al.*²⁶ compared ceramide-containing formulations with topical hydrocortisone in 55 patients with atopic dermatitis (age, 3 months to 14 years). Both formulations were applied to all patients, one on lesions on the right side of the body and the other on lesions on the left side. They found that while symptom improvement was equivalent, ceramide-containing formulations exhibited a superior moisturizing effect.

The effectiveness of ceramide-containing formulations has also been demonstrated in xerosis. The three reports we selected^{35–37} were all comparisons of ceramide-containing creams with cream bases. In these studies, ceramide-containing creams increased the lipid content of the stratum corneum and had a moisturizing effect.

Although only one report was found, the effectiveness of ceramide-containing formulations in hand-foot syndrome caused by molecular target drugs in cancer patients has also been shown.⁴⁷

4 | DISCUSSION

Treatment of the stratum corneum with a chemical solvent to remove intercellular lipids of the stratum corneum, including

ceramides, reduces stratum corneum water content and increases transepidermal water loss; in other words, it reduces skin barrier function.¹⁰ The decrease in ceramide levels with age⁵⁷ causes dryness and wrinkles of the skin⁵⁸ and also leads to a decrease in barrier recovery ability.⁵⁹ Furthermore, a decrease in lipid content, including ceramides, in the stratum corneum has been reported in psoriasis and xerosis.^{60,61} Finally, changes in the ratio of stratum corneum ceramide subtypes have been observed in atopic dermatitis, which is known to cause dry skin and decreased barrier function.⁶² From the above, it has been concluded that ceramides are a central component of the intercellular lipid matrix and that they play a critical role in moisturizing the skin and maintaining barrier function.^{63,64}

Basic research on various functions of ceramides is also ongoing. Recently, the production pathway of acylceramides, the most important ceramide for skin barrier formation, has been elucidated,⁶⁵ and the abnormal production of acylceramides is found to be the cause of ichthyosis. However, systematic review of the literature has not been conducted from clinical viewpoints. Thus, this review collected papers with an LOE of 2 or more that discuss the clinical effects of ceramide-containing formulations on skin moisture and barrier function. After a two-round screening process, we narrowed down our selection to 41 papers that reported on RCT and used statistical methods. From among these, we extracted 12 reports using the PICO method.

In comparisons of ceramide-containing formulations with control moisturizers or placebo formulations, ceramide-containing formulations exhibited equivalent or better efficacy than comparison products in all studies. Many of these studies evaluated results using severity scores and/or improvement scores, and while the standards for these metrics were established prior to the study, in some cases, evaluations of transepidermal water loss, stratum corneum structure, and stratum corneum morphology were added to increase objectivity.^{26,30,39} In these reports, ceramide-containing formulations were shown to reduce transepidermal water loss, improve stratum corneum structure, and/or increase stratum corneum lipid content; thus, these reports detail the efficacy of ceramide-containing formulations. Further, clinical research indicates that, in elderly individuals, topical use of ceramide-containing formulations of sufficiently high concentration improved hydration and the barrier function of the stratum corneum.⁶⁶ Meanwhile, in artificial dry skin, topical use of ceramide-containing formulations increased stratum corneum water content.¹¹ It is not clearly described which ceramides are used in all studies (Table 2). In the future, it will be important to investigate the efficacy of different types of ceramides.

This review clearly indicates that there is clinical significance in the topical use of ceramide-containing formulations in dermatological disorders such as atopic dermatitis. No clinical study indicated any adverse events of note. As far as our qualitative evaluation is concerned, we believe that ceramide-containing formulations exhibit a certain level of efficacy in improving dry skin and skin barrier function. In the future, double-blind comparative trials of

ceramide-containing formulations that incorporate a large number of cases are necessary to determine the illnesses and the severity to which the application of ceramides to the skin surface is clinically useful.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None declared.

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How to cite this article: Kono T, Miyachi Y, Kawashima M. Clinical significance of the water retention and barrier function-improving capabilities of ceramide-containing formulations: A qualitative review. *J Dermatol*. 2021;48: 1807–1816. <https://doi.org/10.1111/1346-8138.16175>