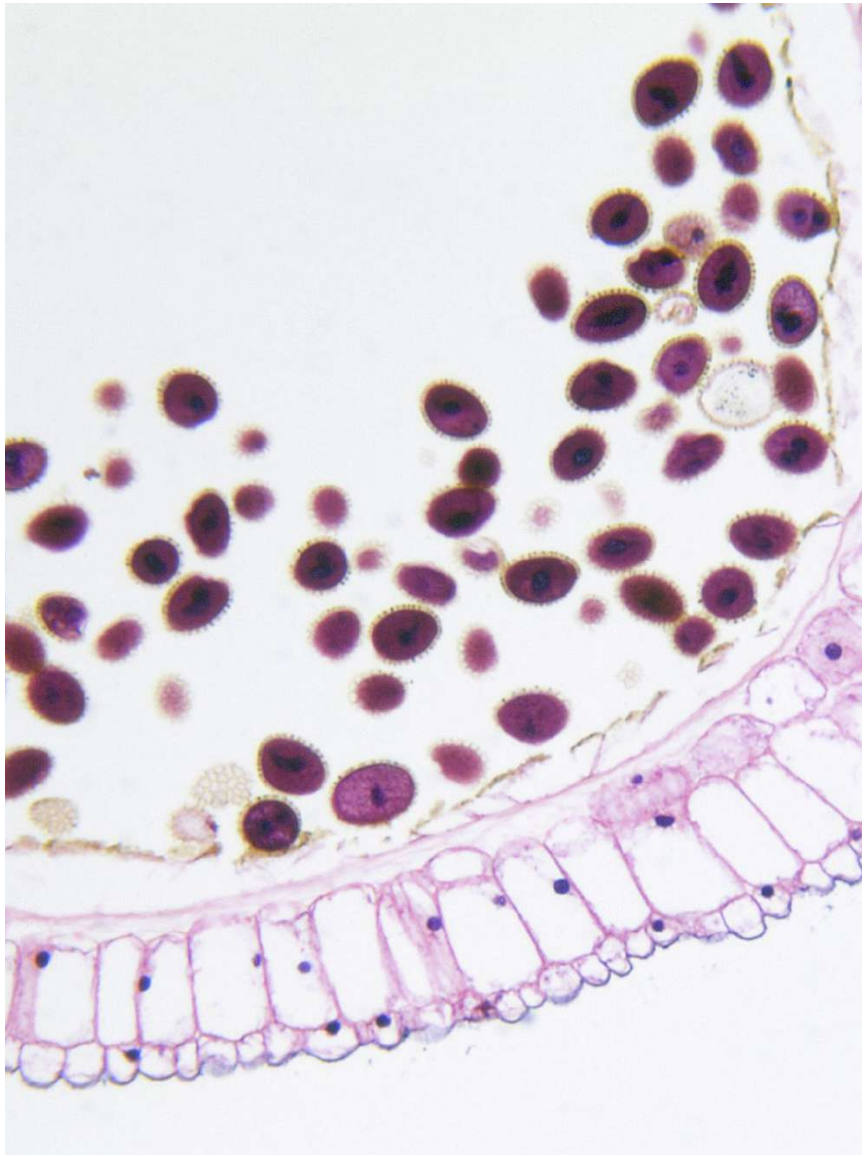
The Role of Ceramides in Skin Barrier Integrity: What you need to know

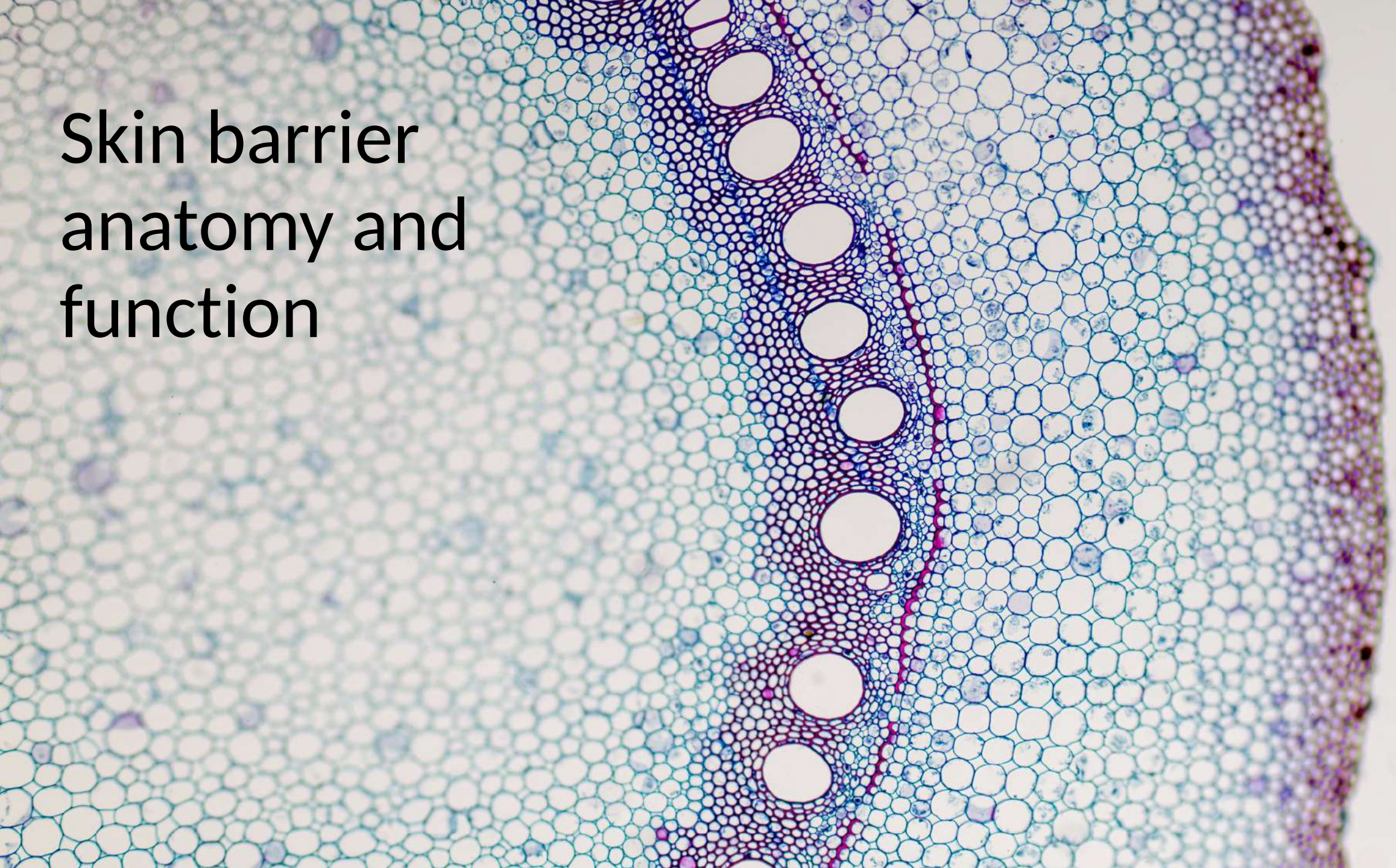
Speaker Deck



Skin barrier function and dysfunction: Outline

- Skin barrier anatomy and function
- Imbalance of skin lipids and elevated skin surface pH
- Skin barrier dysfunction in atopic dermatitis affected skin
- Skin barrier dysfunction in acne affected skin
- Skincare for maintaining a functional skin barrier

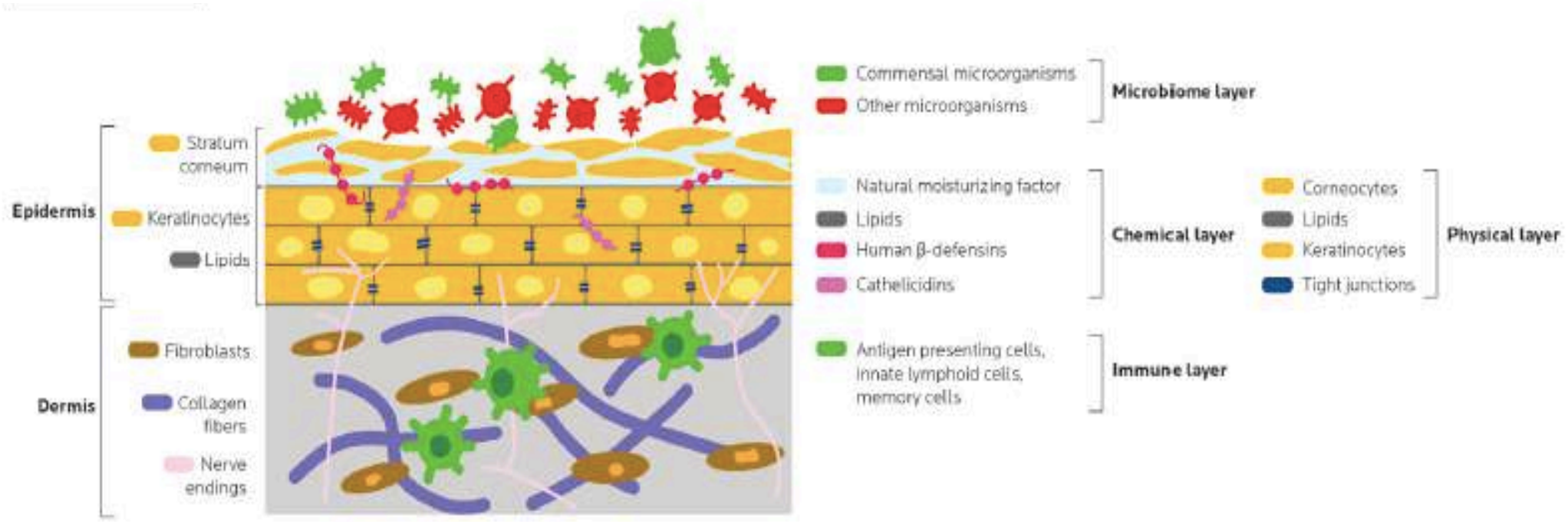
Skin barrier anatomy and function



Skin barrier anatomical and functional layers

Skin anatomical layers

Skin functional layers



Strugar TL, Kuo A, et al. J Drugs Dermatol 2019;18(6):581.

The stratum corneum is essential for the protective barrier functions of the skin

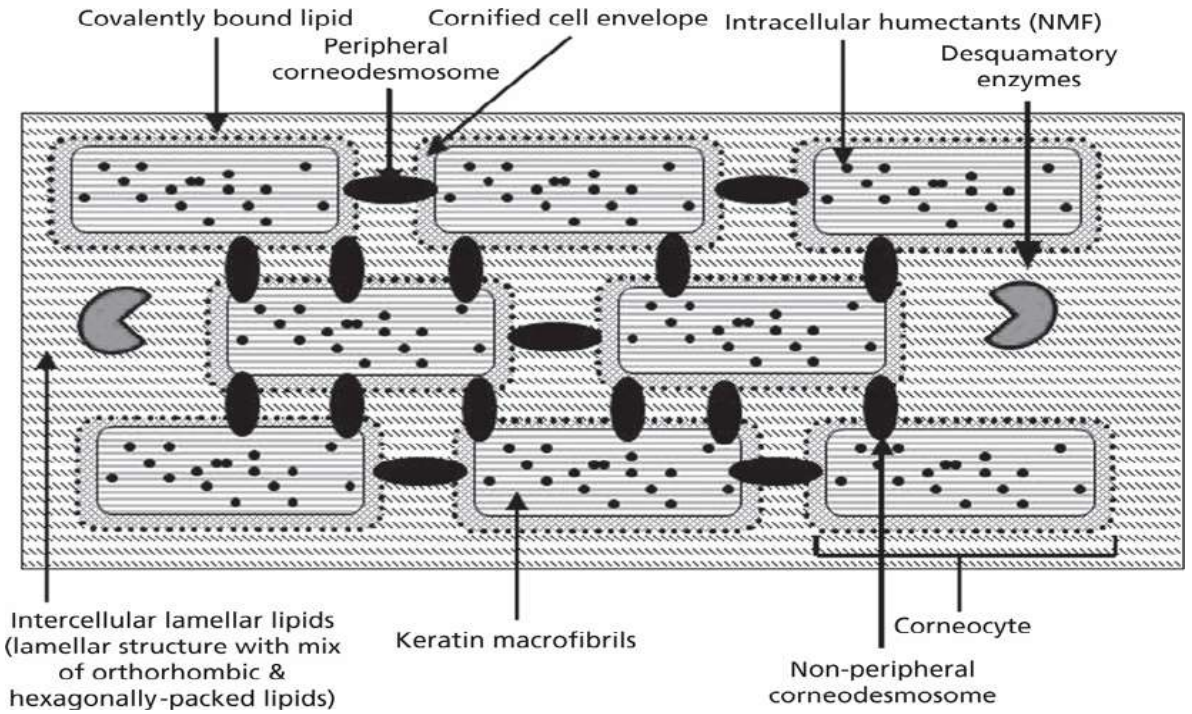
- Corneocytes are the building blocks of the epidermal barrier.
- A water-resistant layer of lipid lamellae encases the corneocytes (cornified lipid envelope), preventing water loss and controlling barrier permeability.
- The cornified lipid envelope and the extracellular mortar-like multilayered lipid lamellae are crucial elements of the epidermal barrier.

Stratum corneum (SC)

Moore JM, Rawlings AV. Int *J Cosmetic Sci*. 2017;39(4):366-372. doi:10.1111/ics.12399.
Skolova B, et al. Biochim Biophys Acta. 2016;1858(2):220-32.

Corneodesmosomes

- Cornedodesmosomes are modified desmosomes that provide tensile strength to skin barrier
- Think of them as “masonry tiles that act like molecular rivets in bricks in a three-dimensional space
- Free fatty acids **form lamellar liquid crystals at pH values of 4.5–6** through partial ionization.

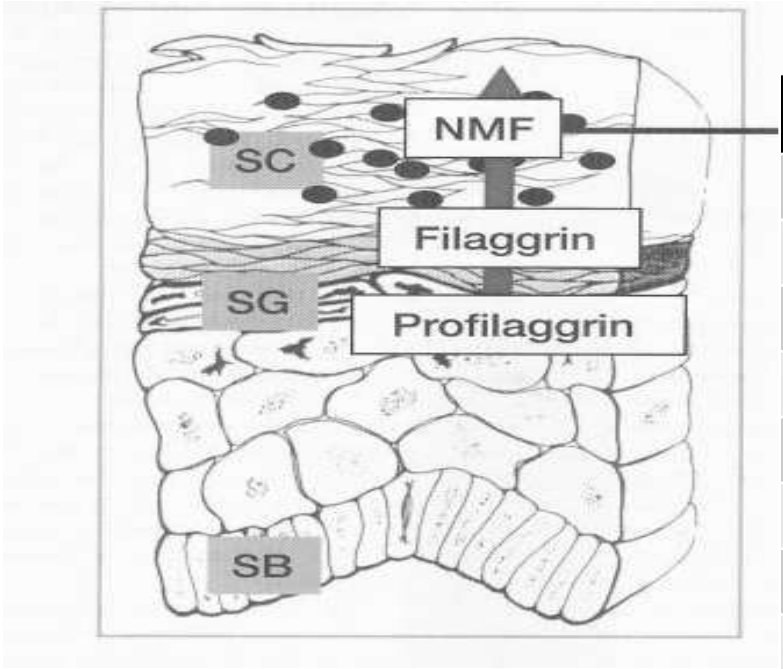


Ali SM, Yosipovitch G. Acta Derm Venereol 2013; 93: 261–267.

Key components of the epidermis

Conversion of profilaggrin to filaggrin and natural moisturizing factor (NMF)

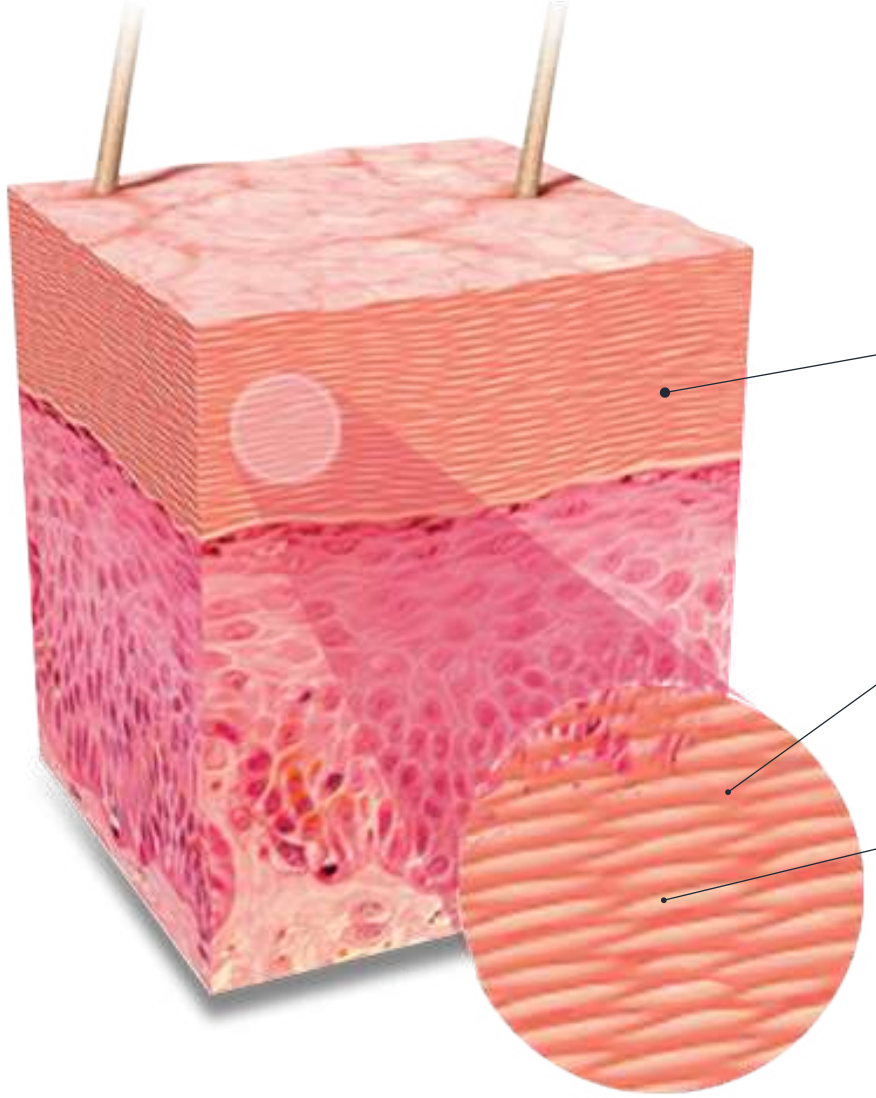
SC = stratum corneum
SG = stratum granulosum
SB = stratum basale



Major NMF Components	% of total
Free amino acids	40
Pyrroidone carboxylic acid	12
Lactate	12
Sugars, organic acids, peptides	9
Urea	7
Chloride	6
Sodium/potassium	9
Others	5

Garidel P, et al. Biophys Chem. 2010;150:144-156.

Stratum corneum: Physical layer



Stratum Corneum

Corneocytes (brick)

Intercellular Lipids

Lipid Bilayer (mortar)

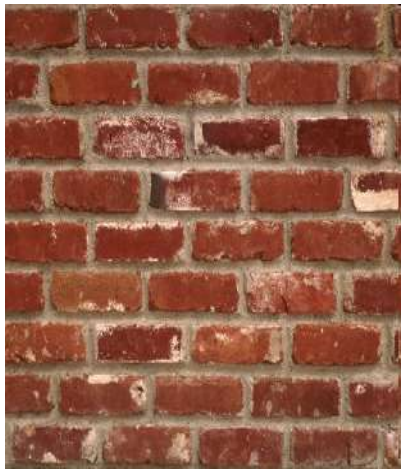
Stratum corneum: Physical layer, cont.

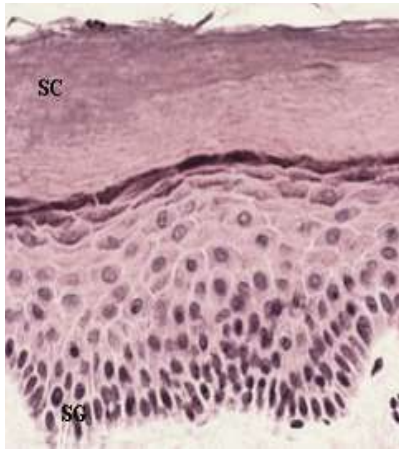
The “brick and wall” analogy has been used to explain the complex stratum corneum

J Phar Pharmacol. 2010;62(6):671-677, DOI: (10.1211/jpp.62.06.0002)

Structure of the stratum corneum

Acqueous	Hydrophobic	Acqueous	Stratum corneum
Hydrophobic membranes	Hydrophillic	Hydrophobic membranes	Nucleated layers



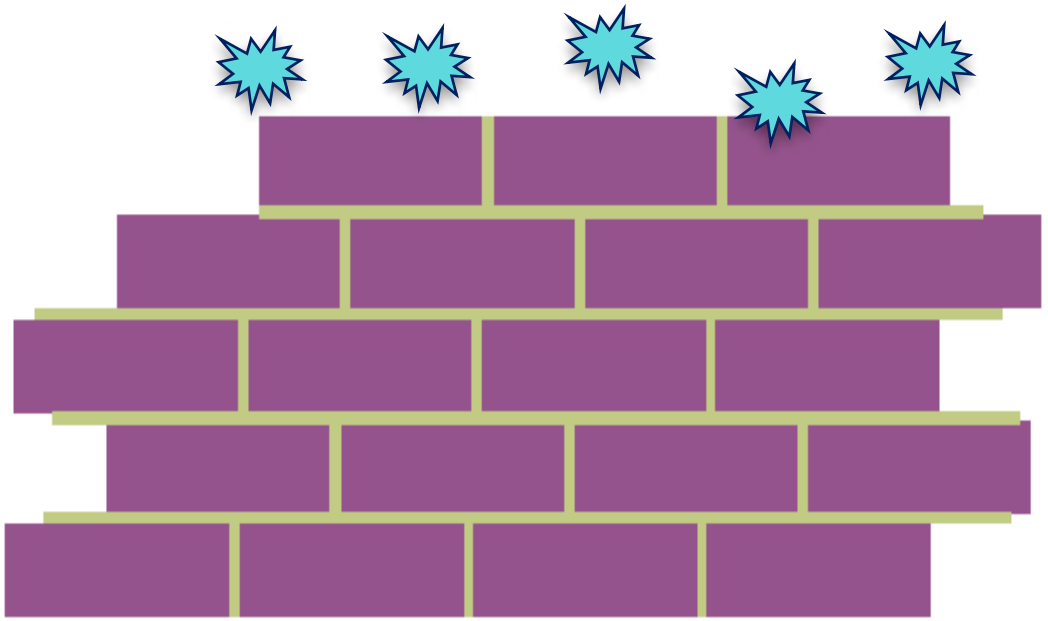


Bricks = anucleate corneocytes
Filled with keratin filaments
Surrounded by highly cross- linked protein cell envelope
Mortar = intercellular matrix

Adapted from L Kircik with kind permission

Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Normal skin barrier



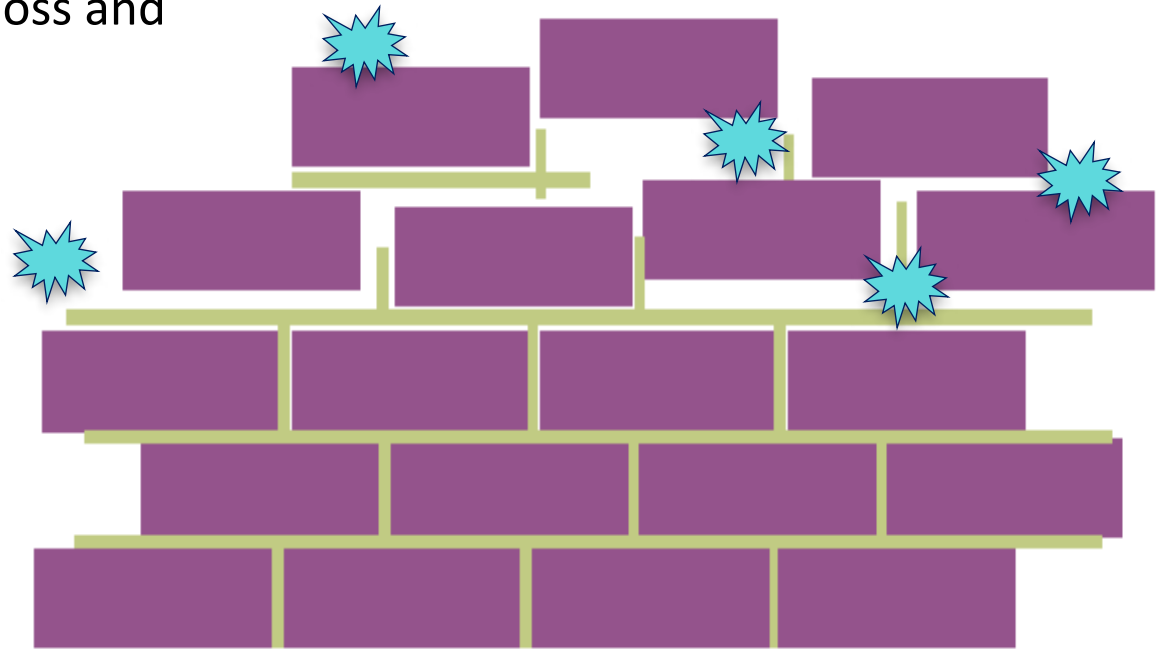
Normal skin barrier is like a perfectly layered bricks on a wall,
Keeping the outside allergens away with its barrier

Adapted from L Kircik with kind permission

Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Skin barrier dysfunction

The skin barrier is open to water loss and invasion of irritants and allergens leading to inflammation



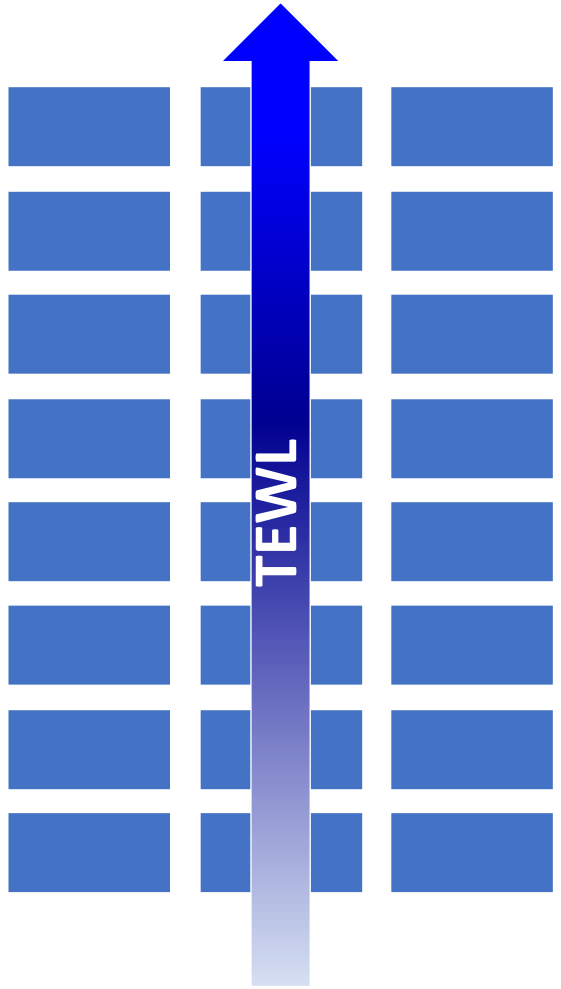
Adapted from L Kircik with kind permission

Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Resilient normal skin barrier

Healthy skin barrier:

1. Swelled corneocytes retain moisture
2. Lipid bilayers prevent water loss between the corneocytes



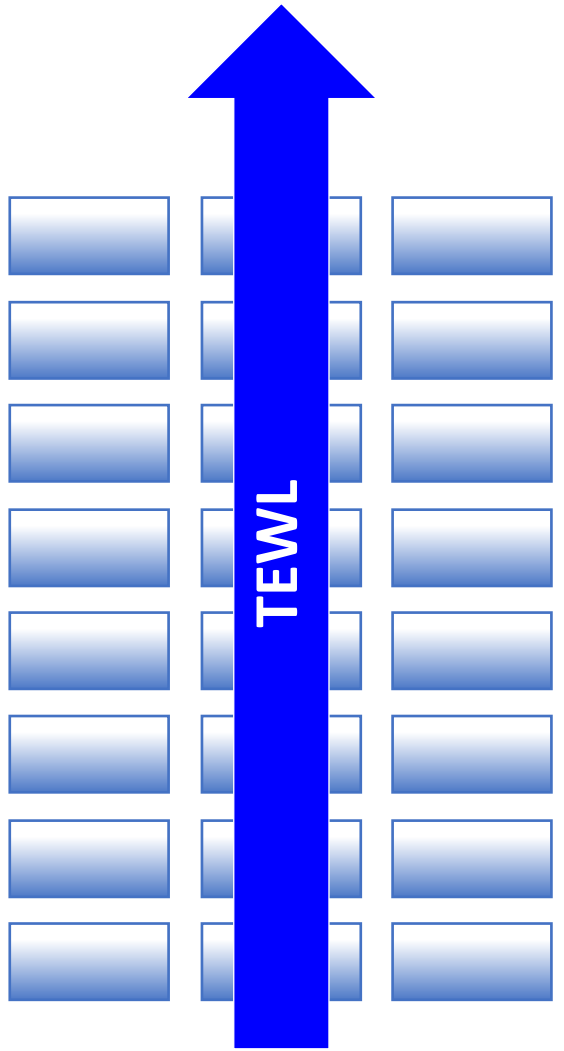
Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Adapted from: Danby SG and Cork MJ; Sheffield Dermatology Research; The University of Sheffield

Breakdown of the skin barrier

Defective Barrier leading to dry skin:

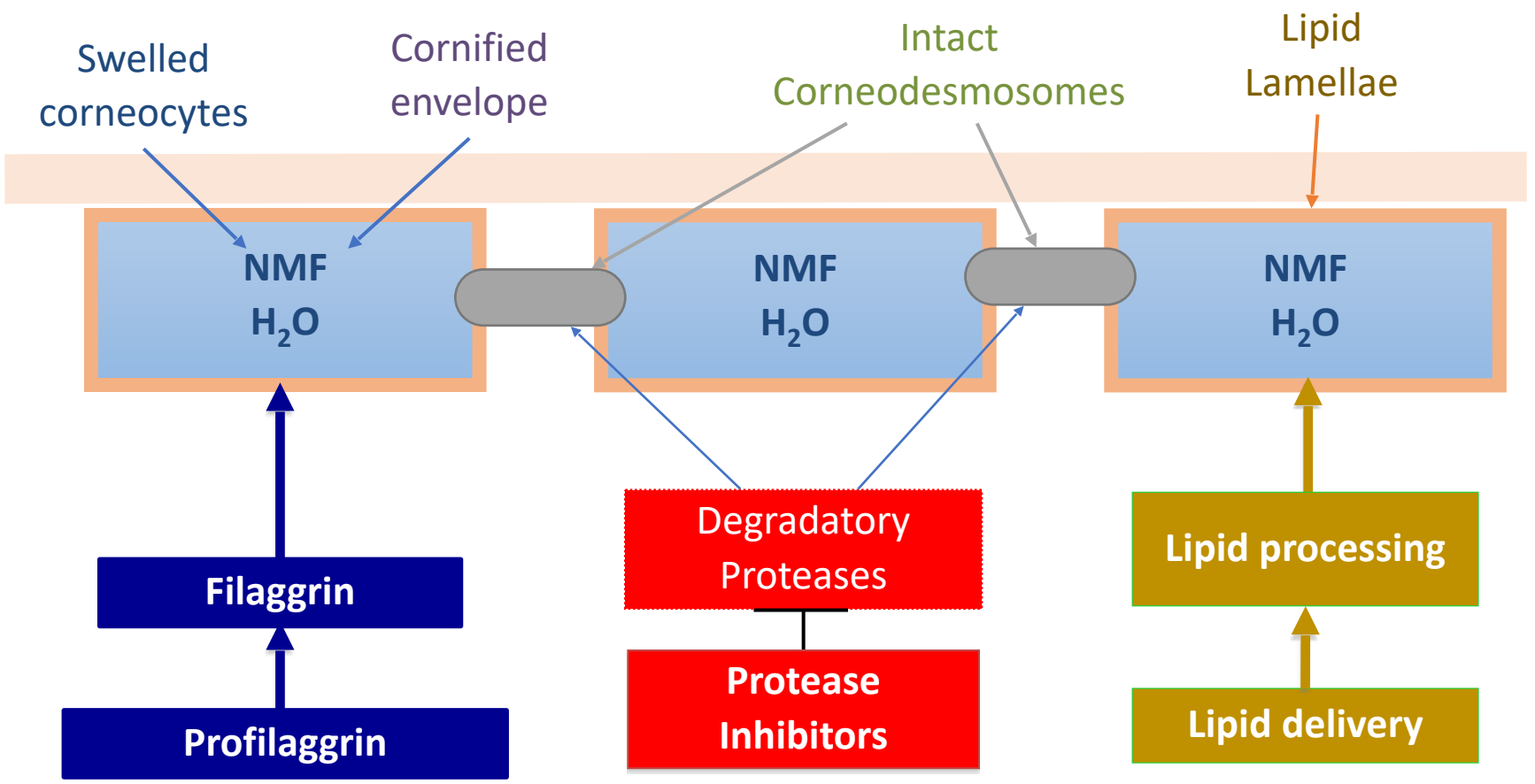
1. Loss of NMF leads to dry skin and the development of cracks
2. An abnormal lipid bilayer provides an inadequate permeability barrier



Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Adapted from: Danby SG and Cork MJ; Sheffield Dermatology Research; The University of Sheffield

A healthy skin barrier: Summary

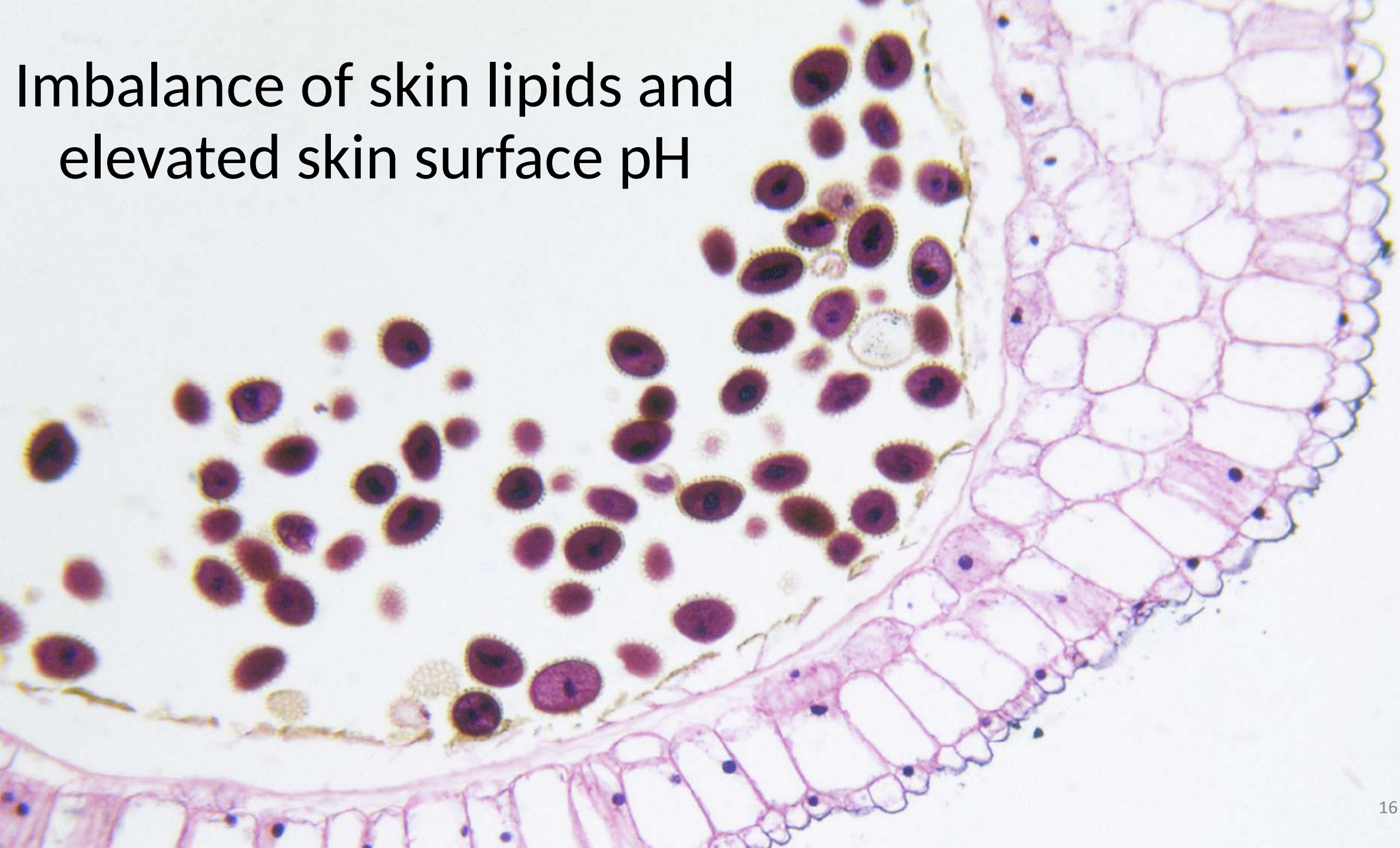


- Corneocytes are filled with natural moisturising factor (NMF)
- The constituents of NMF are derived from profilaggrin
- NMF is important for maintaining an acid environment
- To balance the introduction of new cells, mature corneocytes are shed (desquamation).

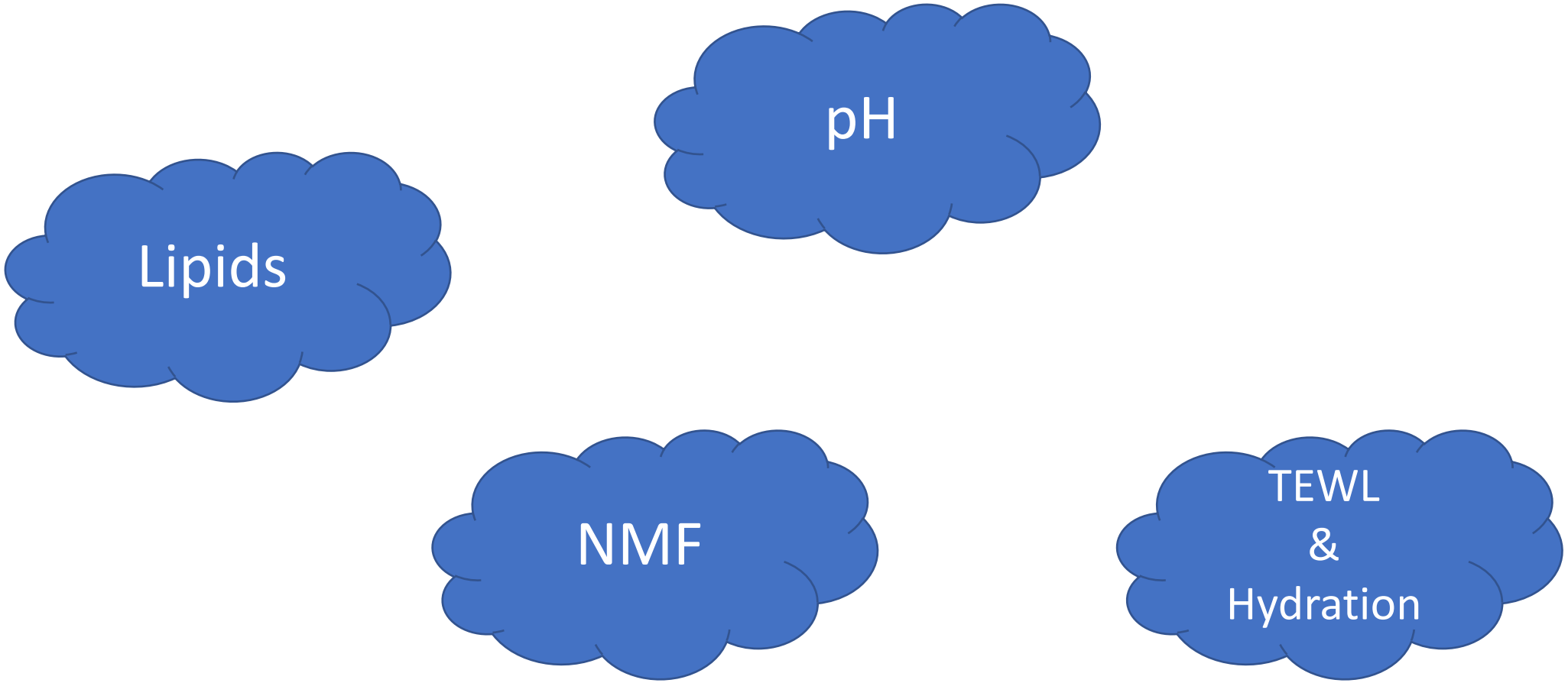
Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Adapted from: Danby SG and Cork MJ; Sheffield Dermatology Research; The University of Sheffield

Imbalance of skin lipids and elevated skin surface pH



Mechanisms influencing skin barrier disruption

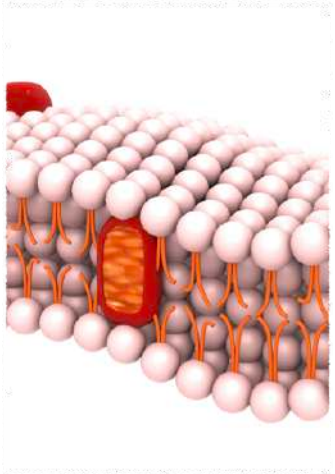


Transepidermal water loss (TEWL); Natural moisturizing factors (NMF)

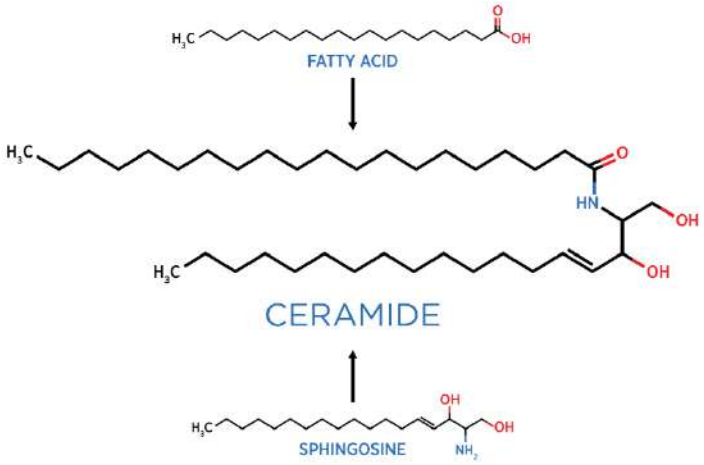
Schachner LA et al. J Drugs Dermatol.2020;(8):769-776. .

Stratum corneum extracellular lipids

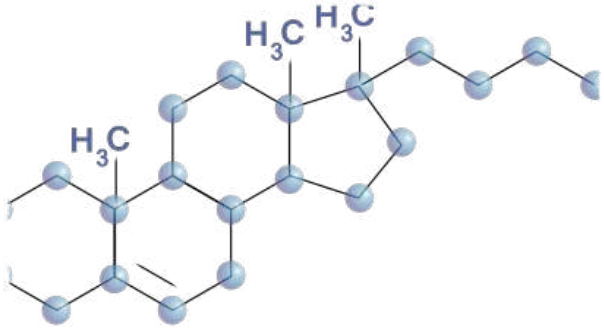
- The SC extracellular lipids are mainly composed of ceramides, cholesterol, and free fatty acids.
- NMFs, derived from pro-filaggrin, help maintain skin hydration.
- Ceramides have an essential role in maintaining the water permeability barrier function of the skin.



Free Fatty Acids



Ceramides



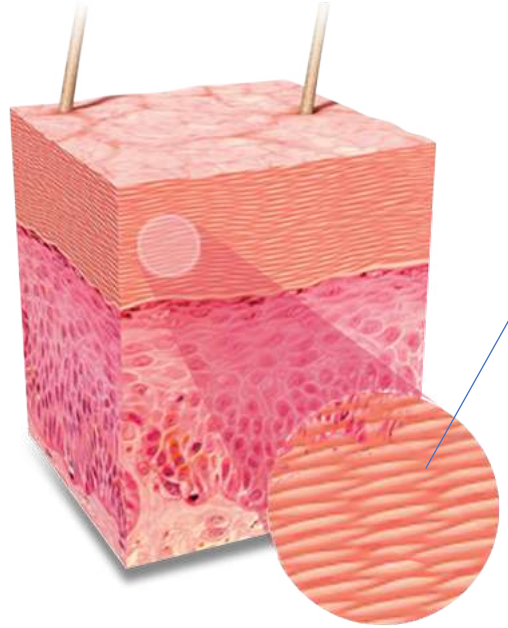
Cholesterol

Moore JM, Rawlings AV. Int *J Cosmetic Sci*. 2017;39(4):366-372. doi:10.1111/ics.12399.
Skolova B, et al. Biochim Biophys Acta. 2016;1858(2):220-32.

Stratum corneum (SC); Natural moisturizing factors (NMFs)

Ceramides are essential for skin barrier function: Composition of lipids of the stratum corneum

- Ceramides are the major type of lipid found in the stratum corneum
- The ratio of free fatty acids/cholesterol/ ceramides is not static.
- The ceramide proportion of the stratum corneum ranges from 40 - 50%.



Lipids of the Stratum Corneum
20 – 33% cholesterol
10 - 33% free fatty acids
40 - 50% ceramides

Rawlings AV. Br J Dermatol. 2014;171 (Suppl 3):19-28

What happens when ceramide levels are lower?

- Without the proper ratio of ceramides, the stratum corneum can become incompetent.
- Impaired synthesis of cholesterol, ceramides, and fatty acid adversely affects lamellar layer formation, thereby impairing barrier homeostasis, leading to dryness, irritation, erythema, and itching.
- Most skin barrier disorders are characterized by a decreased ceramide content.

Moore JM, Rawlings AV. Int *J Cosmetic Sci*. 2017;39(4):366-372. doi:10.1111/ics.12399.
Lowe AJ, et al. *Ann Allergy Asthma Immunol.* 2018;120(2):145-151.
Sahle FFT, et al. *Skin Pharmacol. Physiol.* 2015;28:42–55.

Ceramide levels are significantly reduced in patients with skin conditions[1]

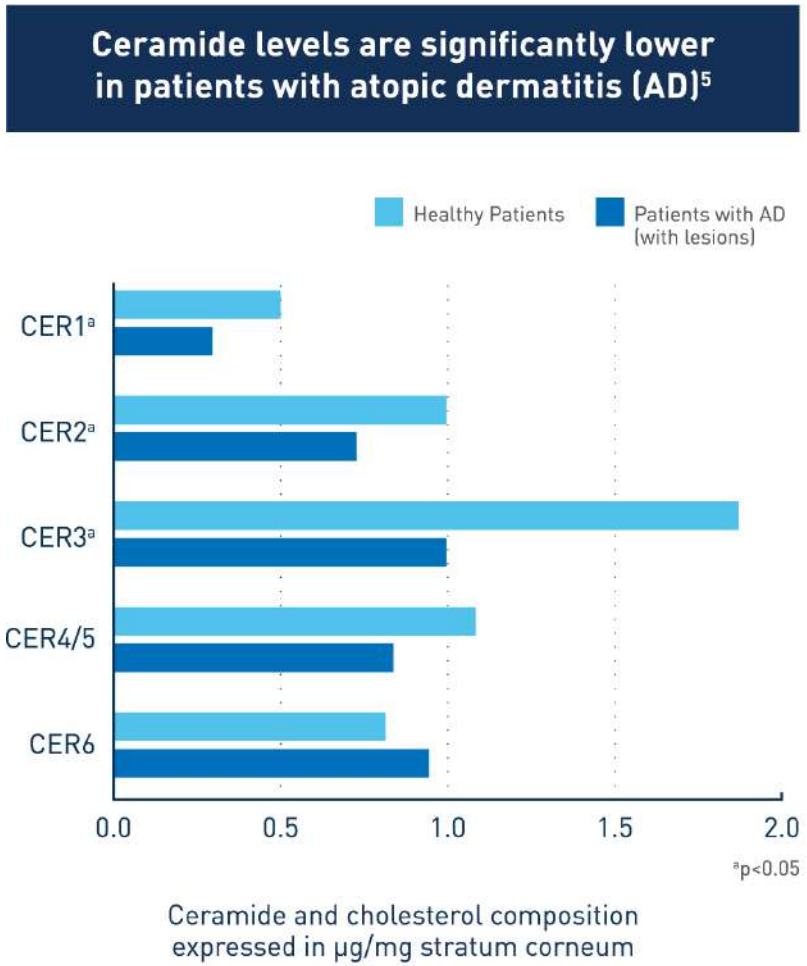
- TEWL is significantly higher in patients with
  - AD[1], Acne[2], Psoriasis[1], and Eczema[1]

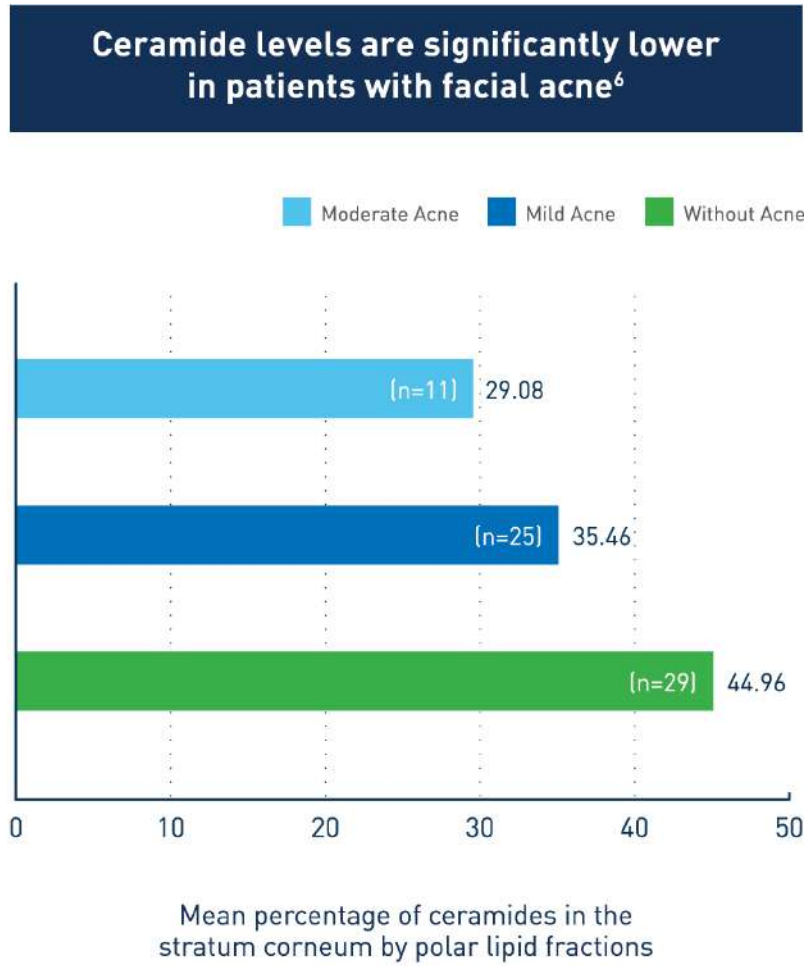
Disease	Decrease of Ceramides
Psoriasis[4]	Ceramides 1, 3, 6 ↓
Ichthyosis[5]	Ceramides 1, 6 ↓
Acne (Vulgaris)[6]	Linoleate in Ceramide 1 ↓
Atopic Dermatitis[3]	Ceramides 3, 6 ↓
Surfactant-induced Dermatitis[7]	Ceramide 1 ↓

CER EOP = Ceramide 1
CER NP = Ceramide 3
CER AP = Ceramide 6-II

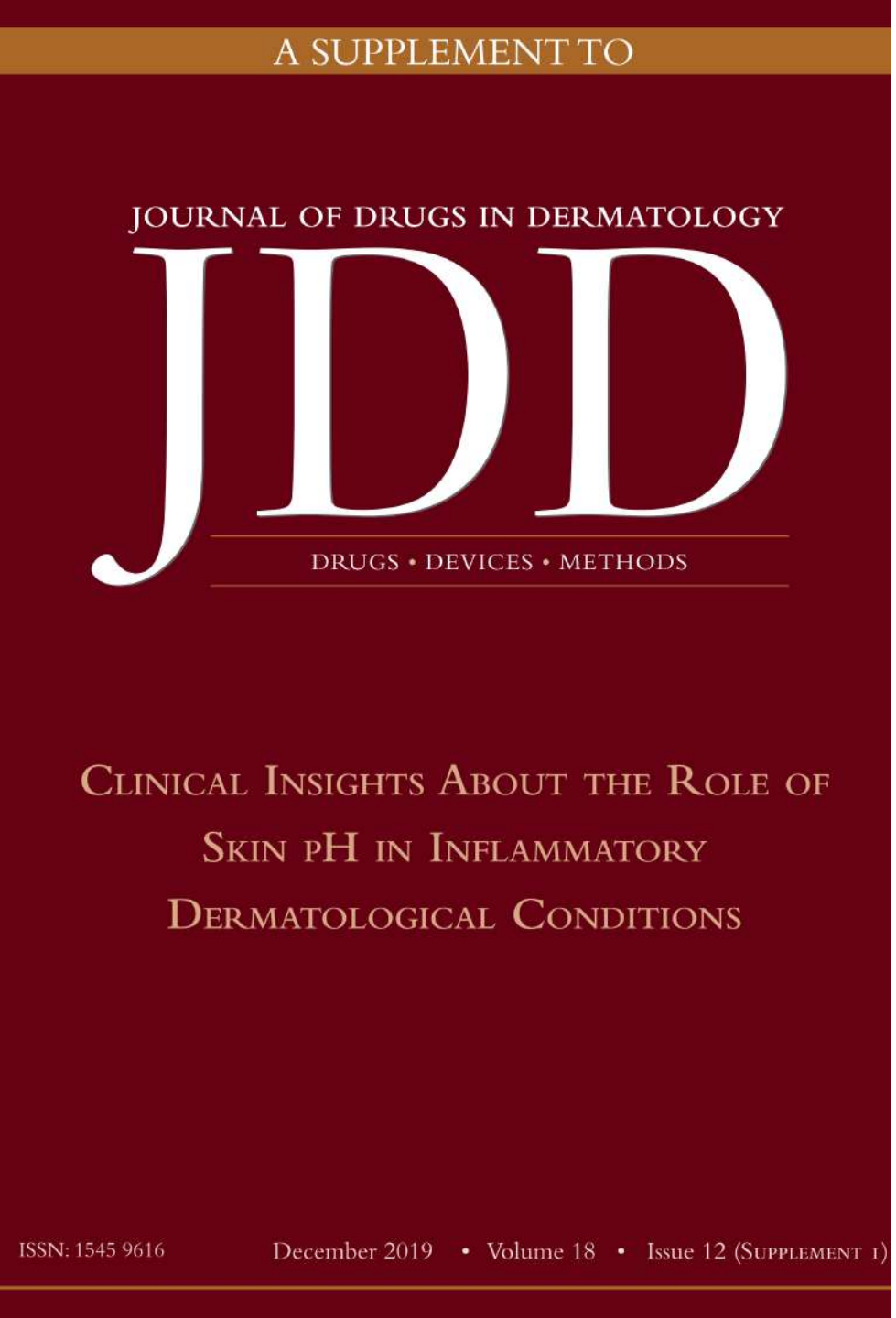
1. Choi MJ, Maibach HI. A*m J Clin Dermatol*. 2005;6(4):215-223.
2. Yamamoto A., et al. *Arch Dermatol Res*. 1995;287:214-218
3. Di Nardo A. et. al., Acta Derm Venereol. 1998;78:27-30.
4. Motta S. et al., Arch. Dermatol. 130, 452-456. 1994
5. Paige DG. et al., Proc. Br. J Dermatol. 131, 23-7. 1994
6. Yamamoto A., et al. *Arch Dermatol Res*. 1995;287:214-218
7. Di Nardo A. et. al., Contact Dermatitis 35, 86-91. 1996

Ceramide levels are significantly reduced in patients with skin conditions, cont.





5. Paige DG et al. *Proc. Br. J Dermatol*. 131, 23-7. 1994.
6. Yamamoto A et al. *Arch Dermatol Res*. 1995;287:214-218



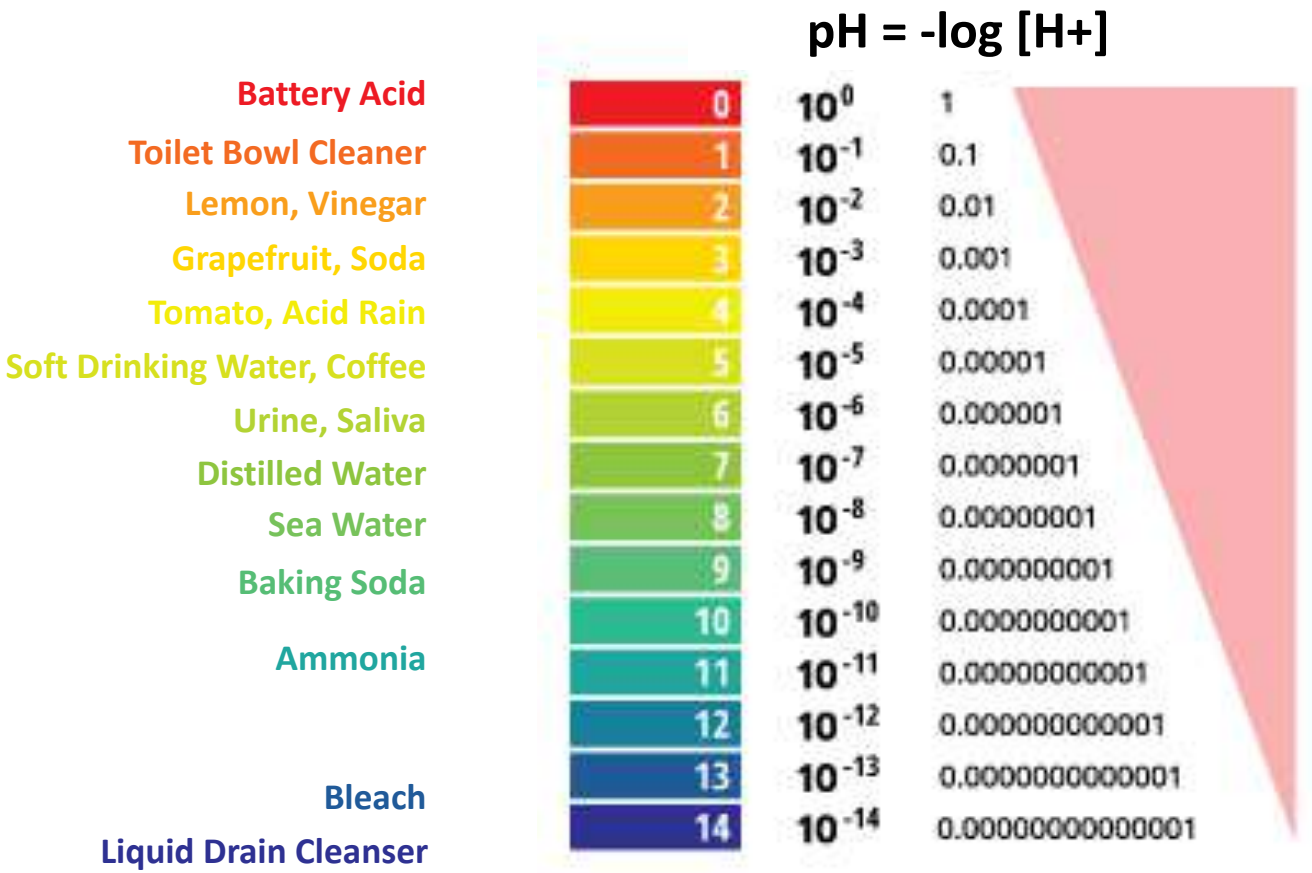
Skin pH in inflammatory dermatological conditions

- Consensus panels of experts in atopic dermatitis and in acne agree that cleansers and moisturizers close to physiologic skin surface pH (4.0–6.0) may support
  - Skin barrier repair,
  - Decreased inflammation
  - Accelerated pH recovery
  - Increased antimicrobial defense
- Despite the importance of maintaining a healthy skin pH, many cleansers and moisturizers have a high pH
  - Not disclosed on the label M
  - May further damage the fragile skin barrier in diseased skin

Lynde CW, Tan J, Skotnicki S, Andriessen A, et al. J Drugs Dermatol 2019;18(12) S-1:1-16.

What is pH?

- pH = the hydrogen ion (H^+) concentration of a solution.
- The pH is equal to minus the log of the H^+ concentration

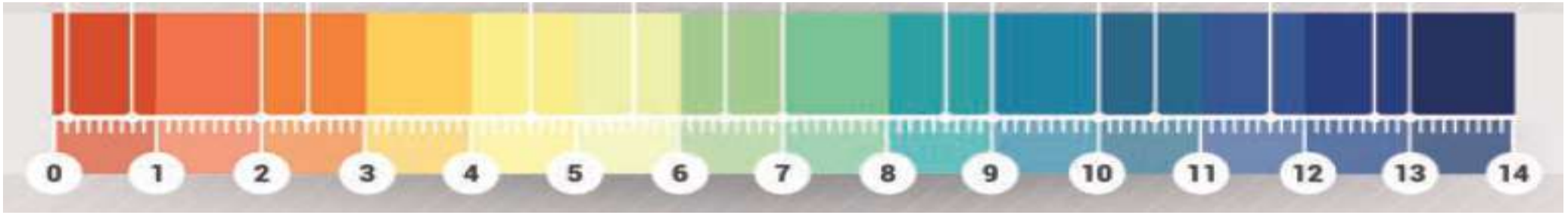


Raphael KL, et al. Clin J Am Soc Nephrol.2016 Jan 14. pii:CJN.06200615.

What is skin surface pH?

Normal or physiological

Skin surface pH[1]



High acidic

Neutral

High basic

- The measure of molar concentration of hydrogen atoms in a solution is expressed as pH
- The acid-alkaline ratio of a substance ranges from the most acidic (0) to the most alkaline (14) with 7 as neutral.[1-3]

1. Prakash C, et al. J Clin Aesthet Dermatol. 2017;10(7):33–39;
2. Raphael KL, et al. Clin J Am Soc Nephrol.2016 Jan 14. pii:CJN.06200615.
3. Lynde CW, Tan J, Skotnicki S, Andriessen A, et al. J Drugs Dermatol 2019;18(12) S-1:1-16.

Potential hydrogen (pH) or Power of hydrogen (pH)

What is buffer capacity?

Buffer Capacity

- The buffer capacity describes the ability to keep the same pH under the influence of acidic or alkaline stressors.
- Skin has a fairly high buffer capacity – this is lower for babies and aged skin.
- Topical formulations typically do not have a high buffer capacity.
- The clinical relevance for the buffer capacity of topical formulations is not well defined.

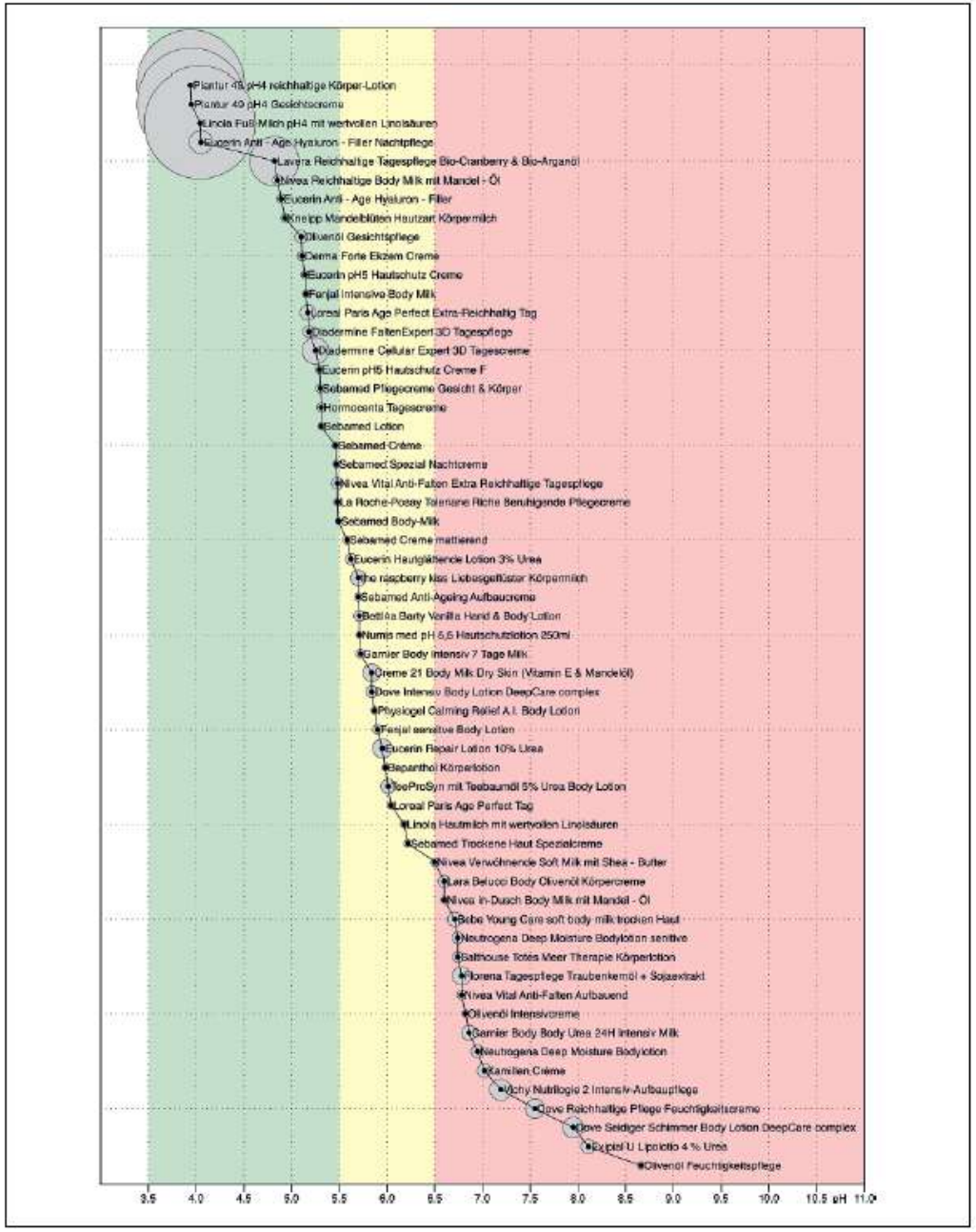


Fig. 2. Ranking of the tested preparations: Green = suitable pH, Yellow = suitable to a limited extend, Red = unsuitable pH, Grey circles = buffer capacity (a larger diameter corresponds with a higher buffer capacity).

Wohlrab J. Karger Publishers 2018;54: 123-131.

Skin pH and buffer capacity

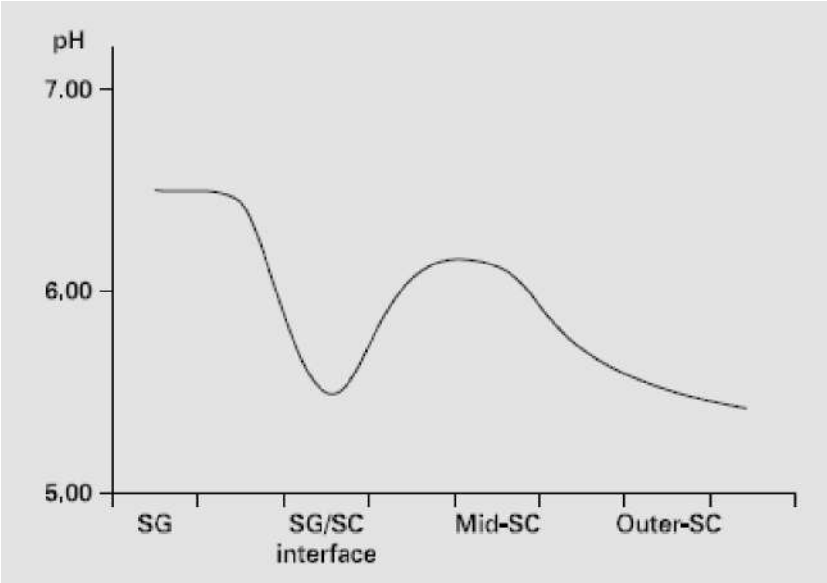
- There is a complex interplay of buffer capacity, stratum corneum pH and filaggrin production into natural moisturizing factors.
- Buffer capacity is lower and skin pH is elevated
  - In babies and elderly
  - Repeat washing with alkaline soap
  - Other

Raphael KL, et al. Clin J Am Soc Nephrol.2016 Jan 14. pii:CJN.06200615.

What is the pH of the Stratum Corneum?

The pH starts at ≈ 5.5 at the surface and increases by increments of 0.2–0.3 units until it reaches 6.8 in the lower stratum corneum

The pH Gradient



Biphasic pH gradient in different stratum corneum (SC) and stratum granulosum (SG) layers

Fluhr JW, Elias PM. Exogenous Dermatology; 2002;1(4) :163-175.

Ali SM, Yosipovitch G. Acta Dermatol Venerol 2013; 93(3): 261-269.

Skin pH and skin barrier function

- Skin barrier function is dependent on the complex interplay of SC pH and the following:
  - Exogenous and endogenous processes that influence skin pH
  - pH dependent lipid processing enzymes which produce the mortar of the brick and walls of the SC
  - Serine proteases which are pH dependent and break down corneodesmosomes in the SC
  - Skin microbiome diversity

Bandier J, et al. *Dermatitis* 2014; 25: 127-129,. Wang B, et al. *J Invest Dermatol*. 2017;137:95-105.

Lynde CW, Tan J, Skotnicki S, Andriessen A, et al. J Drugs Dermatol 2019;18(12) S-1:1-16.

Exogenous and endogenous processes influencing skin surface pH

Exogenous' mechanisms

- Free fatty acids (FFA) from sebum
- Microbial metabolites
- Lactic acid from eccrine sweat glands

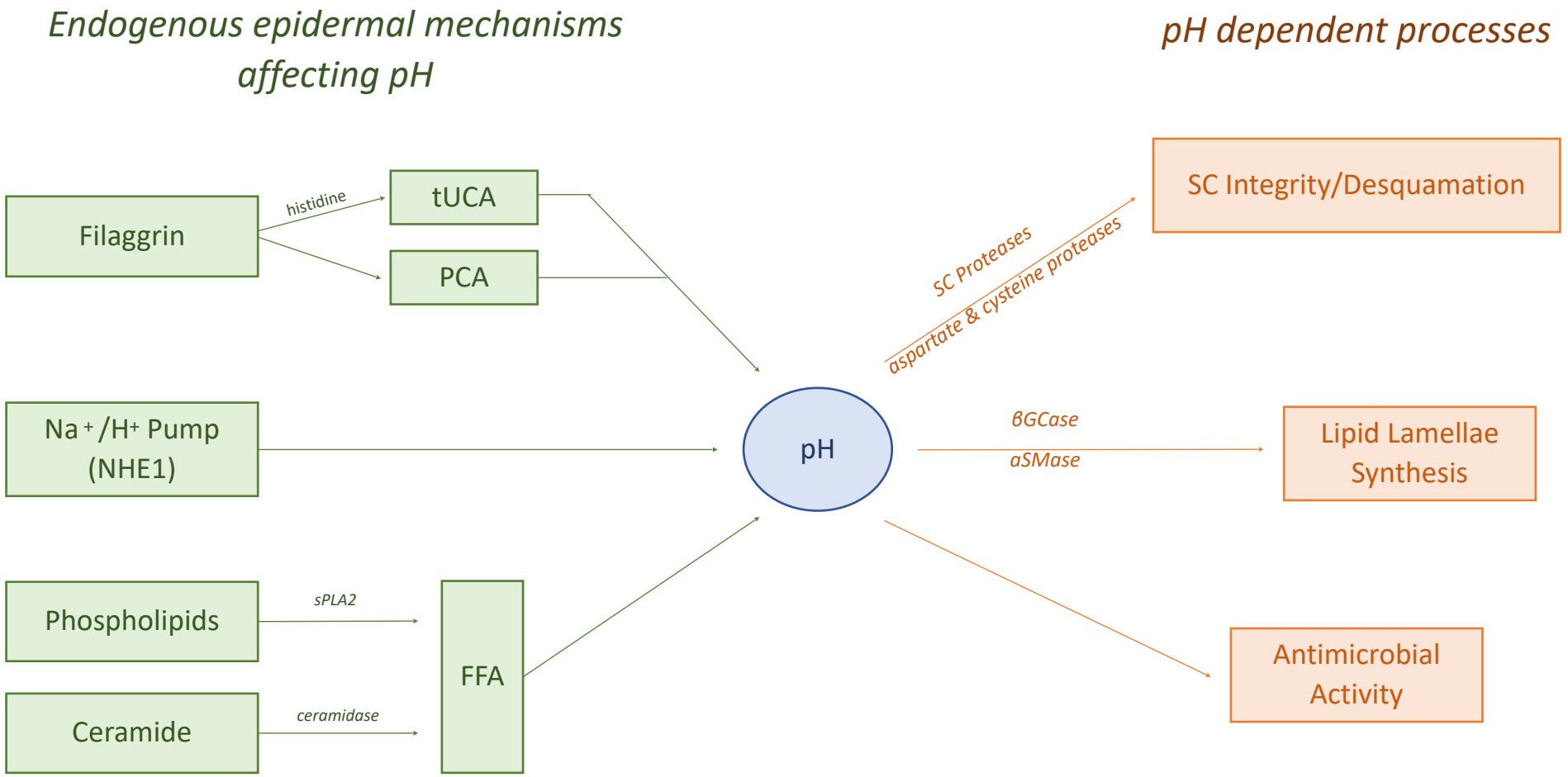
Endogenous epidermal mechanisms

account for up to ≈2 pH units

≈1 Unit	Release of FFA from glycerophospholipids by secretory phospholipase (sPLA2)	↑Barrier ↑Cohesion
≈1/2 Unit	Filaggrin (FLG) breakdown generating polycarboxylic acids (PCA) and uronic acid (UCA)	↑Barrier
≈1/4 Unit	sodium–proton antiporter, type 1 (NHE1) selectively acidifies extracellular domains at the base of the SC	↑Barrier

Elias PM. Experimental dermatology 2015;24(3), 179.
Wang B, et al. *J Invest Dermatol*. 2017;137:95-105.

Endogenous epidermal mechanisms and pH dependent processes

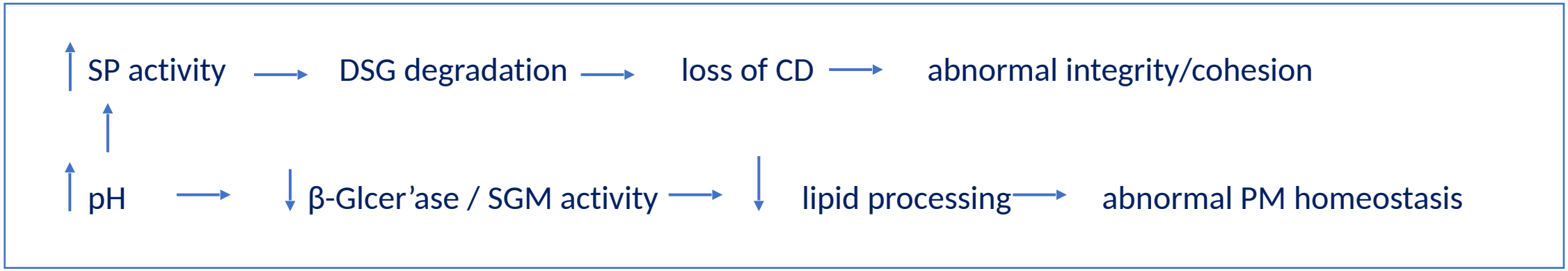


Free fatty acids (FFA); sodium–proton antiporter, type 1 (NHE1) selectively acidifies extracellular domains at the base of the SC.
Filaggrin (FLG) breakdown generating polycarboxylic acids (PCA) and uronic acid (UCA)
Modified from: https://plasticsurgerykey.com/27-the-skin-barrier-in-atopic-dermatitis/

Elias PM. Experimental dermatology 2015;*24*(3), 179.

Mechanism of skin pH: Lipid processing

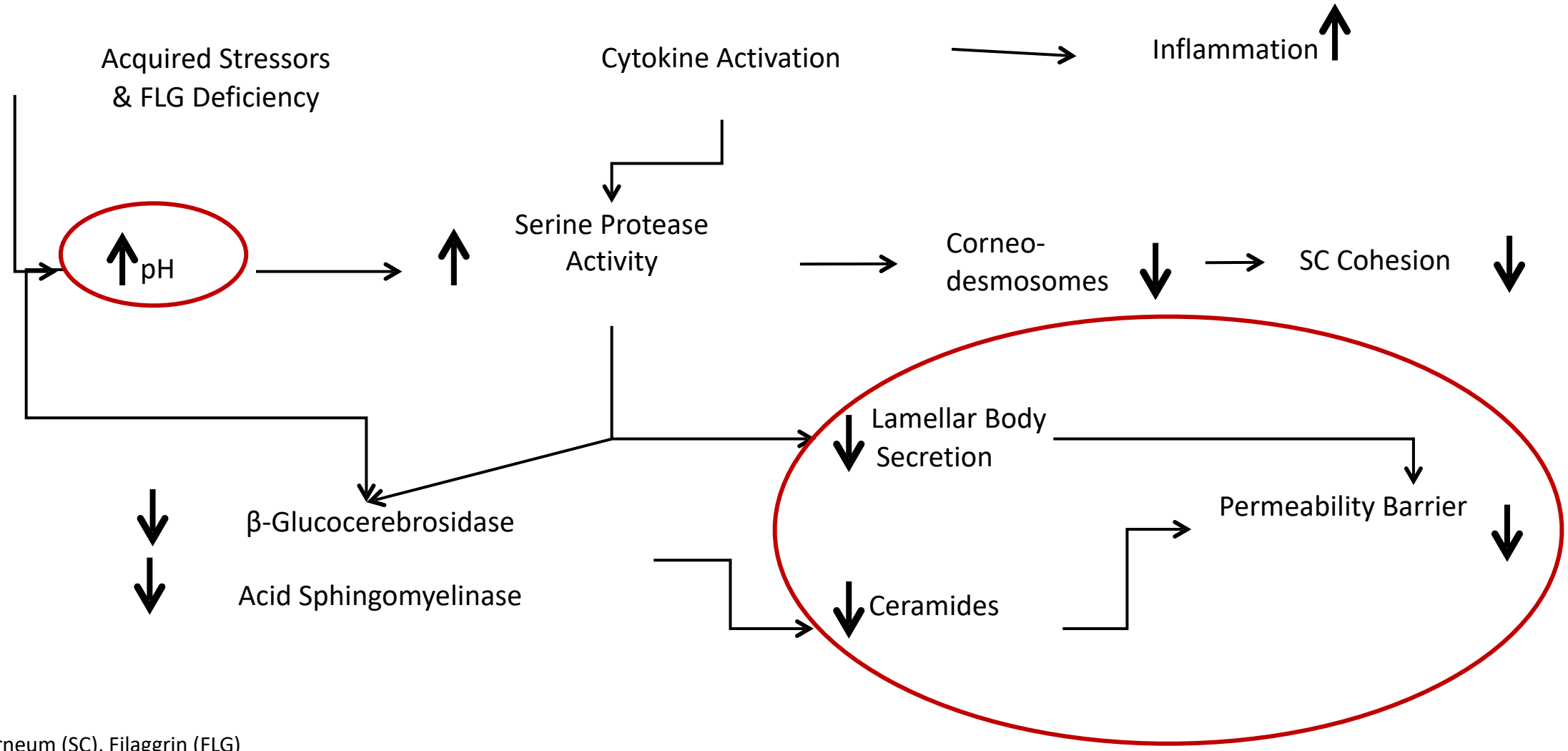
- Lipid processing and formation of lamellar structures requires an **acidic skin pH**
  - **Activity** of β-glcer'ase is **10 times lower *in situ* at pH 7.4 than at pH 5.5.**
  - Free fatty acids **form lamellar liquid crystals at pH values of 4.5–6** through partial ionization.



Stratum corneum (SC); Serine protease (SP); Desmoglein (DSG)
Corneodesmosomes (CD), β-glucocerebrosidase (β-glcer'ase)
Sphingomyelinase (SGM), Permeability (PM)

Ali SM, Yosipovitch G. Acta Derm Venereol 2013; 93: 261–267.

Elevated skin pH may delay barrier recovery and facilitates barrier breakdown



Stratum corneum (SC), Filaggrin (FLG)

Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Skin pH and antimicrobial defence mechanism

- FLG and its degradation products play a key role in controlling TEWL and SC pH.
- When the SC becomes dehydrated FLG undergoes proteolysis to release hygroscopic amino acids.
- A physiological skin pH acts as an antimicrobial defensive mechanism to limit bacterial colonization.
- Pathogenic organisms *Staph. aureus* and *Strep. pyogenes* are inhibited by an acid pH.
- Antimicrobial peptides produced from keratinocytes, neutrophils and mast cells are regulated by pH.

Stratum corneum (SC), Filaggrin (FLG), Trans epidermal water (TEWL)

Grogan MD et al. J Invest Dermatol. 2019;139:747-752.

What can affect stratum corneum pH?

- Individual Factors: Age, Race, Gender, Anatomical Site, Hydration
- Disease States: Atopic Dermatitis, Ichthyosis, Rosacea, Acne
- Skincare: Topical Preparations, Detergents/Cleansing

Fluhr JW, Elias PM.Exogenous Dermatology; 2002;1(4) :163-175.

Ali SM, Yosipovitch G. Acta Dermatol Venerol 2013; 93(3): 261-269.

What can affect Stratum Corneum pH? Cont.

Individual Factors – Age, Race, Gender, Anatomical Site

Age

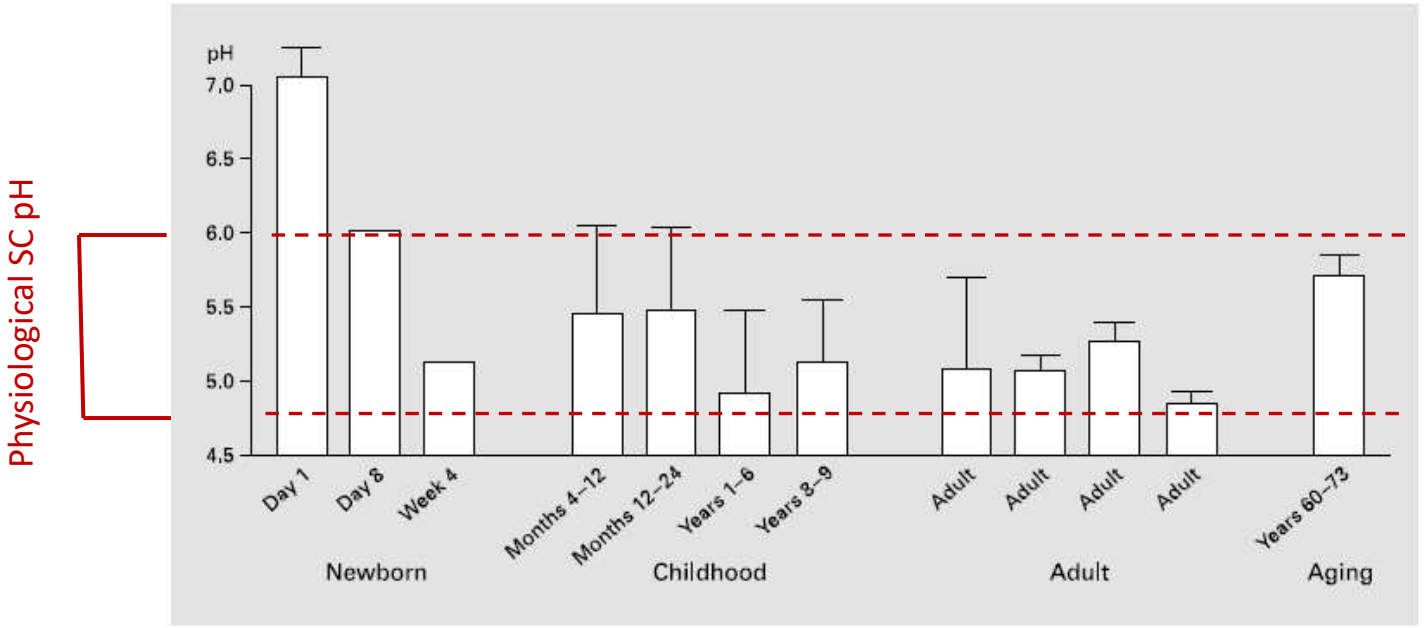


Fig. 3. Changes in pH (means and SD) during different periods of life (data from the literature, tables 1 and 2).

Race

There was a lower pH in Black skin compared with White skin in the superficial layers of the stratum corneum, but not in the deeper layers

Gender

Studies have shown the pH for females trends slightly higher than males

Fluhr JW, Elias PM.Exogenous Dermatol 2002;1(4):163-175.

Wesly NO, Maibach HI. Am J Clin Dermatol 2003;4(12): 843-860.

What can affect stratum corneum pH? Cont.

Site

Table 1. pH at different anatomical localizations in humans

	Forehead	Volar forearm	Leg/back	Inframammary region	Axilla	Vulva/inguinal region
Blank [82]	4.0–5.6 (M) 4.0–6.6 (F)					
Draize [70]	4.2–5.6 (M) 4.8–6.2 (F)					
Elsner [80]						5.99 ± 0.45 (M + F) vulva
Fluhr et al. [76]		5.07 ± 0.62 (M + F)				
Tippelt [83]			5.39 ± 0.03 (M + F) cubita and poplitea		6.59 ± 0.05 (M + F)	
Treffel et al. [78]		4.15 ± 0.85 (M + F)				
Yosipovitch et al. [73]		5.06 ± 0.11 (M) 5.26 ± 0.12 (F)		5.54 ± 0.10 (M) 5.83 ± 0.17 (F)	5.84 ± 0.10 (M) 5.99 ± 0.11 (F)	6.22 ± 0.15 (M + F) inguinal
Yosipovitch et al. [74]	4.95 ± 0.08 (M) 5.22 ± 0.09 (F)	4.84 ± 0.09 (M) 5.74 ± 0.14 (F)	5.06 ± 0.11 (M) 5.26 ± 0.12 (F) back		6.13 ± 0.13 (M) 6.15 ± 0.16 (F)	
Zlotogorsky [75]	4.8 ± 0.02 (M + F)	5.1 ± 0.02 (M + F) cheek				

Hydration

Skin dryness and pH were shown to be directly correlated

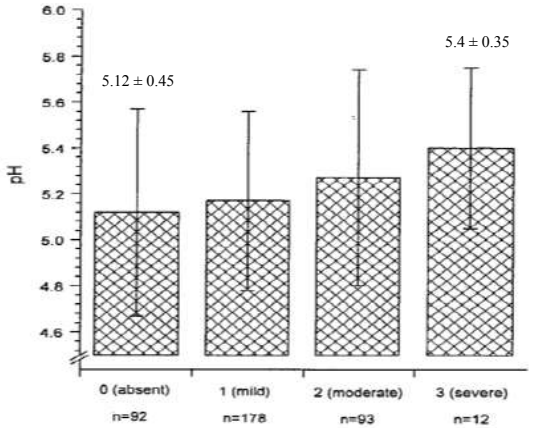


Fig. 1. Mean values ± SD of skin surface pH related to dryness of the skin; $p = 0.004$; $r = 0.147$ (linear regression analysis).

Other studies have shown anatomical sites with higher moisture has a slightly higher normal pH and after 3 days of occlusion pH increased from pH 4.9 to 7.1

Fluhr JW, Elias PM.Exogenous Dermatology; 2002;1(4) :163-175.

Ring J et al. Acta Dermatology-Venerology. 2002; 80, 188-191.

What can affect stratum corneum pH? Cont.

Topical Preparations

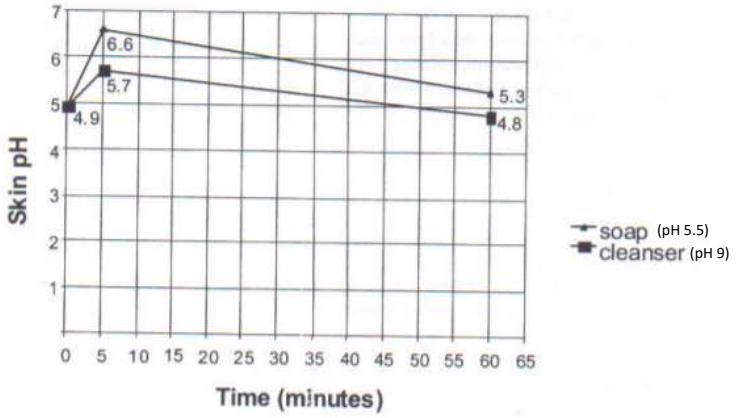
Interaction with the stratum corneum of surfactants used in topical formulations may cause:

- Erythema
- Dryness
- Skin barrier impairment
- Elevated skin pH
- Sensorial irritation

Detergents/Cleansing

Cleanser type is an important consideration – soaps are typically alkaline (pH 9-10) and syndets are acidic to neutral (pH 5.5-7)

Cleansers can temporarily increase the pH of the skin, but this returns to normal after ~1 hrs for acidic cleansers and ~3 hrs for alkaline soaps.

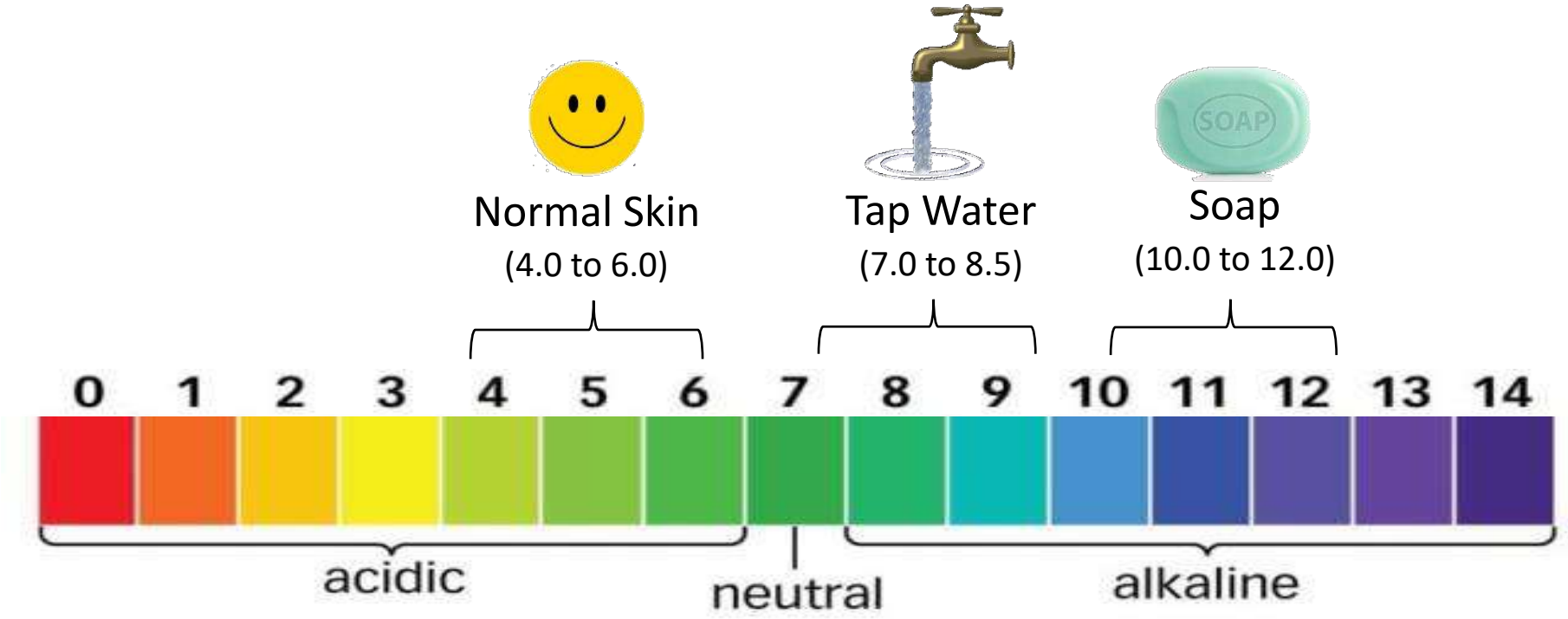


There is limited experimental evidence on the clinical implications of low pH cleansers.

Walters RM, et al. *Dermatol Res Pract*. 2012:495917.
Ananthapadmanabhan KP, et al. J Drugs Dermatol 2019;18(1s):80-88.
Draelos ZD. The science behind skin care: Cleansers. J Cosmetic Dermatol 2018;17(1): 8-14.

The types of skin care we use influence skin pH

The measure of concentration of hydrogen atoms in a solution is expressed as pH



Potential hydrogen (pH) or Power of hydrogen (pH)

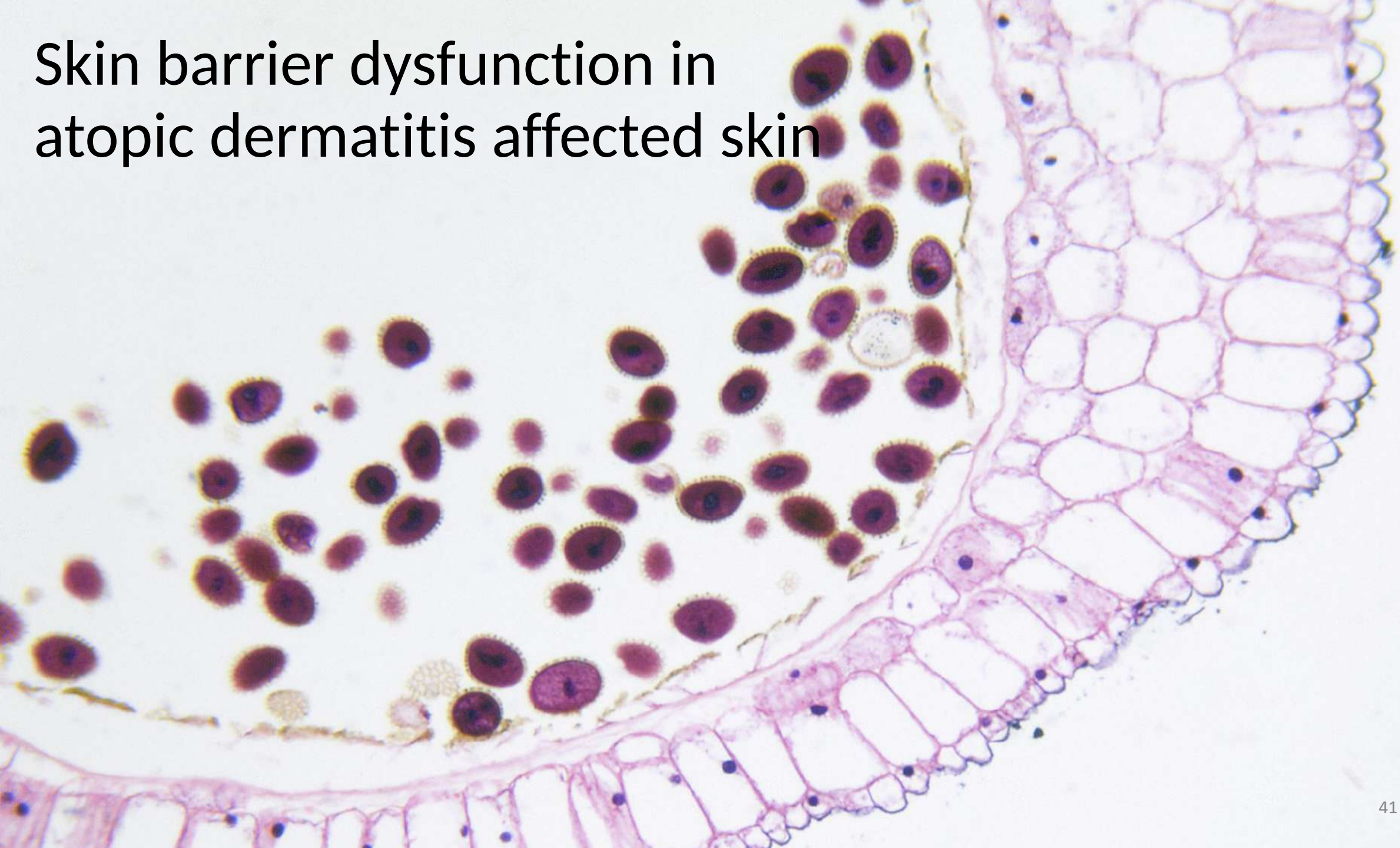
1. Prakash C, et al. J Clin Aesthet Dermatol. 2017;10(7):33–39;
2. Raphael KL, et al. Clin J Am Soc Nephrol.2016 Jan 14. pii:CJN.06200615.

Requirements for a competent skin barrier

- Maintain a near physiological (pH 4-6) stratum corneum pH
  - The process of skin acidification plays a vital role in skin barrier function
- Reduce inflammation
  - The activation of enzymes is involved in the extracellular processing of stratum corneum lipids.
- Maintain sufficient amounts of lipids and their correct proportion
  - Correct 3 Lipids: Ceramides, Free fatty acids, Cholesterol

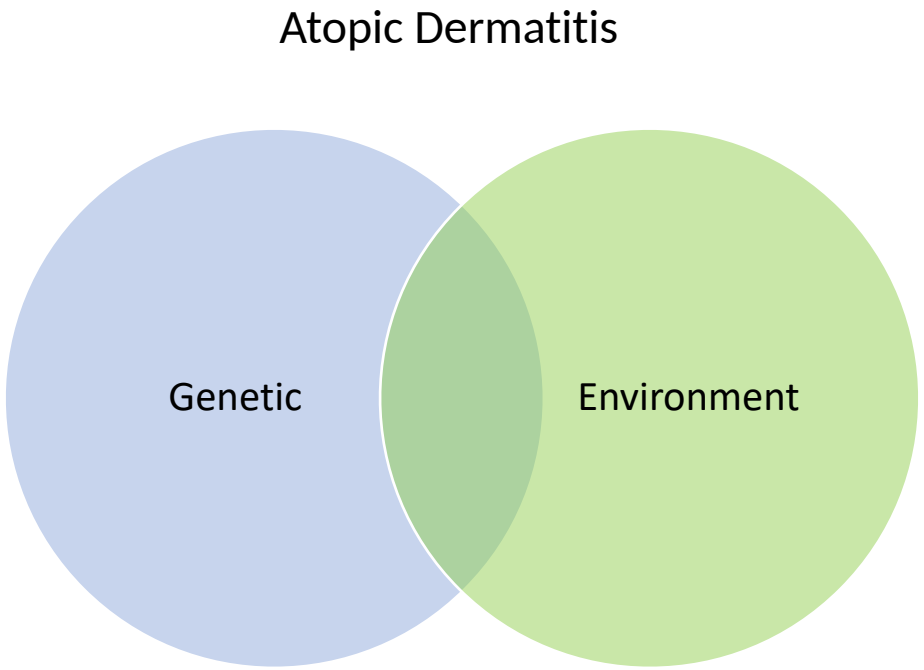
Elias PM. *Experimental Dermatol 2017*;26:999-1003. Browning J. Dermatology Eds. Bolognia JL, Schaffer JV, Cerroni L. Fourth edition China: Elsevier, 2018, ISBN 978–0-7020–6275–9. Ped Dermatol;35(2):289-289.

Skin barrier dysfunction in atopic dermatitis affected skin



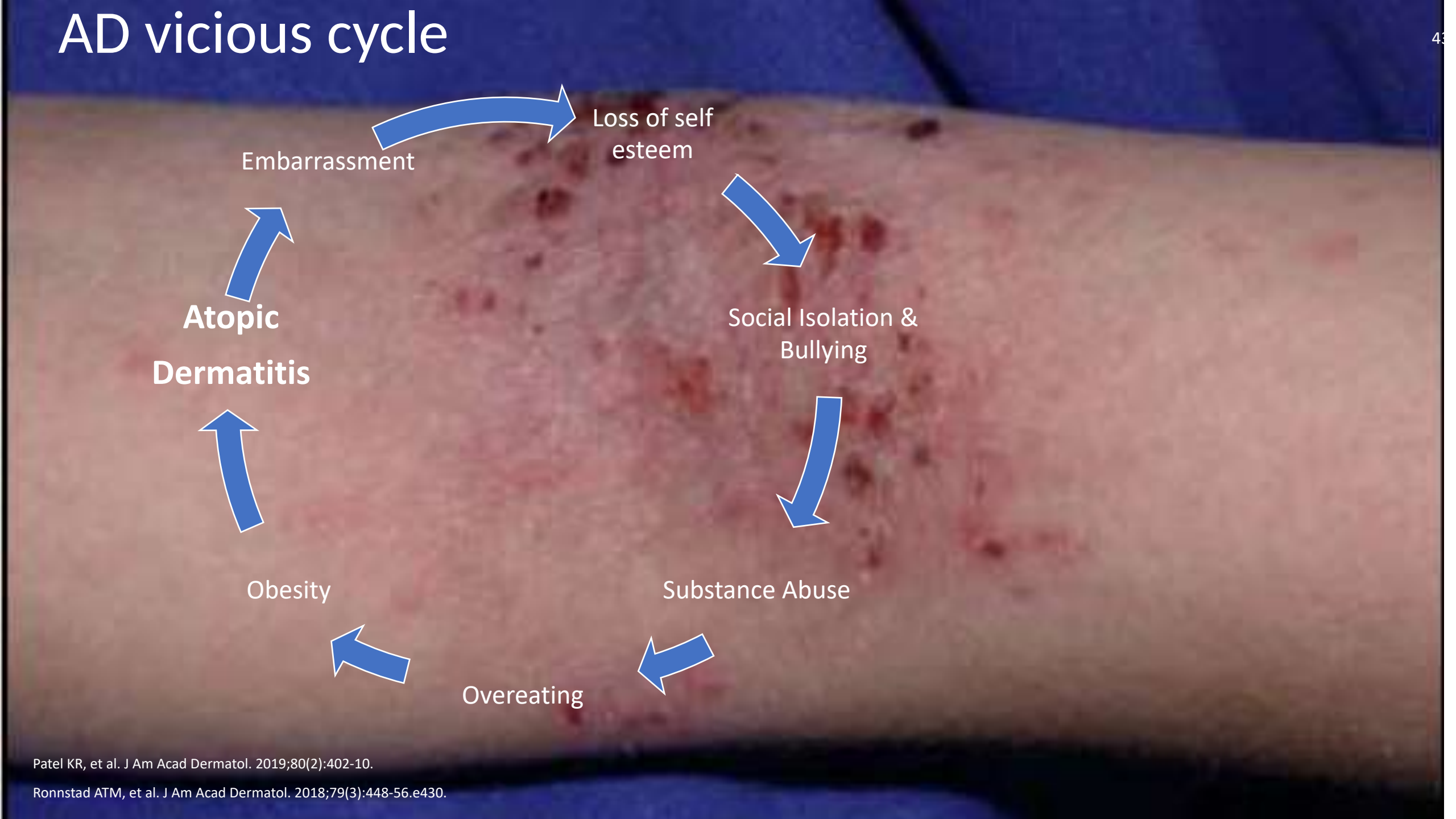
Atopic dermatitis key points

- Prevalence of atopic dermatitis has dramatically increased over the last 50 years worldwide.
- Likely a complex interplay between genetic factors predisposing to atopic dermatitis and environmental triggers.
- Prevalence appears to be higher in wealthier, developed regions.
- Understanding potentially modifiable environmental risk factors may allow for exposure reduction, mitigation of disease and/or prevention.



Kantor et al. Exp Rev Clinical Immunology, 2016

AD vicious cycle



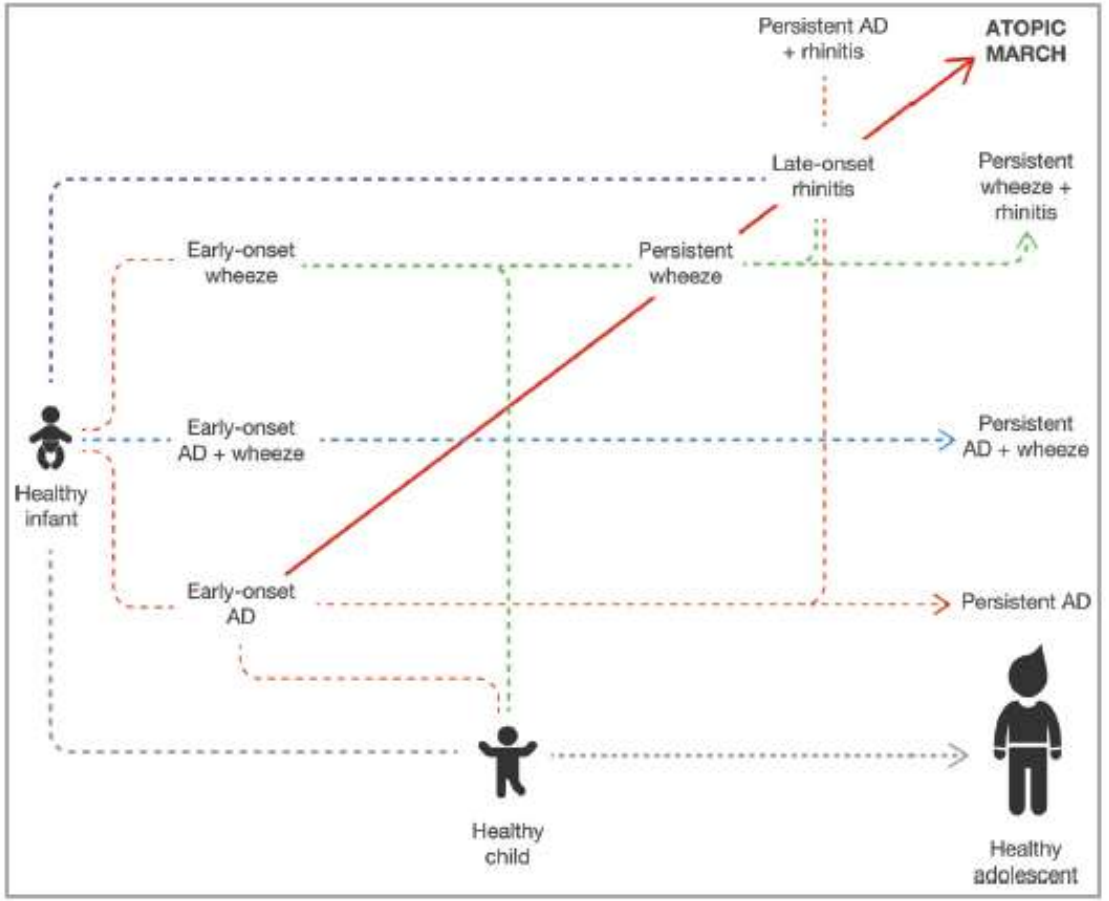
Patel KR, et al. J Am Acad Dermatol. 2019;80(2):402-10.

Ronnstad ATM, et al. J Am Acad Dermatol. 2018;79(3):448-56.e430.

The atopic march

The complex pathophysiology of AD translates into a heterogeneous clinical presentation and trajectories of disease progression.

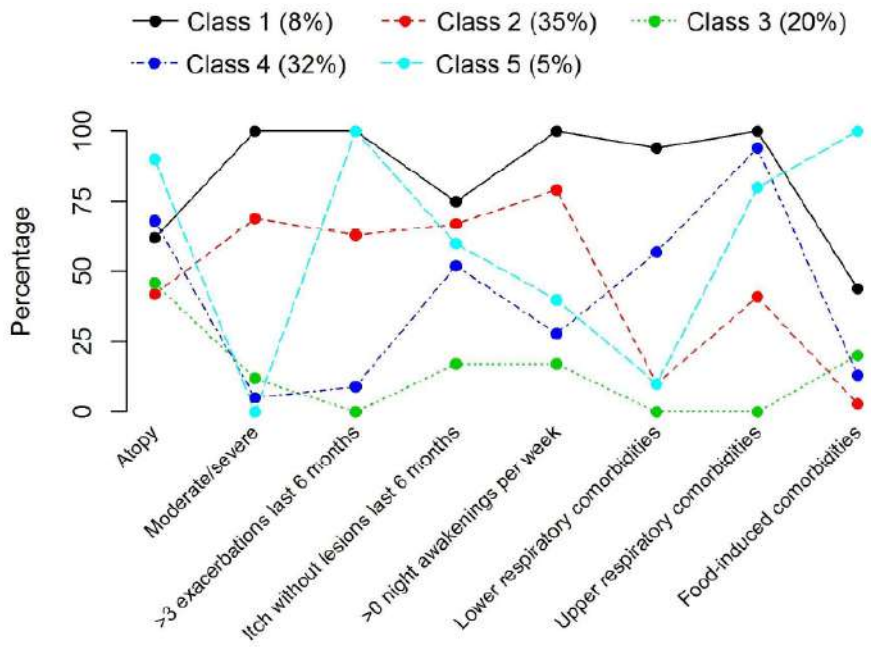
- A significant proportion will develop persistent AD and/or other atopic conditions.



Atopic dermatitis (AD)

Irvine AD. Br J Dermatol 2019

The atopic march : Phenotypes in preschool and school-age children



- Class 1: “moderate-severe, comorbid AD”
- Class 2: “moderate-severe, low comorbid AD”
- Class 3: “mild, low comorbid AD”
- Class 4: “mild AD, respiratory comorbidity”
- Class 5: “mild AD, food-induced comorbidity”

Phenotype	Pre-school-age	School-age
Class 1	8%	24%
Class 2	35%	10%
Class 3	20%	16%
Class 4	32%	49%
Class 5	5%	

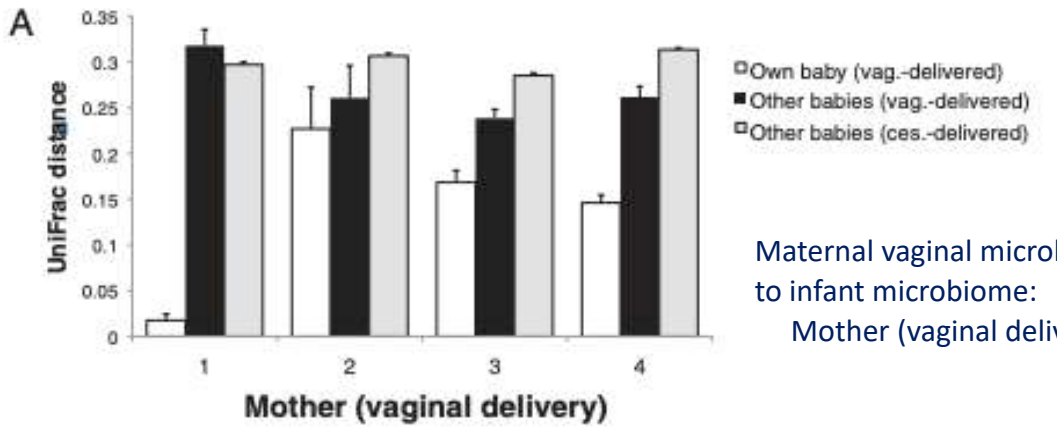
- Lower respiratory comorbidities (wheezing, asthma or exercise-induced bronchoconstriction)
- Upper respiratory comorbidities (allergic rhinitis or conjunctivitis or rhino-conjunctivitis)
- Food-induced comorbidities (urticaria, angioedema, oral allergic syndrome or anaphylaxis due to nutrition).

Atopic dermatitis (AD)

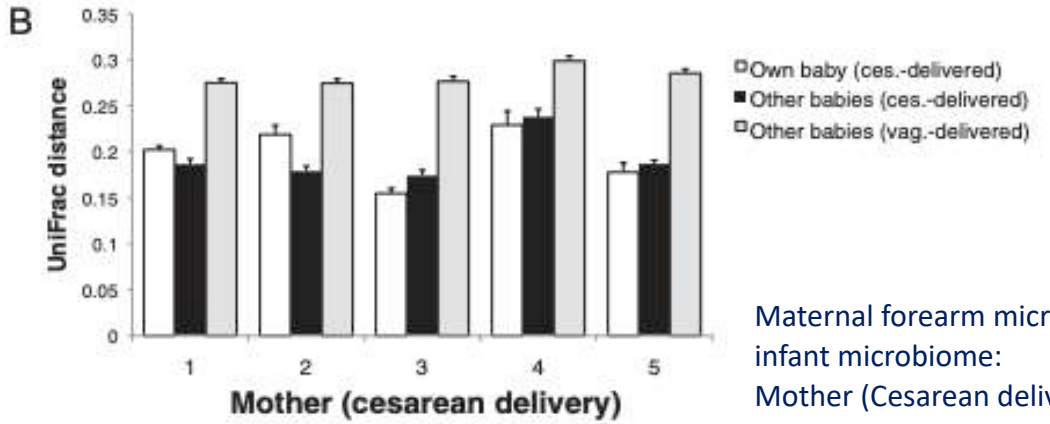
Galli E. J Investig Allergol Clin Immunol

Skin microbiome

- Development of skin microbiota starts at birth
  - Fetus was already in contact via meconium
  - Influenced by delivery mode



Maternal vaginal microbiome comparison to infant microbiome:
Mother (vaginal delivery) #1, #2, #3, #4

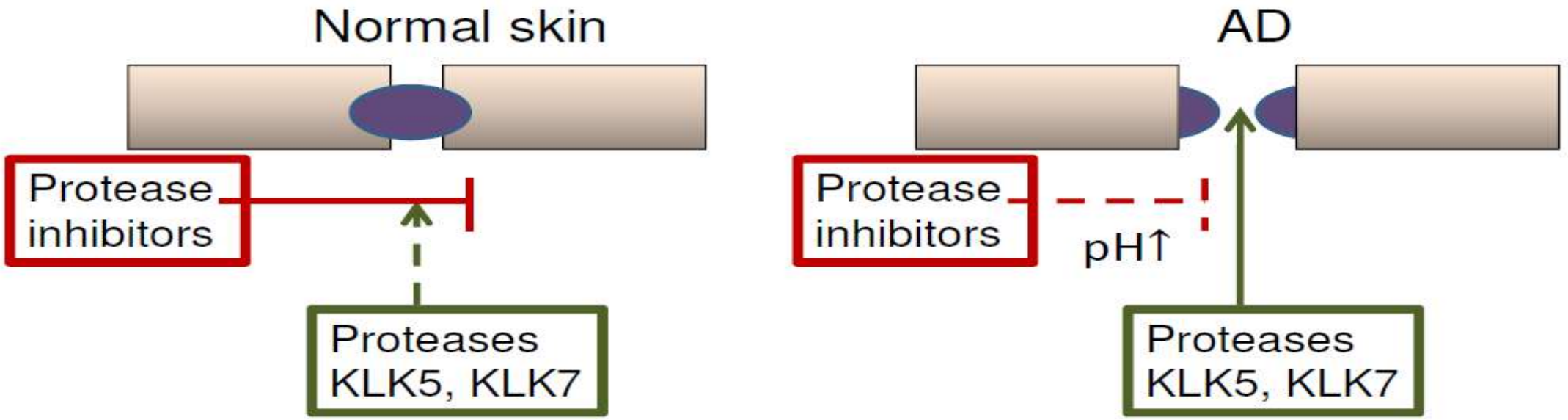


Maternal forearm microbiome comparison to infant microbiome:
Mother (Cesarean delivery): #1, #2, #3, #4, #5

Dominguez-Bello MG, et al. *PNAS.* 2010;107(26

Compromised integrity of the skin barrier in atopic dermatitis affected skin

- The integrity of the skin barrier is dependent on a cocktail of proteases and protease inhibitors.
- The balance between the expression and activity of proteases determines the rate of desquamation (corneocytes shedding) and thereby the thickness of the barrier.



Increase of pH inhibits protease inhibitor (LEKTI)

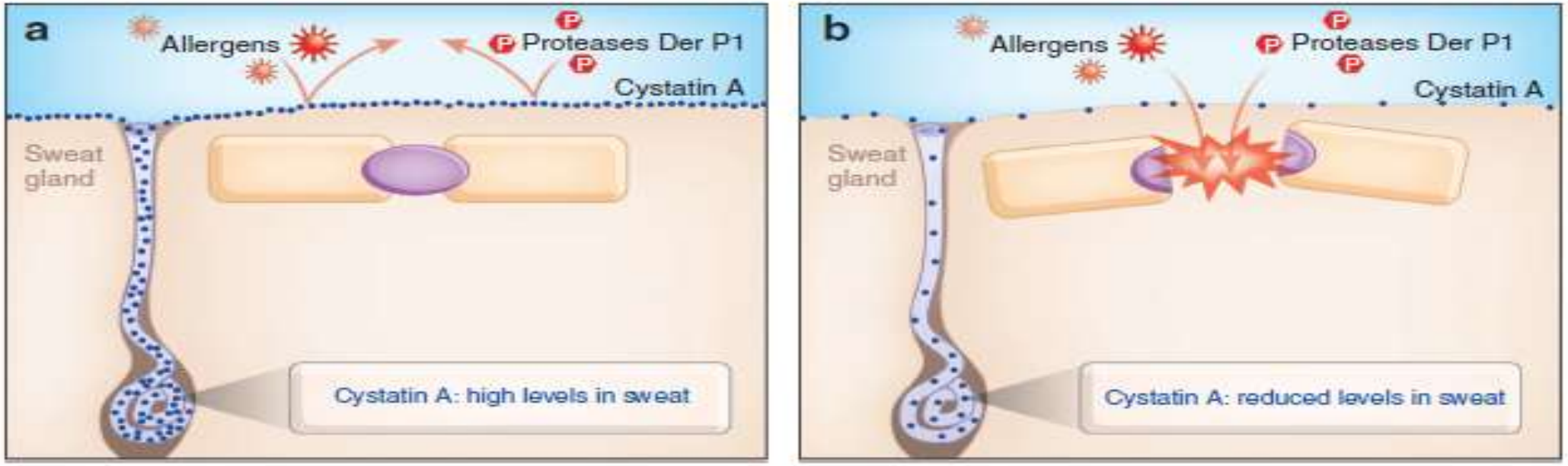
Atopic dermatitis (AD)
Corneocytes (beige rectangles), corneodesmosomes (blue spheres)
KLK5 and KLK7 are proteases
LEKTI is a protease inhibitor

Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Healthy skin versus atopic dermatitis-affected skin

Normal skin

Atopic dermatitis skin

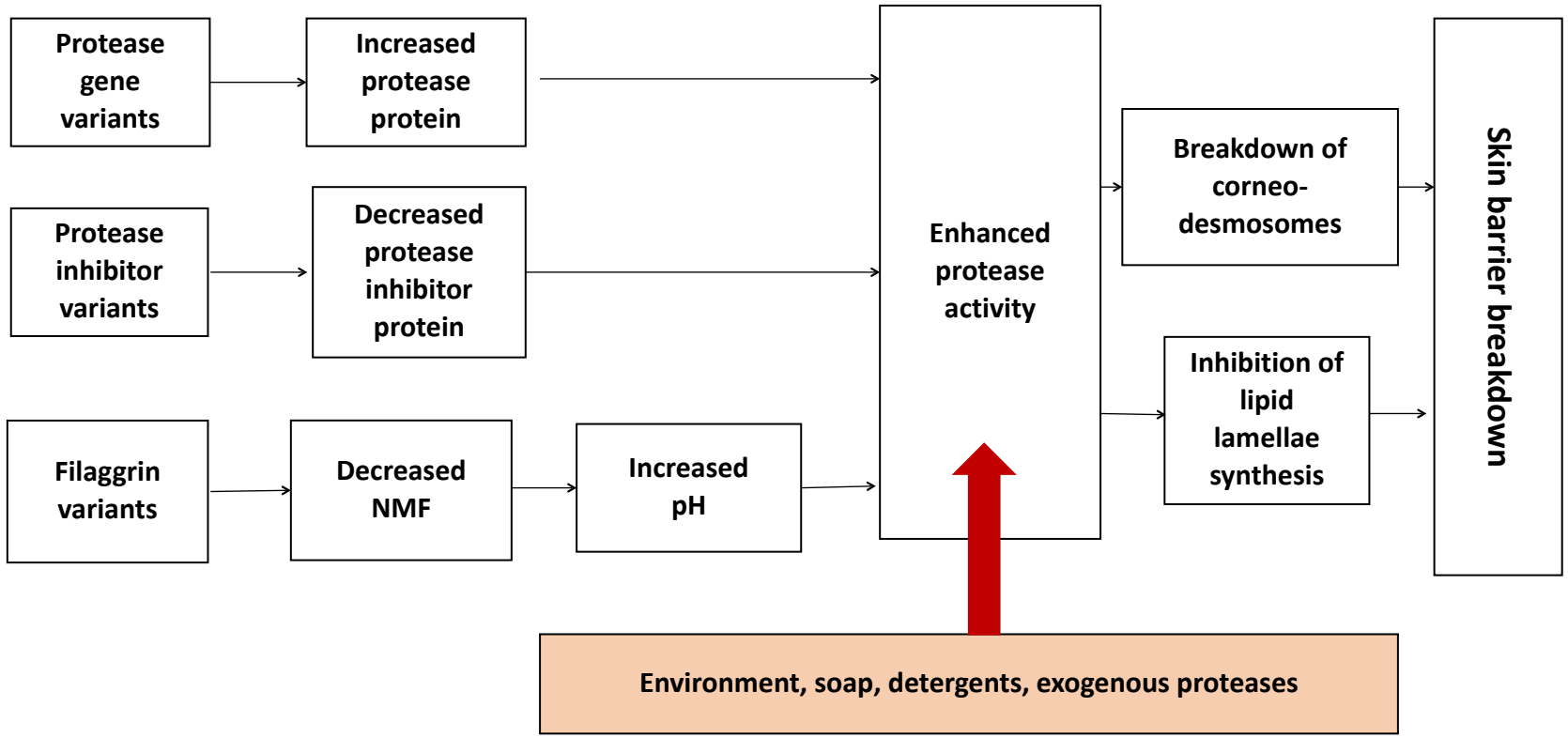


In normal skin the protease inhibitor cystatin A (blue dots) is secreted in sweat and flows out onto the surface of the skin forming a protective layer.

Altered expression of cystatin A leads to an incomplete protective barrier against exogenous proteases leading to breakdown of the skin barrier.

Cork MJ, et al. *J Invest Dermatol*. 2009;129:1892-1908.

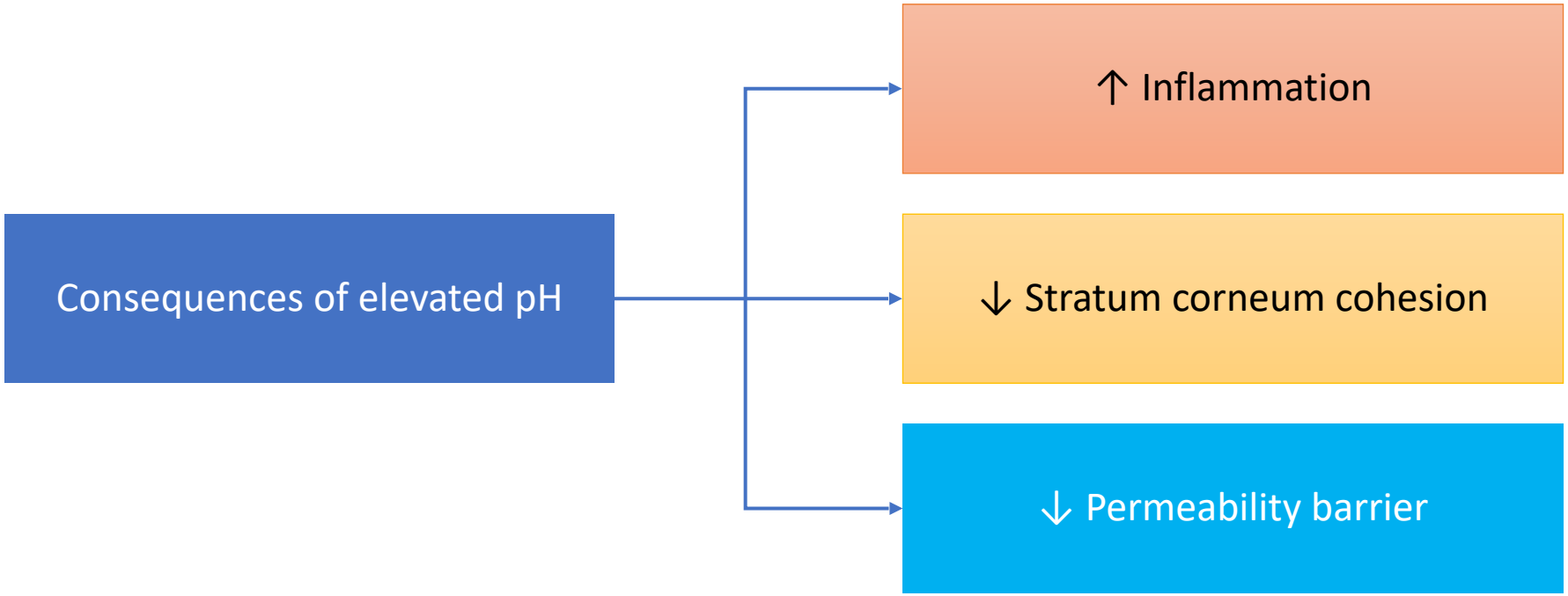
Skin barrier dysfunction in atopic dermatitis



Atopic dermatitis (AD); Natural moisturizing factors (NMF)

Adapted from Cork MJ, et al. *J Invest Dermatol*. 2009;129:1892-1908

What happens when pH increases in atopic dermatitis



Skin cannot retain sufficient water which leads to dry skin and the itch, scratch and damaged skin and inflammation cycle".

Lynde CW et al. Clinical & Aesthetic dermatology. 2014;7(3):40-48

Ceramide levels are significantly reduced in patients with skin conditions[1]

- TEWL is significantly higher in patients with
  - AD[1], Acne[2], Psoriasis[1], and Eczema[1]

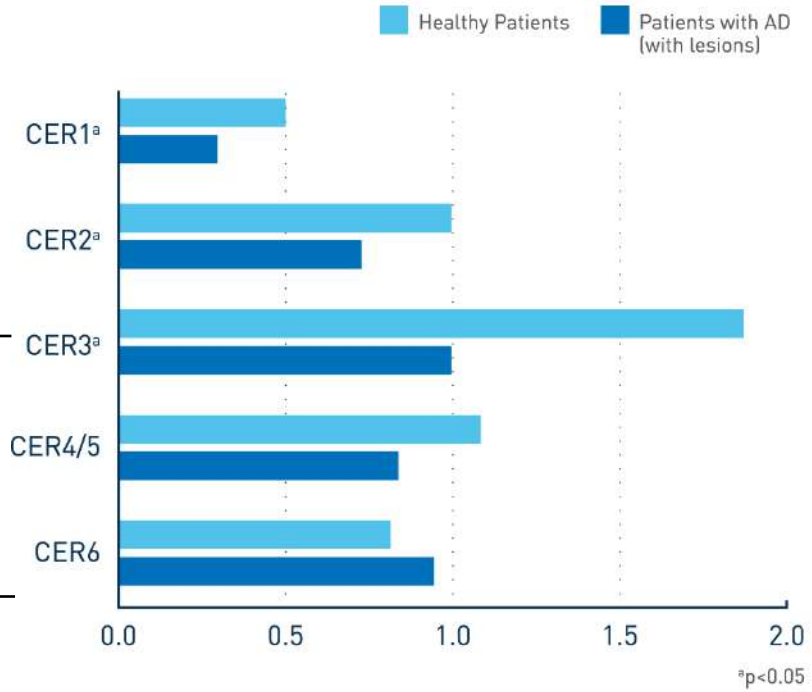
Disease	Decrease of Ceramides
Psoriasis[4]	Ceramides 1, 3, 6 ↓
Ichthyosis[5]	Ceramides 1, 6 ↓
Acne (Vulgaris)[6]	Linoleate in Ceramide 1 ↓
Atopic Dermatitis[3]	Ceramides 3, 6 ↓
Surfactant-induced Dermatitis[7]	Ceramide 1 ↓

CER EOP = Ceramide 1
CER NP = Ceramide 3
CER AP = Ceramide 6-II

1. Choi MJ, Maibach HI. A*m J Clin Dermatol*. 2005;6(4):215-223.
2. Yamamoto A., et al. *Arch Dermatol Res*. 1995;287:214-218
3. Di Nardo A. et. al., Acta Derm Venereol. 1998;78:27-30.
4. Motta S. et al., Arch. Dermatol. 130, 452-456. 1994
5. Paige DG. et al., Proc. Br. J Dermatol. 131, 23-7. 1994
6. Yamamoto A., et al. *Arch Dermatol Res*. 1995;287:214-218
7. Di Nardo A. et. al., Contact Dermatitis 35, 86-91. 1996

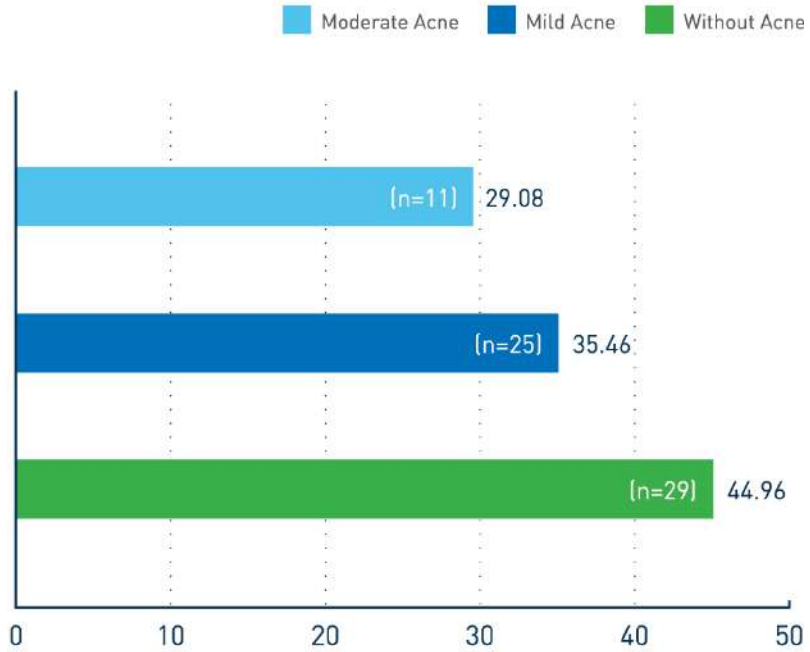
Ceramide levels are significantly reduced in patients with skin conditions, cont.

Ceramide levels are significantly lower in patients with atopic dermatitis (AD)[5]



Ceramide and cholesterol composition expressed in µg/mg stratum corneum

Ceramide levels are significantly lower in patients with facial acne[6]



Mean percentage of ceramides in the stratum corneum by polar lipid fractions

5. Paige DG et al. *Proc. Br. J Dermatol*. 131, 23-7. 1994.
6. Yamamoto A et al. *Arch Dermatol Res*. 1995;287:214-218

Atopic Dermatitis Guidelines support moisturizer use

- Evidence-based guidelines for AD support the use of moisturizers for skin hydration and AD symptom improvement.
- The guideline recommends moisturizers be used in primary treatment for mild disease and in conjunction with other agents for moderate and severe disease.

J Am Acad Dermatol. 2014 July ; 71(1): 116–132. doi:10.1016/j.jaad.2014.03.023.

GUIDELINES OF CARE FOR THE MANAGEMENT OF ATOPIC DERMATITIS:

Part 2: Management and Treatment of Atopic Dermatitis with Topical Therapies

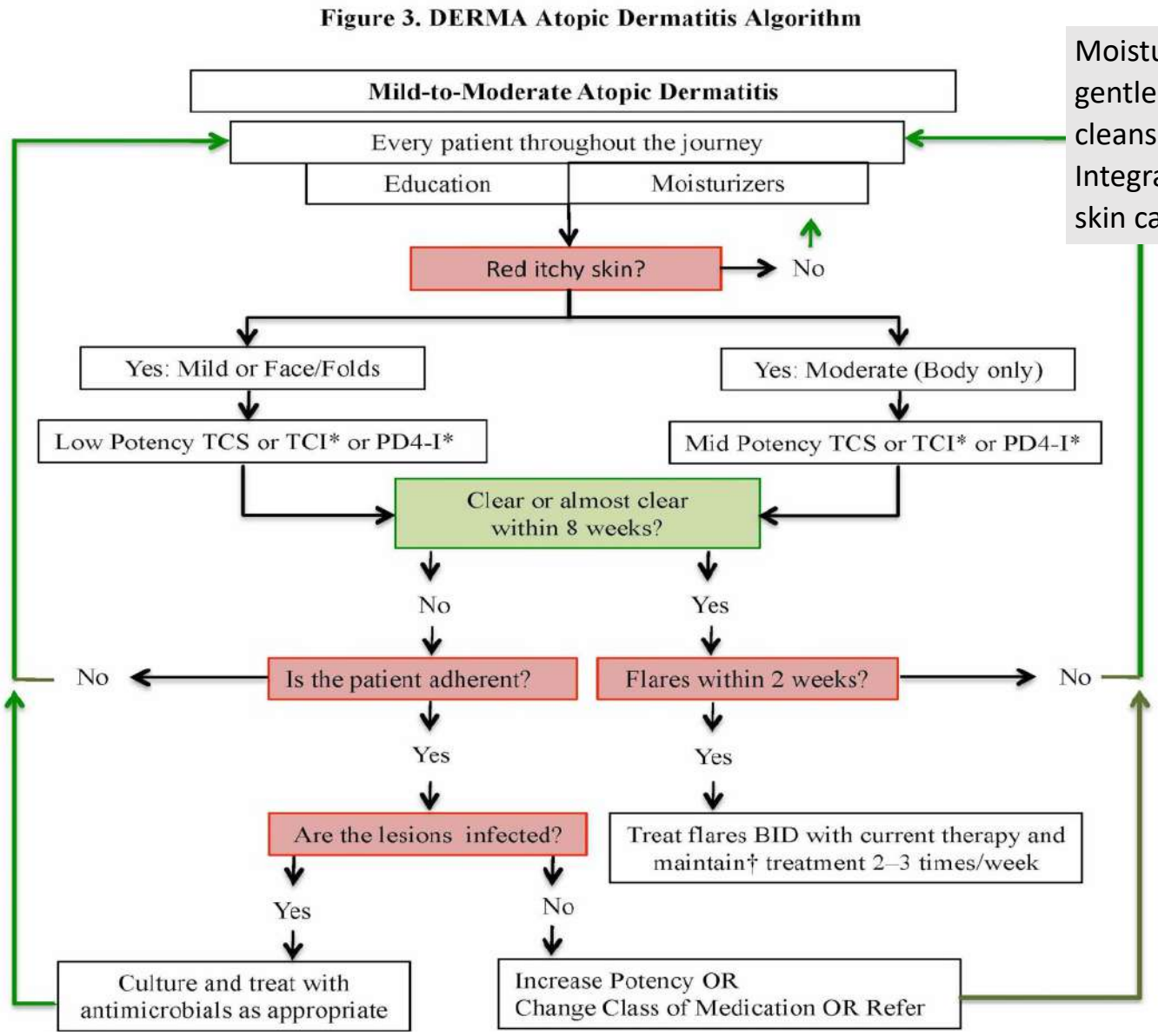
Lawrence F. Eichenfield, MD[a] [Co-chair], Wynnis L. Tom, MD[b], Timothy G. Berger, MD[c], Alfons Krol, MD[d], Amy S. Paller, MS, MD[e], Kathryn Schwarzenberger, MD[f], James N. Bergman, MD[g], Sarah L. Chamlin, MD, MSCI[h], David E. Cohen, MD[i], Kevin D. Cooper, MD[j], Kelly M. Cordoro, MD[k], Dawn M. Davis, MD[l], Steven R. Feldman, MD, PhD[m], Jon M. Hanifin, MD[n], David J. Margolis, MD, PhD[o], Robert A. Silverman, MD[p], Eric L. Simpson, MD[q], Hywel C. Williams, DSc[r], Craig A. Elmets, MD[s], Julie Block, BA[t], Christopher G. Harrod, MS[u], Wendy Smith Begolka, MBS[v,*], and Robert Sidbury, MD[w] [Co-chair]

Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71(1):115-132.

How to reduce inflammation?

2018 Canadian Algorithm:

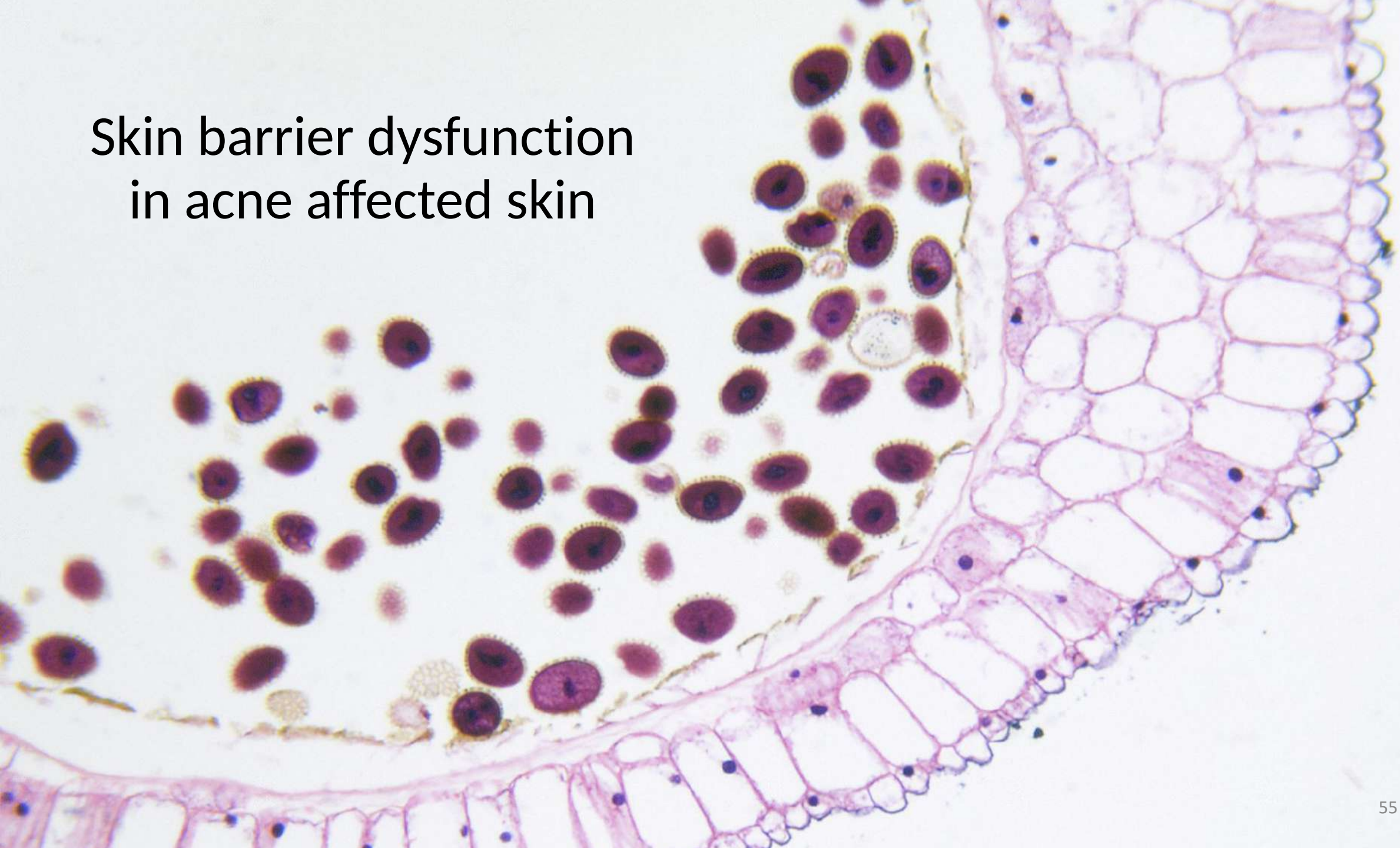
Education and skincare such as moisturizers are a key part of the prevention, maintenance and treatment



Moisturizers and gentle cleansers are an Integral part of skin care.

Lynde CW, et al. *J Cutan Med Surg*. 2019, Vol. 23(3S) 3S–13S

Skin barrier dysfunction in acne affected skin



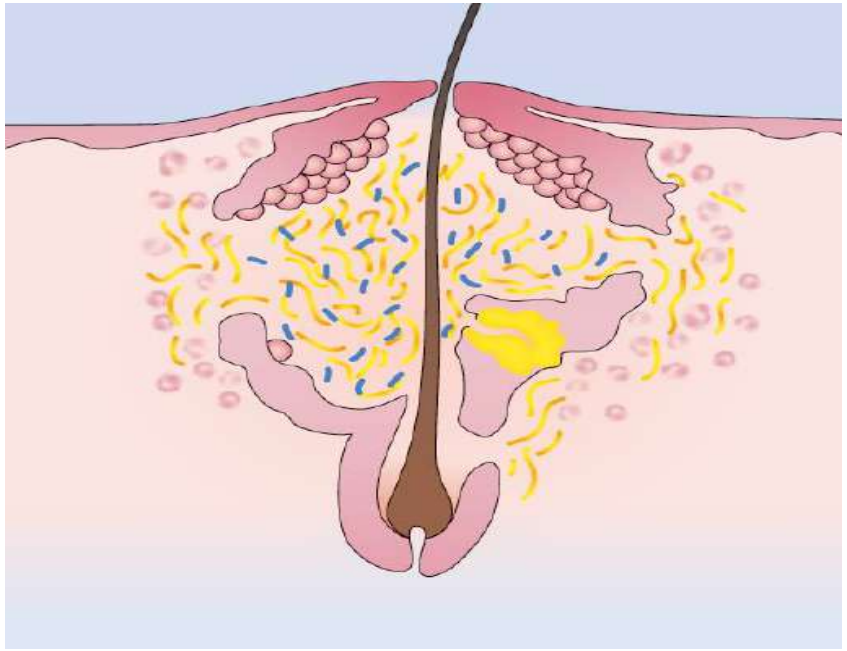
Acne key points: Acne is a complex, multifactorial inflammatory skin disease

Inflammation
Early – innate
Later - adaptive

Inflammation

P. acnes

Initiating factors
C. acnes?
Altered Sebum?
Short chain FA?
Other?



Follicular hyper-keratinization

Androgens

Sebum production

IGF-1

Thiboutot D. J Clin Aesthet Dermatol. 2013;6(2):18-24.

Impaired water barrier function in acne

Table 1 Comparison of water barrier function between acne patients and control subjects

Values are mean ± SD
** All values significantly different ($P < 0.01$) from one another

	Acne patients		Control subjects ($n = 29$)
	Moderate ($n = 11$)	Mild ($n = 25$)	
TEWL (g/m²/h)	16.8 ± 3.8**	14.4 ± 2.5**	10.3 ± 2.4**
Conductance (μΩ⁻¹)	52.1 ± 6.7**	92.8 ± 8.0**	188.9 ± 12.7**

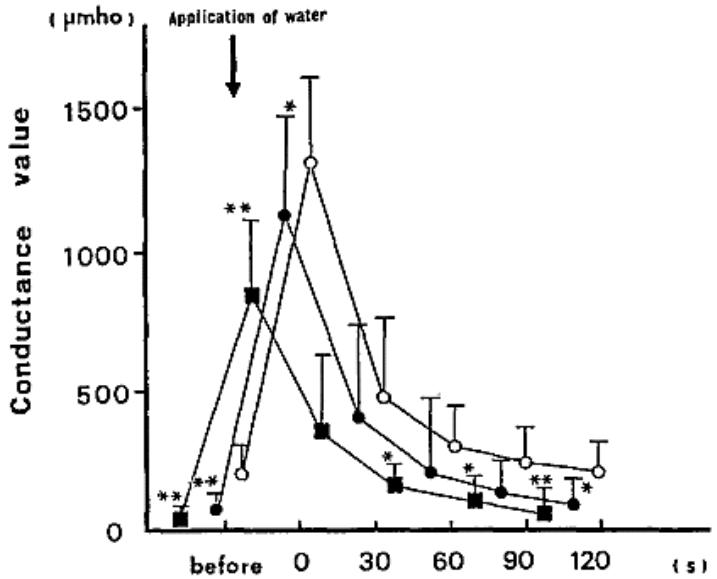


Fig. 1 Results of the water sorption–desorption test for patients with mild (●) and moderate acne (■) and control subjects (○). *Bars* represent SD. * $P < 0.05$, ** $P < 0.01$ versus control subjects

Arch Dermatol Res (1995) 287:214–218

ORIGINAL PAPER

Ayako Yamamoto · Kaoruko Takenouchi · Masaaki Ito

Impaired water barrier function in acne vulgaris

Impaired water barrier function in acne, cont.

Table 2 Sebum secretion rates (mg/40 cm²/3 h) and mean weights (µg/cm²) of the stratum corneum lipid fraction of acne patients and control subjects

	Acne patients		Control subjects
	Moderate ($n = 11$)	Mild ($n = 25$)	($n = 29$)
Sebum secretion rates	13.23 ± 2.85*	9.83 ± 2.55	10.58 ± 4.30
Squalene	27.42 ± 4.46	16.37 ± 3.80	16.66 ± 2.58
Wax esters	51.03 ± 7.10	36.60 ± 5.50	39.21 ± 3.39
Triglycerides	40.88 ± 6.00	35.33 ± 3.50	35.81 ± 3.18
Free fatty acids	27.81 ± 1.32	31.24 ± 3.57	31.54 ± 3.16
Cholesterol	5.79 ± 0.71	6.53 ± 0.80	5.72 ± 0.65
Cholesterol esters	7.65 ± 0.30	6.85 ± 0.94	5.77 ± 0.87
Cholesterol sulphate	0.54 ± 0.18	0.74 ± 0.20	0.87 ± 0.18
Total ceramides	3.40 ± 0.45*	4.07 ± 0.87*	6.49 ± 0.98
Phospholipids	0.77 ± 0.15	0.75 ± 0.21	0.79 ± 0.09
Total lipids	165.29 ± 20.1	138.48 ± 10.22	142.86 ± 15.75

Values are mean ± SD
* $P < 0.05$ versus control subjects

Table 3 Mean percentages of free sphingosine and total ceramides in the polar lipid fractions from the stratum corneum of acne patients and control subjects

Sphingolipid	Acne patients		Control subjects
	Moderate ($n = 11$)	Mild ($n = 25$)	($n = 29$)
Free sphingosine	0.18 ± 0.05**	0.30 ± 0.07**	0.74 ± 0.09**
Total ceramides	29.08 ± 2.07**	35.46 ± 3.94**	44.96 ± 5.83**

Values are mean ± SD
** All values significantly different ($P < 0.1$) from one another

Arch Dermatol Res (1995) 287 : 214–218

ORIGINAL PAPER

Ayako Yamamoto · Kaoruko Takenouchi · Masaaki Ito

Impaired water barrier function in acne vulgaris

Acne – Compromises Barrier Integrity

Functional

- Sebum excretion higher
- Sebaceous glands larger
- Subclinical inflammation

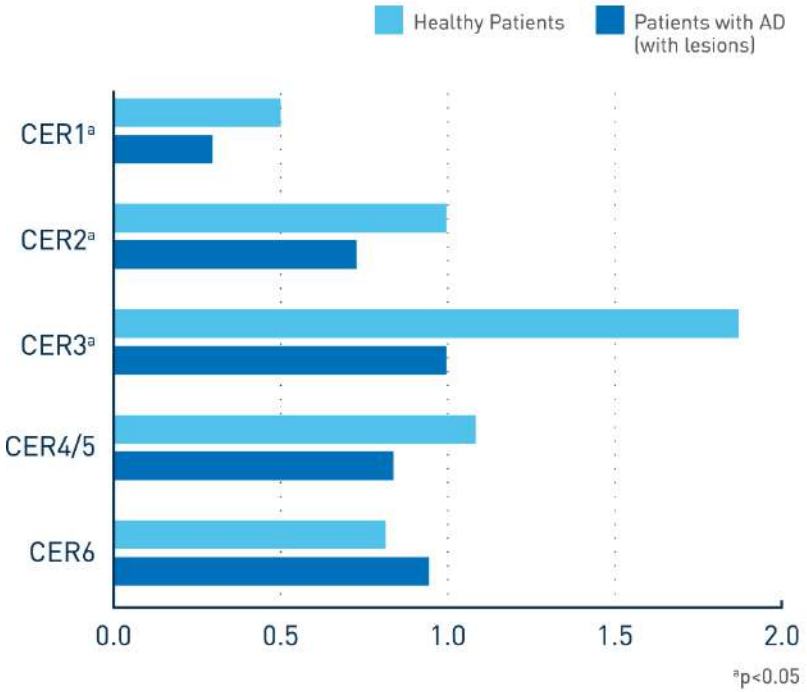
Ultrastructural

- ↑ filaggrin expression
- ↓ free fatty acids
- ↓ linoleic acid
- ↓ free sphingosine and total ceramides

Thiboutot D, Del Rosso JQ. *J Clin Aesthet Dermatol*. 2013 Feb; 6(2): 18–24.

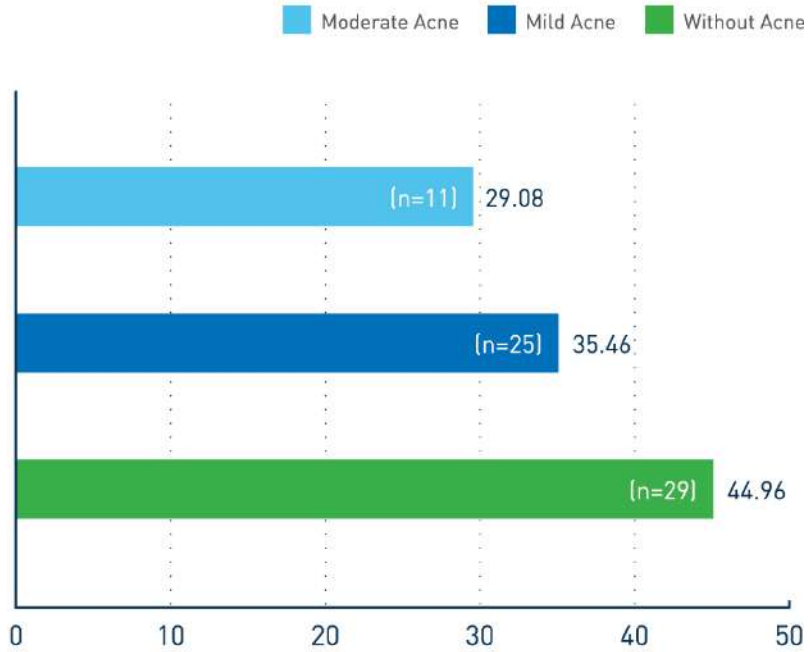
Ceramide loss and the link to dermatological skin conditions

Ceramide levels are significantly lower in patients with atopic dermatitis (AD)[5]



Ceramide and cholesterol composition expressed in µg/mg stratum corneum

Ceramide levels are significantly lower in patients with facial acne[6]



Mean percentage of ceramides in the stratum corneum by polar lipid fractions

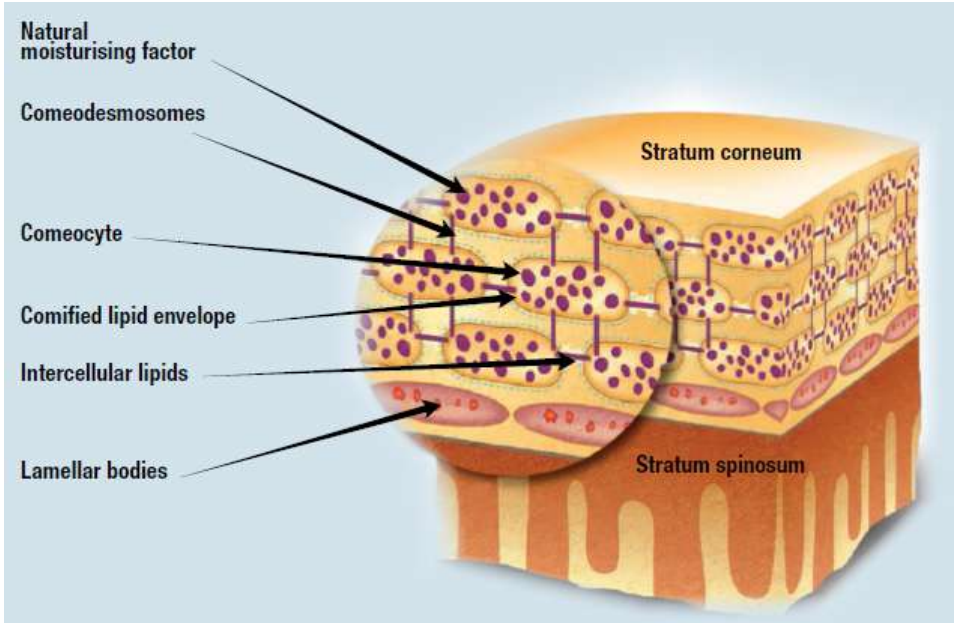
6. Yamamoto A., et al. *Arch Dermatol Res*. 1995;287:214-218

Skin pH: Biophysical Parameter for Assessing Barrier Function in Acne

The structural and functional integrity of the SC is highly dependent on adequate water and pH

Together with the hydrophobic cornified lipid envelope, the intercellular lipids maintain the moisture balance.

Lamellar bodies produce the lipid phase, a mixture of ceramides, cholesterol, and free fatty acids.



Boer M, et al. Postepy Dermatol Alergol. 2016;33(1):1-5.

Is skin pH different in those with acne?

- N=200 with acne; N=200 controls
- Skin pH levels (Skin-pH Meter)

SKIN SURFACE pH IN ACNE VULGARIS: Insights from an Observational Study and Review of the Literature

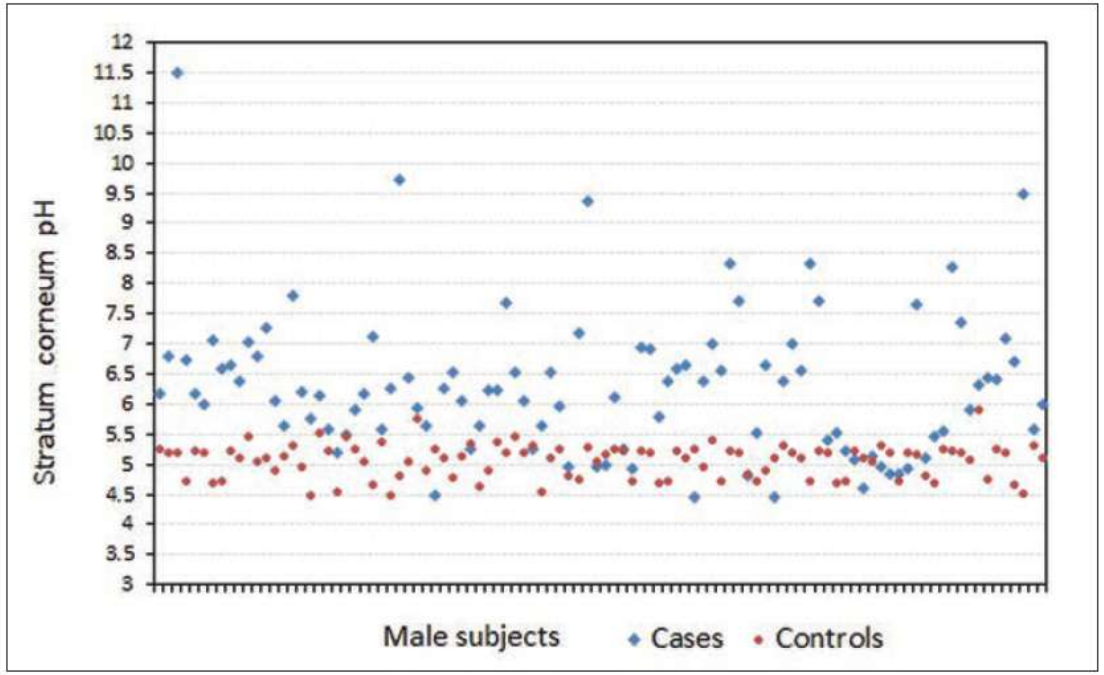
by CHAITRA PRAKASH, MD; PUNEET BHARGAVA, MD; SIDDHI TIWARI, MD; BANASHREE MAJUMDAR, MD; and RISHI KUMAR BHARGAVA, MD

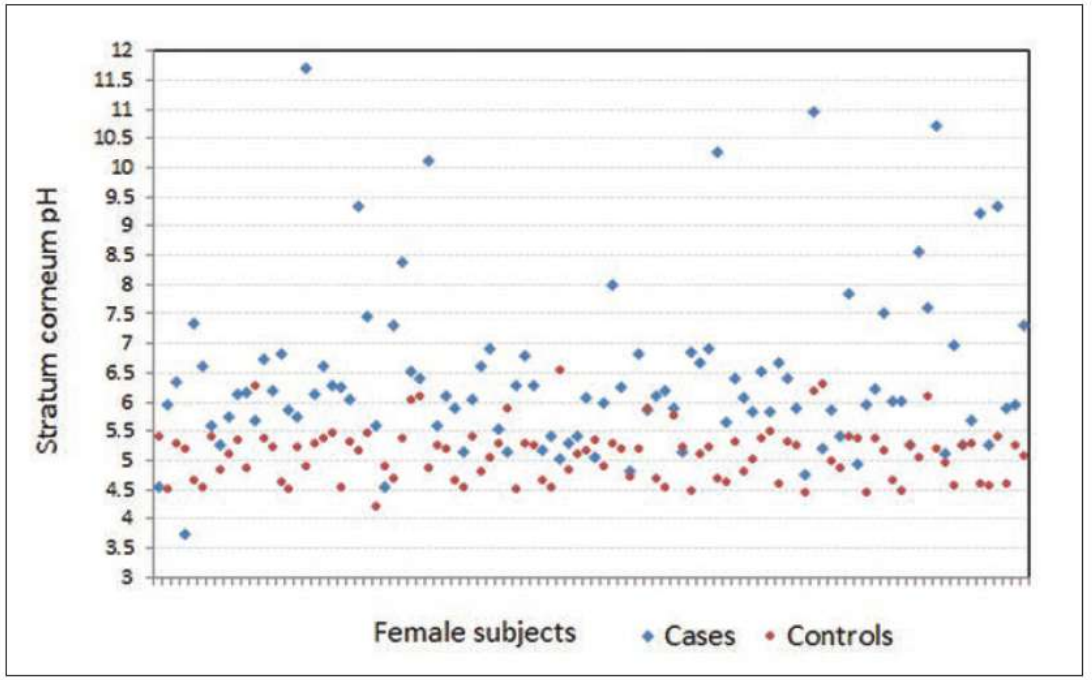
Drs. Prakash, P. Bhargava, Tiwari, and Majumdar are with the Department of Dermatology, Venereology and Leprosy, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, Rajasthan, India. Dr. R.K. Bhargava is with Gandhar Hospital and Research Centre, Jaipur, Rajasthan, India.

J Clin Aesthet Dermatol. 2017;10(7):33–39

Prakash C, et al. J Clin Aesthet Dermatol. 2017;10(7):33–39

Elevated pH in acne patients, both genders





Mean pH 5.09 ± 0.39 controls versus 6.35 ± 1.30 acne cases ($p<0.001$).

Prakash C, et al. J Clin Aesthet Dermatol. 2017;10(7):33–39

Is skin pH different in acne patients due to gender or age?

Skin Research and Technology 2013; 19: 131–136
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doi: 10.1111/srt.12023

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Published by Blackwell Publishing Ltd
Skin Research and Technology

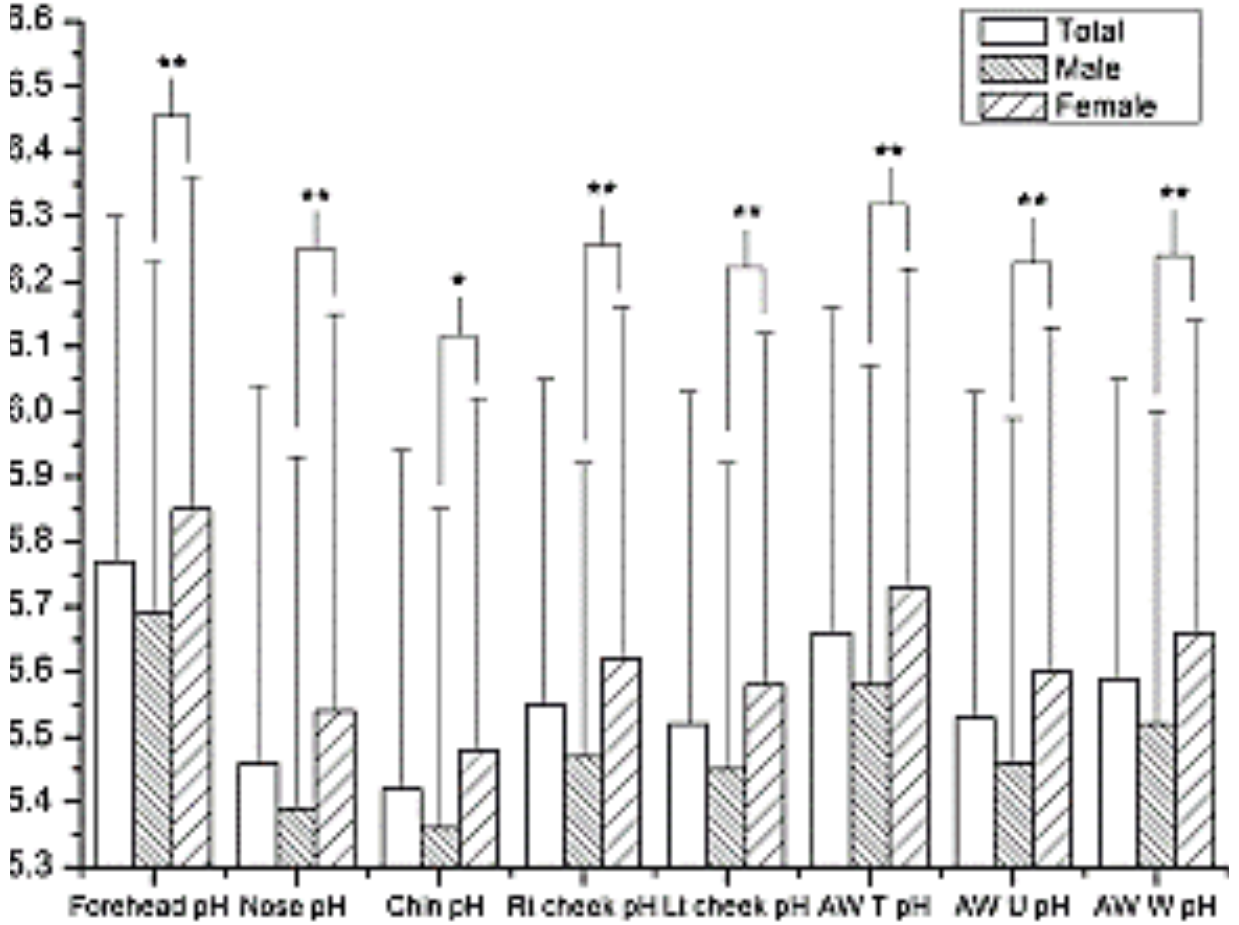
The skin surface pH and its different influence on the development of acne lesion according to gender and age

S. H. Youn[1], C. W. Choi[2], J. W. Choi[1] and S. W. Youn[1]

[1]Department of Dermatology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi, Korea and [2]Department of Dermatology, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Korea

Youn SH, et al. Skin Research Technol 2013;19:131-136.

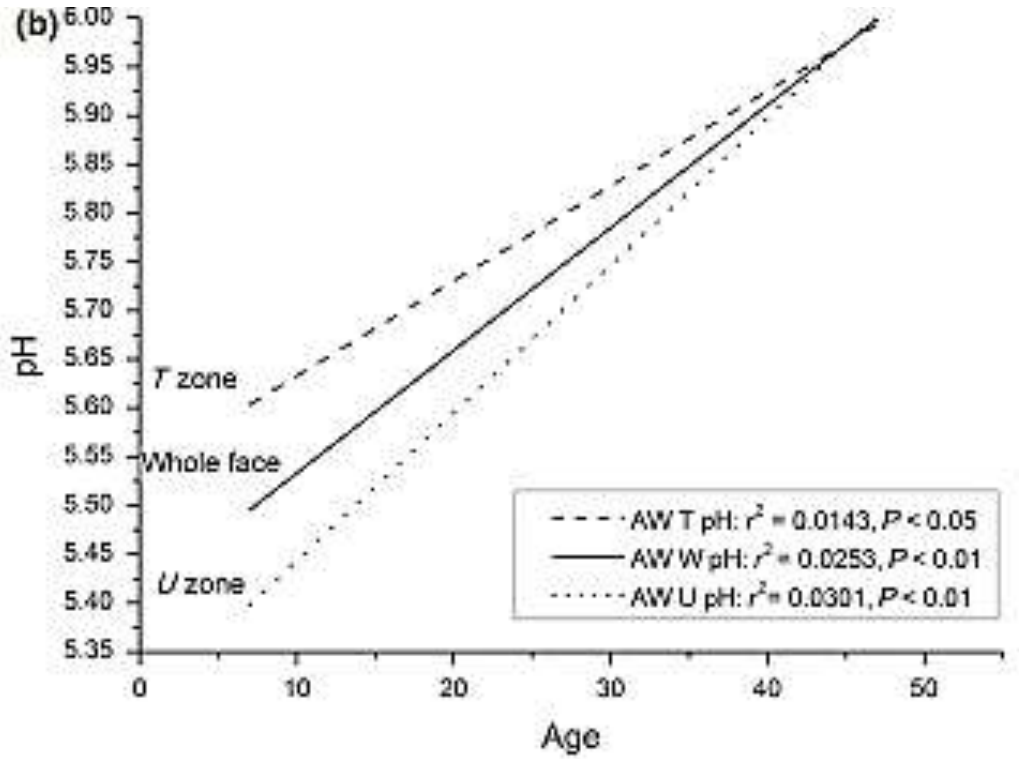
Higher skin pH in females – all facial zones



Youn SH, et al. Skin Research Technol 2013;19:131-136.

Elevated skin pH with age in females

- No significant difference in males



Youn SH, et al. Skin Research Technol 2013;19:131-136.

Negative correlations for skin pH and acne varies with gender and lesion type

- For FEMALES
  - Negative correlation skin pH and comedones and inflammatory acne lesions at T zone

- For MALES
  - Negative correlation skin pH and inflammatory acne lesions at T zone

TABLE 2. The Pearson's correlation coefficients between the area-weight pH and the number of acne lesions on the each zone of the face

Number of acne lesions	The Pearson's correlation coefficients		
	Total	Male	Female
T com	−0.032 (0.455)	0.052 (0.394)	−0.137 (0.025)*
T inf	−0.019 (0.652)	0.131 (0.032)*	−0.123 (0.043)*
T total	−0.029 (0.495)	0.101 (0.099)	−0.143 (0.019)*
U com	0.037 (0.746)	−0.013 (0.833)	0.076 (0.211)
U inf	−0.013 (0.758)	0.052 (0.393)	−0.035 (0.565)
U total	0.013 (0.756)	0.024 (0.697)	0.030 (0.619)
W com	−0.015 (0.722)	0.012 (0.846)	−0.058 (0.343)
W inf	−0.033 (0.443)	0.094 (0.124)	−0.114 (0.061)
W total	−0.026 (0.540)	0.06 (0.328)	−0.091 (0.135)

Data presented as Pearson's correlation coefficient (*P*-value).
*$P < 0.05$, correlation test.

T-zone (the forehead, nose and chin); com, comedones; inf, inflammatory lesions; U, U-zone (both cheeks); W, whole face.

Youn SH, et al. Skin Research Technol 2013;19:131-136.

Skin barrier in acne: Summary

- Acne-affected skin has been shown to have an elevated pH compared to normal skin and may be more prone to irritation resulting from acne treatment.[1]
- Systemic and topical medications, such as retinoids, antibiotics, and benzoyl peroxide are associated with skin-barrier alteration, causing irritation and dry skin conditions[2,3]
- These unwanted effects can reduce adherence to treatment and therapeutic outcomes[2-4]
- Over-the-counter non-comedogenic cleansers and moisturizers have been successfully used to reduce skin irritation[4,5]
- However, some of these products, such as those with a high pH, are shown to interfere with the efficacy of topical treatments[4,5]

1.Prakash C, et al. J Clin Aesthet Dermatol. 2017;10(7):33–39.
2.Nast A et al. *J Eur Acad Dermatol Venereol.* 2016;30(8):1261-8.
3.Gollnick HP. *J Eur Acad Dermatol Venereol.* 2015;29 Suppl 5:1-7.
4.Lynde CW, Andriessen A, Barankin B, et al. *J Cosmet Dermatol.* 2014;7(3):18-26.
5.Lynde CW, Tan J, Skotnicki S, Andriessen A, et al. J Drugs Dermatol 2019;18(12) S-1:1-16.

Skin barrier in acne: Summary, cont.

- Acne is associated with skin barrier dysfunction, which presents with a reduced water binding capacity due to multiple factors.
- Treatment can exacerbate this dysfunction, leading to dry skin and irritation, which in turn leads to poor treatment adherence and suboptimal outcomes.
- As an adjunct to treatment for acne, pH-balanced and ceramide-containing cleansers and moisturizers may help maintain skin barrier function.

Lynde CW, Andriessen A, Barankin B, et al. *J Cosmet Dermatol.* 2014;7(3):18-26.

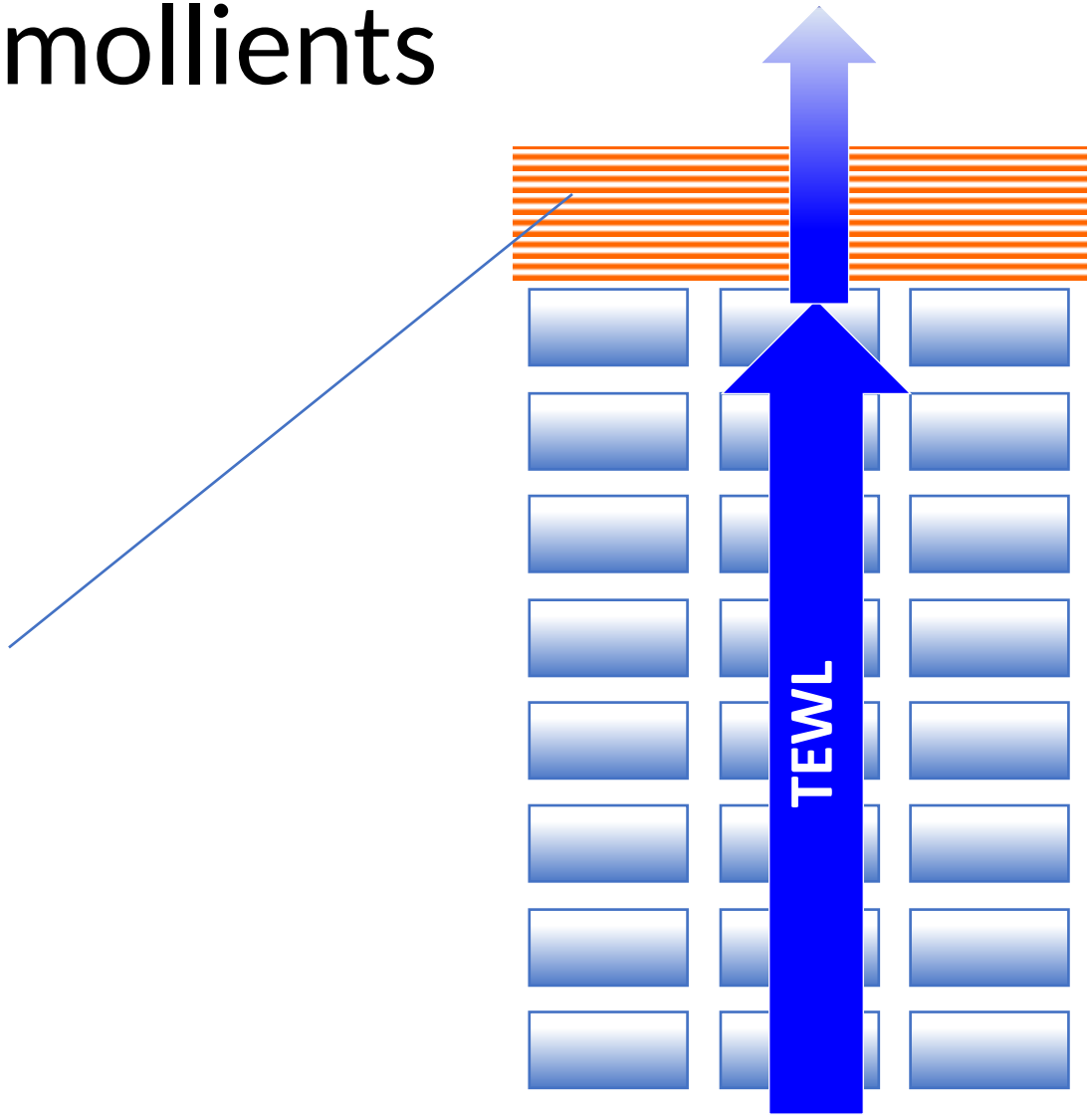
Skincare for maintaining a functional skin barrier

Not all emollient formulations are the same

Simple occlusive emollients

Artificial restoration of the barrier in dry skin:

1. Occlusive emollients trap moisture in the skin, transiently increasing hydration
2. An artificial permeability barrier is formed above the stratum corneum



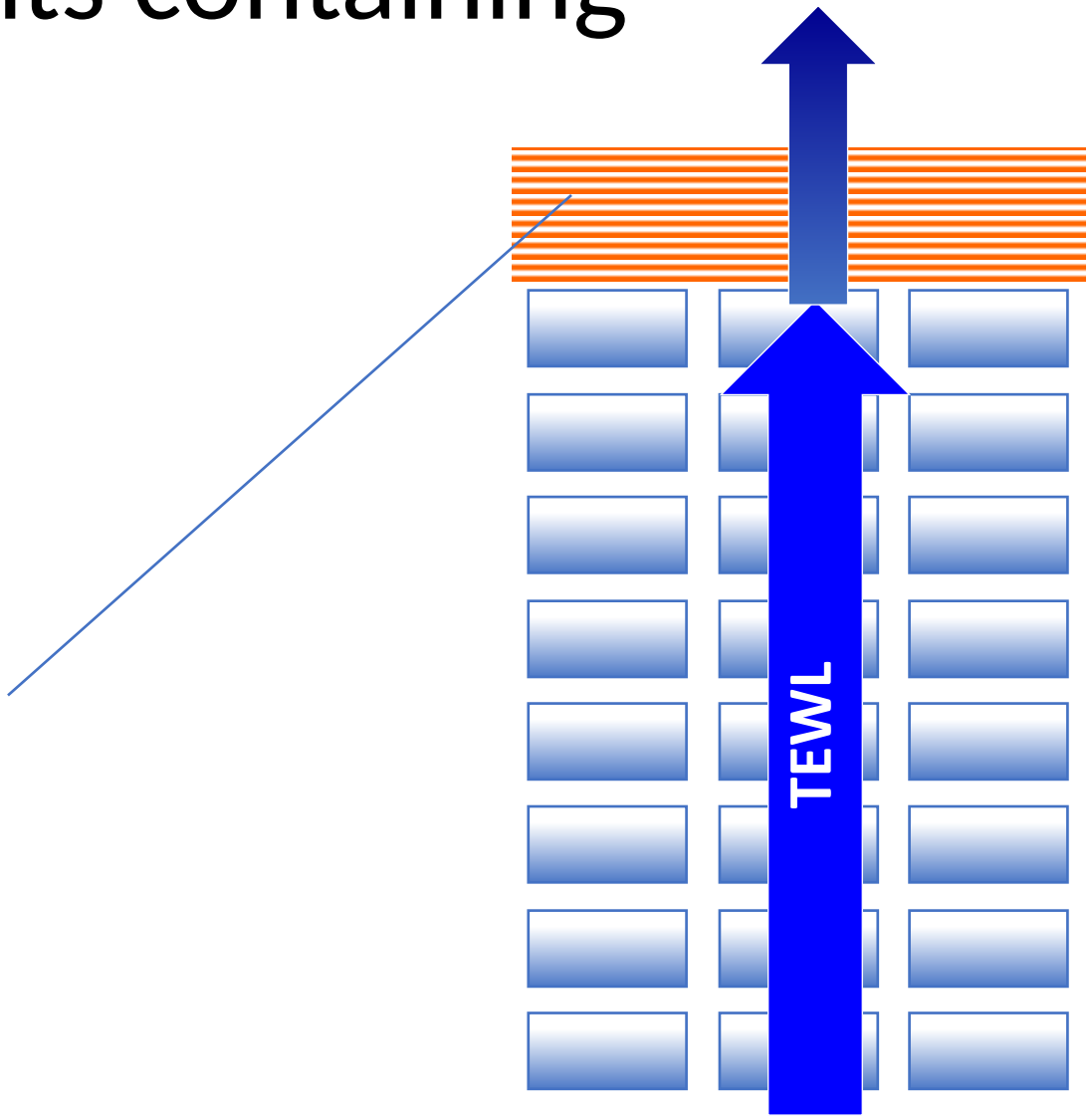
Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Adapted from: Danby SG and Cork MJ; Sheffield Dermatology Research; The University of Sheffield

Occlusive emollients containing humectants

Artificial restoration of the barrier in dry skin:

1. Added humectants help retain moisture in the skin, increasing hydration
2. An artificial permeability barrier is formed above the stratum corneum



Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Adapted from: Danby SG and Cork MJ; Sheffield Dermatology Research; The University of Sheffield

Physiological lipids

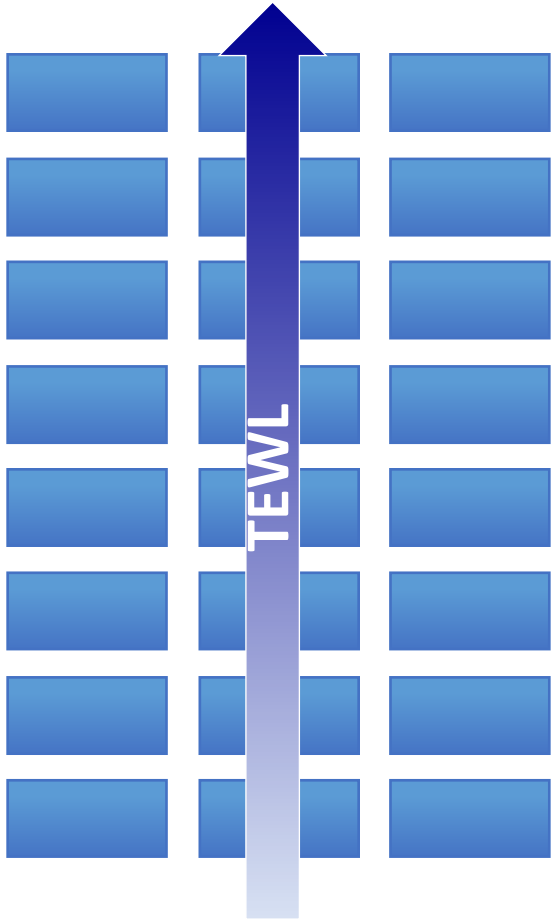
Feature	Component	Property

Lipid lamellae	• Ceramides
	• Cholesterol
	  • Plant sterols (Phytosterols)
	• FFA
	  • linoleic acid
	  • Palmitic acid
		• Improve integrity
		• Moisturizing (via barrier restoration)
		• Decrease SC pH
		• Antimicrobial
		• Enhance barrier development
		  • Modify gene expression

Emollients containing humectants and physiological lipids

Artificial restoration of the barrier in xerotic skin:

1. Added humectants help retain moisture in the skin, increasing hydration
2. Ceramides help to restore normal barrier function



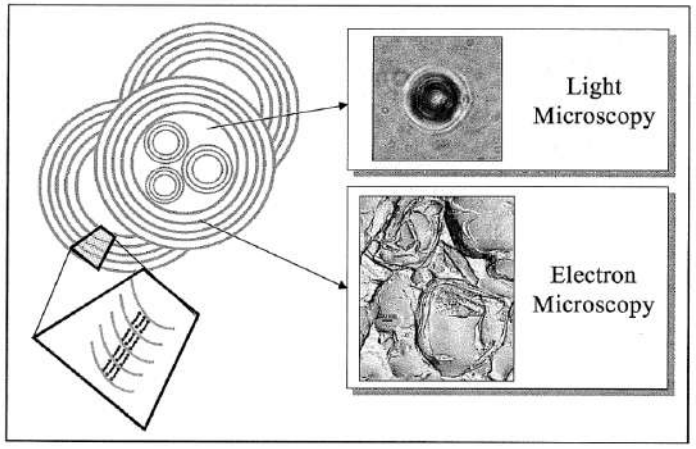
Cork M et al. J Invest Dermatol 2009;129:1892-1908.

Adapted from: Danby SG and Cork MJ; Sheffield Dermatology Research; The University of Sheffield

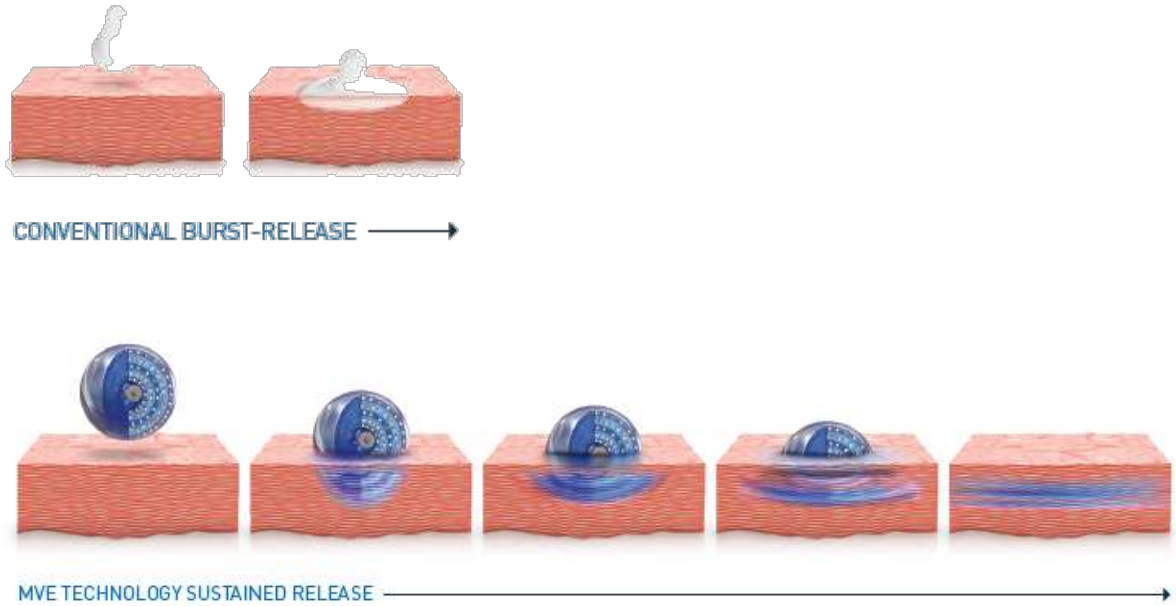
Cerave Multivesicular Emulsion System

MVE is a multi-phase, oil-in-water emulsion system consisting of a series of concentric spheres of oil and water phases

MVE traps ingredients into its oil or water layers and releases them slowly, layer by layer into the skin over time



Progressive release of moisturizing ingredients vs ‘quick-burst’ of traditional emulsion



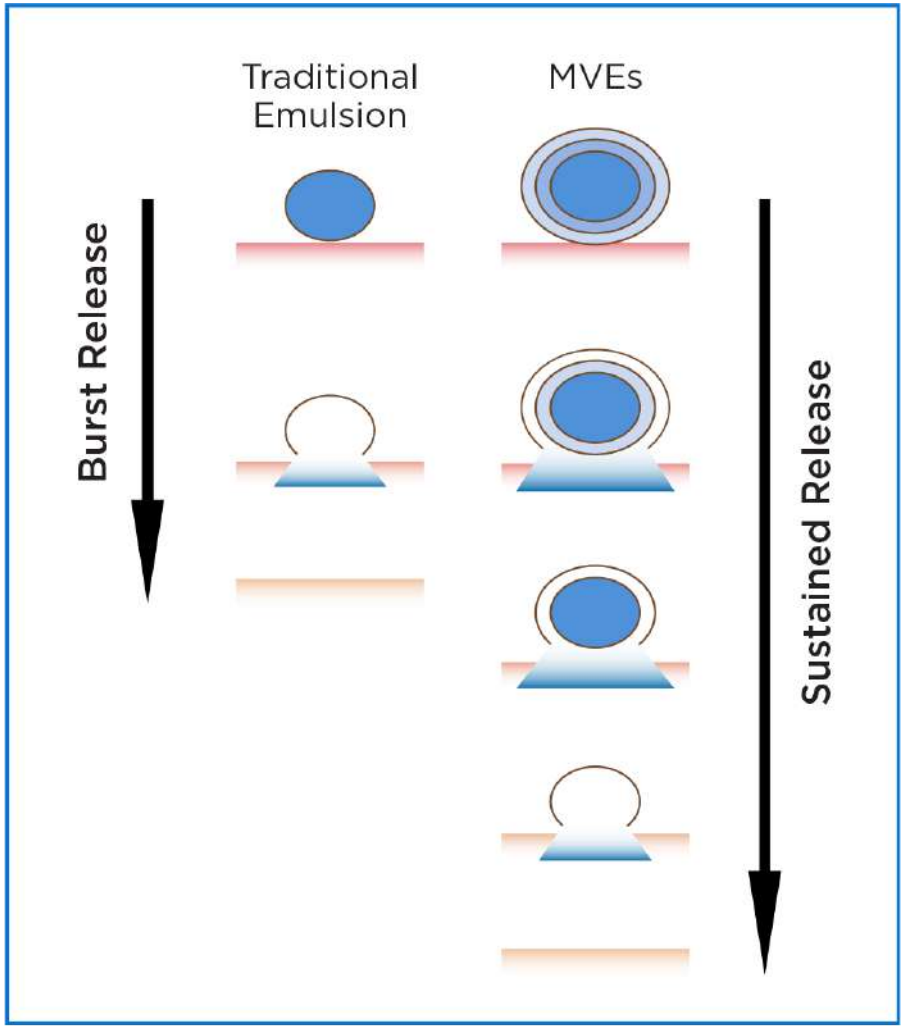
Multivesicular Emulsion (MVE)

Espinoza RA, inventor; HealthPoint, Ltd, assignee., Multivesicular emulsion drug delivery systems (MVE) US patent 6,709,663 B2. March 23, 2004.

MVE versus Traditional Emulsion Ingredient Release

Key Point

- MVE® system of Cerave provides slow and sustained release over time versus the rapid (burst) ingredient release of traditional moisturizers



Multivesicular Emulsion (MVE)

REF-CVE-130. Healthpoint, Inc. May 23, 2005.

Cerave technology and components

FORMULATIONS	ALL	MOST	LIMITED
	— Ingredients integral to formulation or benefit skin barrier — Ceramides EOP, NP, AP — Fragrance-free — Non-irritating; gentle on skin — Hypoallergenic	— Hyaluronic acid — MVE technology — Non-comedogenic	— Parabens — Sulfates — Endocrine disruptors — Dyes — Propylene glycol — Mineral, nut, coconut oils

MVE Technology

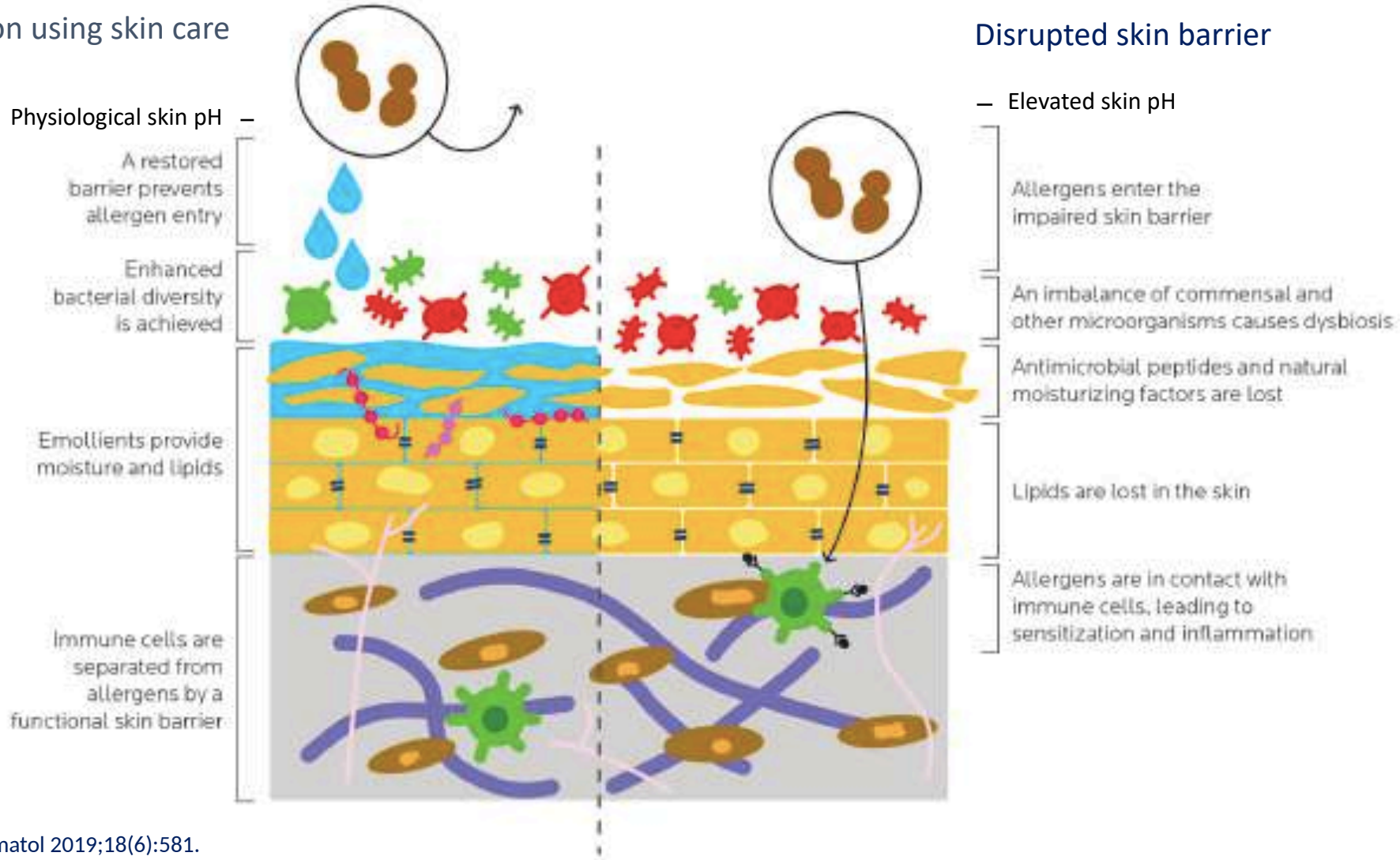
Ceramides

Espinoza RA, inventor; HealthPoint, Ltd, assignee., Multivesicular emulsion drug delivery systems (MVE) US patent 6,709,663 B2. March 23, 2004.

Not all emollient formulations are the same

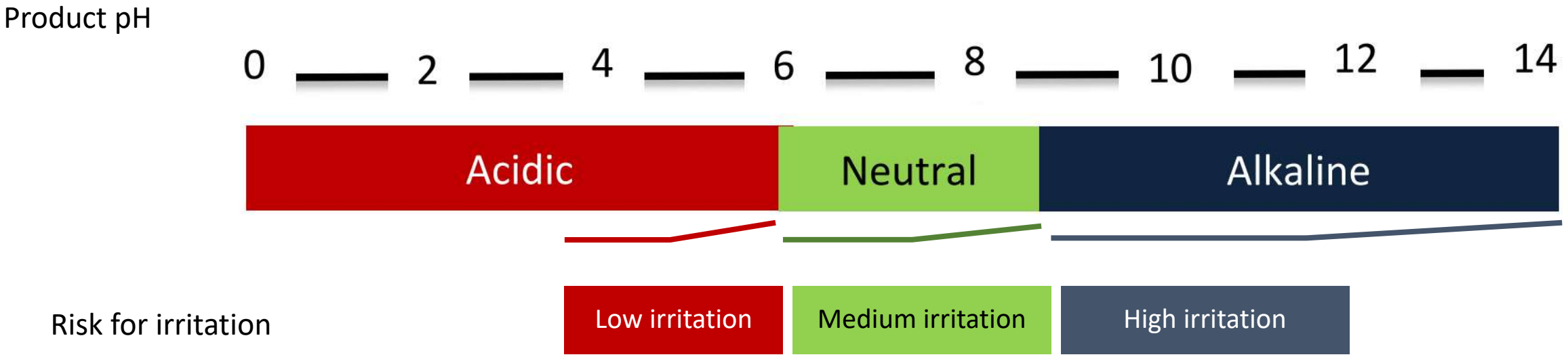
Emollient Property	Effect	Zerobase/Glaxobase	CeraVe
Occlusive barrier	Reduce water loss (TEWL)	Liquid paraffin & white soft paraffin	White soft paraffin
Film formers	Help create a protective barrier		Dimethicone
Humectants	Bind water		Glycerin Sodium Hyaluronate
Physiologic lipids	Components of the stratum corneum lipid matrix		Triglycerides Ceramide NP, AP, EOP Phytosphingosine Cholesterol
Emulsifiers	Mix oil in water	Cetomacrogol, Cetostearyl Alcohol,	Cetearyl alcohol, Cetyl alcohol, Ceteareth-20 Sodium lauroyl lactylate
Nicotinamide	Induce ceramide production		Nicotinamide

Physiological pH cleanser and moisturizer for restoring



Strugar TL, Kuo A, et al. J Drugs Dermatol 2019;18(6):581.

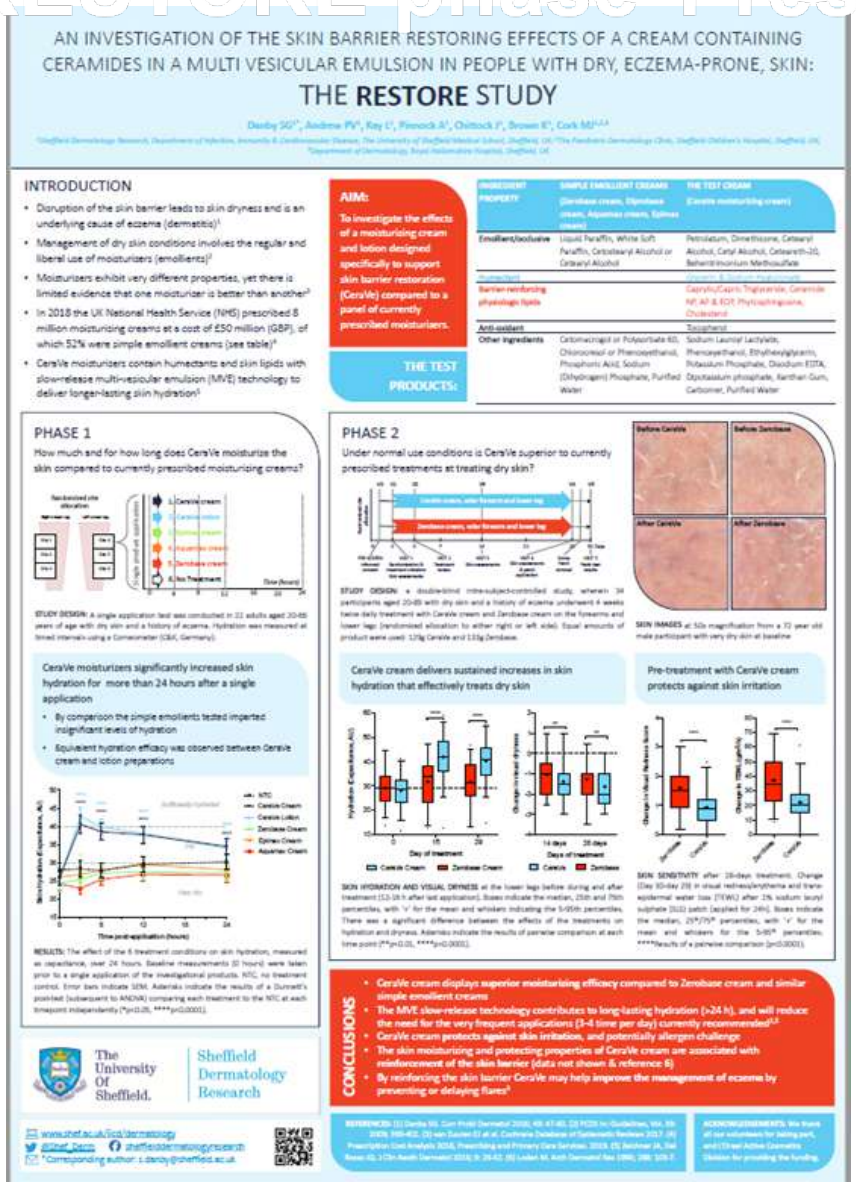
Topical formulation pH: Risk for irritation



Cleansers and moisturizers close to physiological skin surface pH (4.0–6.0) may reduce skin irritation and improve skin barrier function.

Lynde CW, Tan J, Skotnicki S, Andriessen A, et al. J Drugs Dermatol 2019;18(12) S-1:1-16.

RESTORE phase 1 results



AN INVESTIGATION OF THE SKIN BARRIER RESTORING EFFECTS OF A CREAM CONTAINING CERAMIDES IN A MULTI VESICULAR EMULSION IN PEOPLE WITH DRY, ECZEMA-PRONE, SKIN:

THE **RESTORE** STUDY

INTRODUCTION

- Disruption of the skin barrier leads to skin dryness and is an underlying cause of eczema (dermatitis)[1]
- Management of dry skin conditions involves the regular and liberal use of moisturizers (emollients)[2]
- Moisturizers exhibit very different properties, yet there is limited evidence that one moisturizer is better than another[3]
- In 2018 the UK National Health Service (NHS) prescribed 8 million moisturizing creams at a cost of £50 million (GBP), of which 52% were simple emollient creams (see table)[4]
- CeraVe moisturizers contain humectants and skin lipids with slow-release multi-vesicular emulsion (MVE) technology to deliver longer-lasting skin hydration[5]

AIM:

To investigate the effects of a moisturizing cream and lotion designed specifically to support skin barrier restoration (CeraVe) compared to a panel of currently prescribed moisturizers.

THE TEST PRODUCTS:

INGREDIENT PROPERTY	SIMPLE EMOLLIENT CREAMS (Zerobase cream, Diprobase cream, Aqueous cream, Epimax cream)	THE TEST CREAM (CeraVe moisturizing cream)
Emollient/occlusive	Liquid Paraffin, White Soft Paraffin, Cetostearyl Alcohol or Cetearyl Alcohol	Petrolatum, Dimethicone, Cetearyl Alcohol, Cetyl Alcohol, Ceteareth-20, Behentrimonium Methosulfate
Humectant		Glycerin & Sodium Hyaluronate
Barrier-reinforcing physiologic lipids		Caprylic/Capric Triglyceride, Ceramide NP, AP & EOP, Phytosphingosine, Cholesterol
Anti-oxidant		Tocopherol
Other ingredients	Carbomer/acrylol or Polysorbate 60, Chlorocresol or Phenoxyethanol, Phosphoric Acid, Sodium (Dihydrogen) Phosphate, Purified Water	Sodium Lauroyl Lactylate, Phenoxyethanol, Ethylhexylglycerin, Potassium Phosphate, Disodium EDTA, Dipotassium phosphate, Xanthan Gum, Carbomer, Purified Water

PHASE 1

How much and for how long does CeraVe moisturize the skin compared to currently prescribed moisturizing creams?

STUDY DESIGN: A single application test was conducted in 22 adults aged 20-66 years of age with dry skin and a history of eczema. Hydration was measured at timed intervals using a Corneometer (C&K, Germany).

CeraVe moisturizers significantly increased skin hydration for more than 24 hours after a single application

- By comparison the simple emollients tested imparted insignificant levels of hydration
- Equivalent hydration efficacy was observed between CeraVe cream and lotion preparations

RESULTS: The effect of the 6 treatment conditions on skin hydration, measured as capacitance, over 24 hours. Baseline measurements (0 hours) were taken prior to a single application of the investigational products. NTC, no treatment control. Error bars indicate SEM. Asterisks indicate the results of a Dunnett's post-test (subsequent to ANOVA) comparing each treatment to the NTC at each timepoint independently (*p<0.05, ****p<0.0001).

PHASE 2

Under normal use conditions is CeraVe superior to currently prescribed treatments at treating dry skin?

STUDY DESIGN: a double-blind intra-subject-controlled study, wherein 34 participants aged 20-65 with dry skin and a history of eczema underwent 4 weeks twice daily treatment with CeraVe cream and Zerobase cream on the forearms and lower legs (randomized allocation to either right or left side). Equal amounts of product were used: 128g CeraVe and 132g Zerobase.

SKIN IMAGES at 52x magnification from a 72 year old male participant with very dry skin at baseline

CeraVe cream delivers sustained increases in skin hydration that effectively treats dry skin

Pre-treatment with CeraVe cream protects against skin irritation

SKIN HYDRATION AND VISUAL DRYNESS at the lower legs (before dosing and after treatment (13-28 h after last application). Boxes indicate the median, 25th and 75th percentiles, with 'x' for the mean and whiskers indicating the 5-95th percentiles. There was a significant difference between the effects of the treatments on hydration and dryness. Asterisks indicate the results of pairwise comparison at each time point (**p<0.01, ****p<0.0001).

SKIN SENSITIVITY after 28-days treatment. Change (Day 30-day 29) in visual redness/erythema and trans-epidermal water loss (TEWL) after 1% sodium lauryl sulphate (SLS) patch (applied for 24h). Boxes indicate the median, 25th/75th percentiles, with 'x' for the mean and whiskers for the 5-95th percentiles. ****results of a pairwise comparison (p<0.0001).

CONCLUSIONS

- CeraVe cream displays superior moisturising efficacy compared to Zerobase cream and similar simple emollient creams
- The MVE slow-release technology contributes to long-lasting hydration (>24 h), and will reduce the need for the very frequent applications (3-4 time per day) currently recommended[6,7]
- CeraVe cream protects against skin irritation, and potentially allergen challenge
- The skin moisturizing and protecting properties of CeraVe cream are associated with reinforcement of the skin barrier (data not shown & reference 8)
- By reinforcing the skin barrier CeraVe may help improve the management of eczema by preventing or delaying flares[9]

REFERENCES: [1] Danby SG[1], Andrew PV[1], Kay LJ[1], Pinnock A[1], Chittock J[1], Brown K[1], Cork MJ[1,2,3]

ACKNOWLEDGEMENTS: We thank all our volunteers for taking part, and L'Oreal Active Cosmetics Division for providing the funding.

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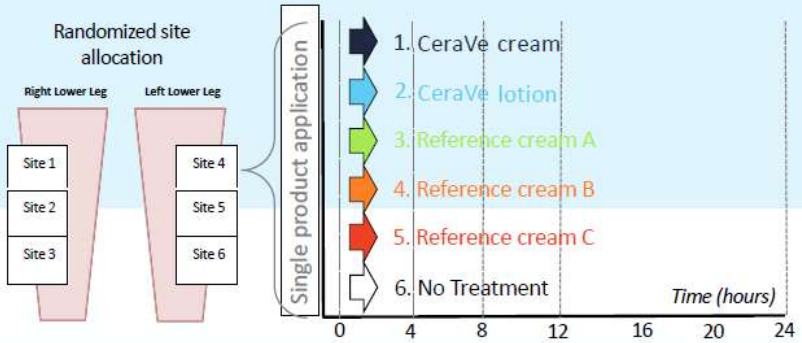
*Corresponding author: s.danby@sheffield.ac.uk

PHASE 1

How much and for how long do the test products **moisturize the skin** compared to currently used emollient creams?



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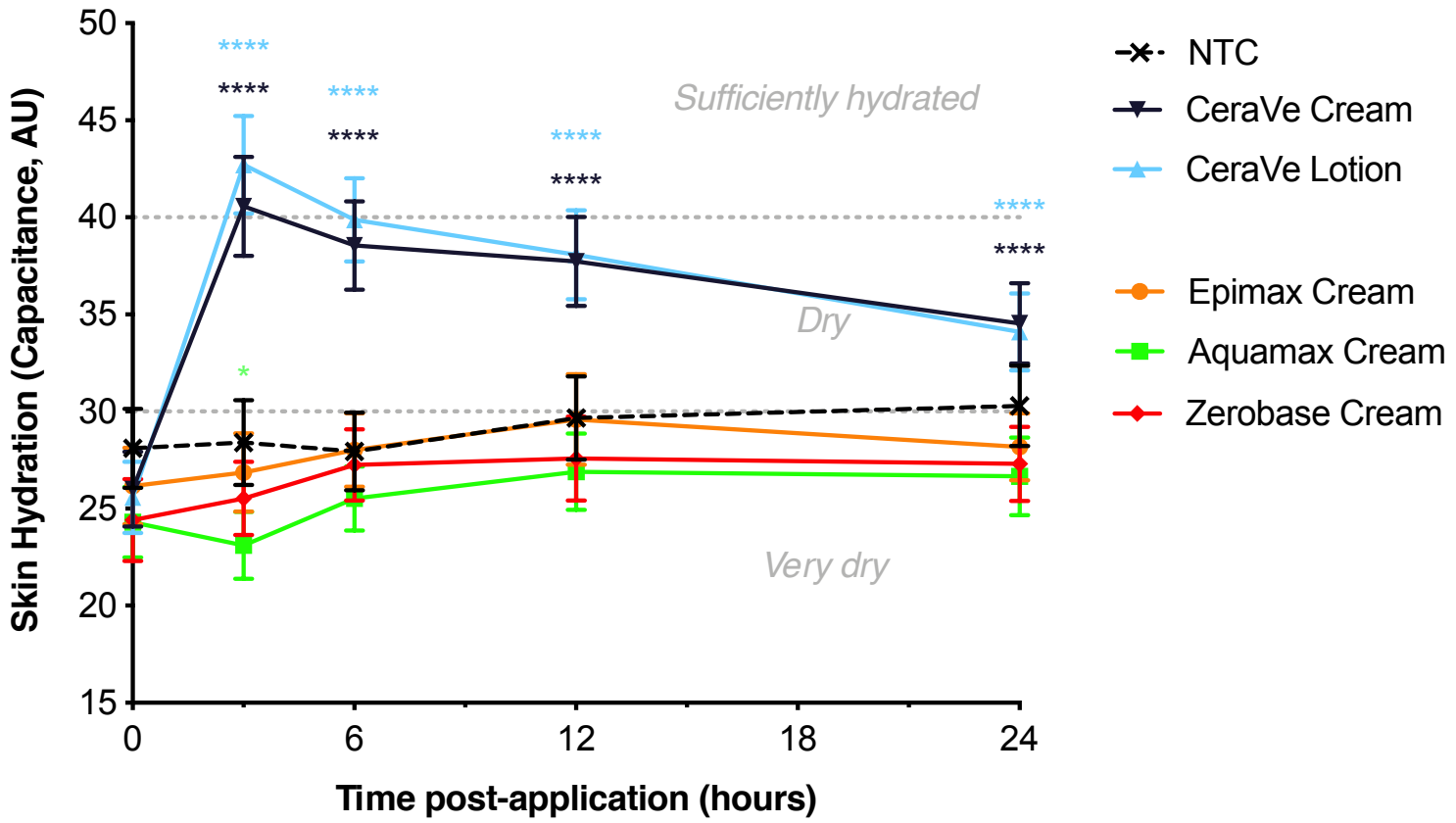
- By comparison the simple emollients tested imparted insignificant levels of hydration
- Equivalent hydration efficacy was observed between CeraVe cream and lotion preparations

CONFIDENTIAL: Sheffield Dermatology Research, The University of Sheffield.

RESTORE phase 1 results



Professor Michael Cork – Restore 2 Study

The University Of Sheffield.

[1]Sheffield Dermatology Research, Department of Infection, Immunity & Cardiovascular Disease, The University of Sheffield Medical School, Sheffield, UK; [2]The Paediatric Dermatology Clinic, Sheffield Children's Hospital, Sheffield, UK; [3]Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK

AN INVESTIGATION OF THE SKIN BARRIER RESTORING EFFECTS OF A CREAM CONTAINING CERAMIDES IN A MULTI VESICULAR EMULSION IN PEOPLE WITH DRY, ECZEMA-PRONE, SKIN:

THE **RESTORE** STUDY PHASE 2

Danby SG[1*], Andrew PV[1], Kay LJ[1], Pinnock A[1], Chittock J[1], Brown K[1], Cork MJ[1,2,3]

Sheffield Dermatology Research

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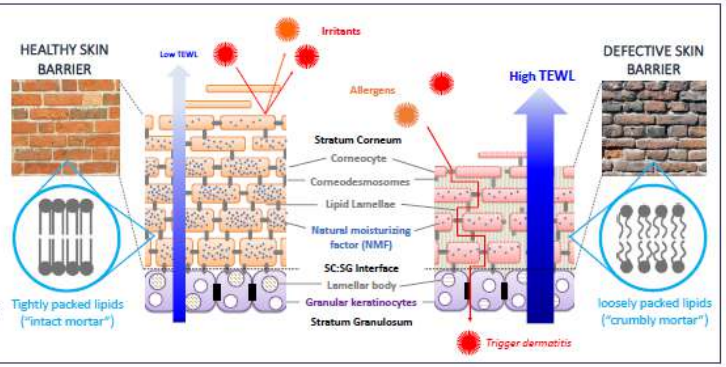
Sheffielddermatologyresearch
www.shef.ac.uk/iicd/dermatology

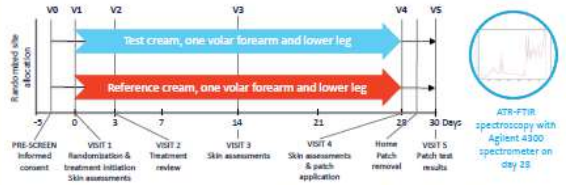
INTRODUCTION

- The skin of atopic dermatitis (AD) patients is characterized by abnormal stratum corneum (SC) lipid levels [1,2,3].
- Consequently, the lamellar matrices are disrupted and skin barrier function is diminished, increasing skin sensitivity to irritants and allergens.

OBJECTIVE: To investigate whether a cream containing skin lipids (ceramides, triglycerides & cholesterol) in a multi-vesicular emulsion [4] (the test cream) can reinforce the skin barrier.



METHODS

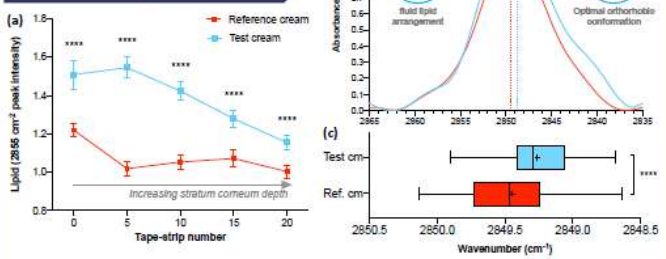


- A double-blind intra-subject-controlled study involving 34 participants aged 20-89 with dry eczema-prone skin
- 4 weeks twice-daily treatment of the right or left forearms and lower legs
- Randomized allocation of the test cream or the reference cream (a basic SLS-free emollient commonly prescribed by National Health Service (UK) [5]

CONCLUSIONS

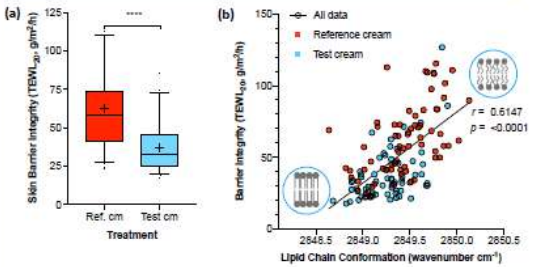
- The test cream delivers essential skin lipids deep within the SC where they reinforce the skin barrier and protect the skin from dryness and irritation.
- Compared to the reference emollient cream, commonly prescribed in the UK, the test cream is highly suited to the management of dry, sensitive, skin.

The test cream increased lipid levels deep within the stratum corneum and enhanced lipid structure



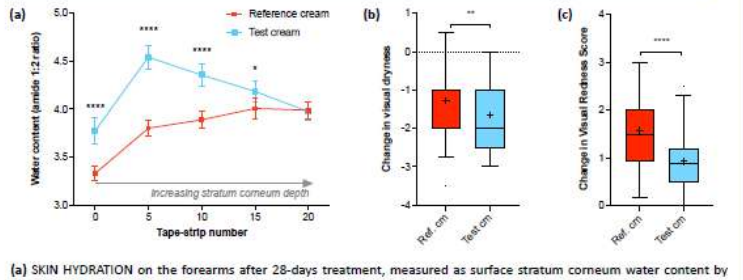
(a) LIPID CONCENTRATION (relative to amide II) within the stratum corneum (forearm) measured by FTIR spectroscopy after 28 days of treatment **(b)** LIPID CHAIN ORDER is indicated by the centre of gravity (COG) of the FTIR spectrum lipid band at 2850 cm^{-1}[6]. **(c)** MEAN LIPID CHAIN ORDERING across the stratum corneum. Asterisk indicate results of pairwise comparison (****p<0.0001)

Enhanced lipid structure was significantly associated with improved skin barrier integrity



(a) SKIN BARRIER INTEGRITY on the forearm after 28 days treatment. TEWL20, trans-epidermal water loss measured after 20 consecutive tape-strips to experimentally disrupt the skin. **(b)** CORRELATION between skin barrier integrity and lipid chain conformation. ****results of a pairwise comparison (p<0.0001)

Improved skin barrier structure was accompanied by increased hydration, decreased dryness and reduced sensitivity to irritants



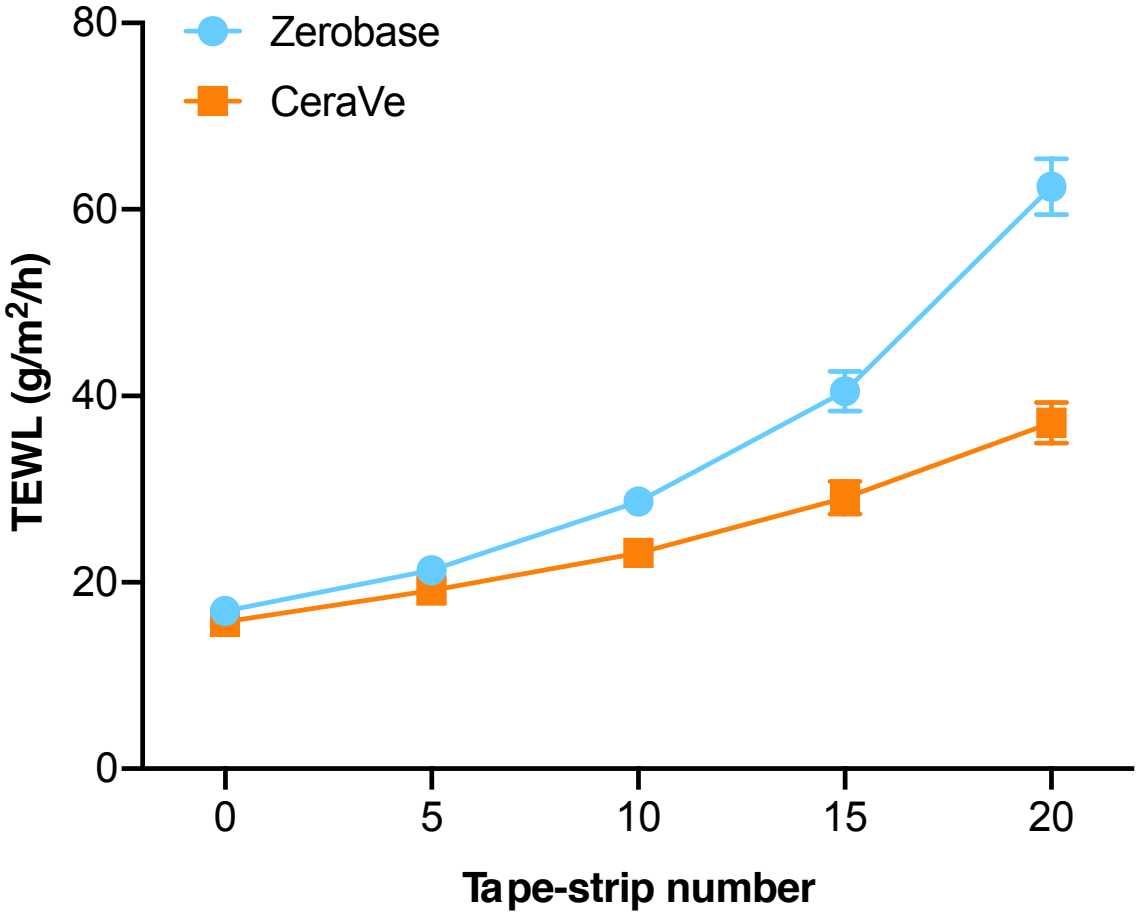
(a) SKIN HYDRATION on the forearms after 28-days treatment, measured as surface stratum corneum water content by FTIR spectroscopy during tape-stripping [7]. **(b)** VISUAL DRYNESS scored (0-4) on the lower legs after 28 days treatment. **(c)** SKIN SENSITIVITY after 28-days treatment. Change (Day 30-day 29) in visual redness/erythema after 1% sodium lauryl sulphate (SLS) patch (applied for 24h). Boxes indicate the median, 25th/75th percentiles, with '+' for the mean and whiskers for the 5-95th percentiles. Asterisks indicate the results of pairwise comparison (*p<0.05, **p<0.01, ****p<0.0001).

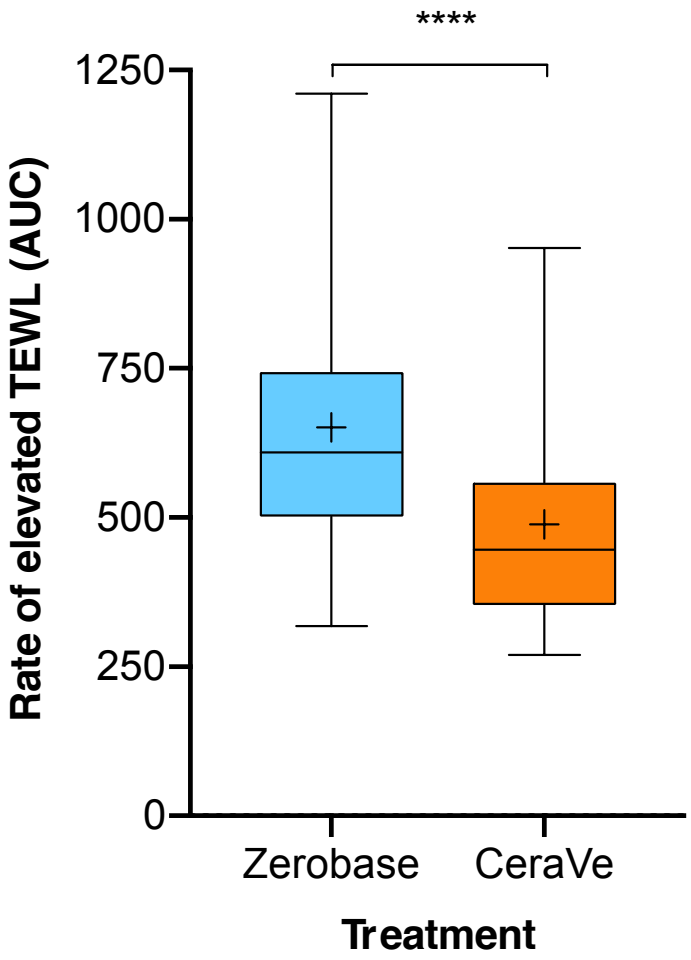
ACKNOWLEDGEMENTS: We thank all our volunteers for taking part, and L'Oreal Active Cosmetics Division for providing the funding.

REFERENCES: [1] Danby SG. *Curr Probl Dermatol* 2016; 49: 47-60. [2] Di Nardo A et al. *Acta Derm Venereol* 1998; 78: 27-30. [3] van Smeden J, Bouwstra JA. *Curr Probl Dermatol* 2016; 49: 8-26. [4] Zeichner JA and Del Rosso JQ. J Clin Aesthetic Derm. 2016; 9: 26-32. [5] Prescription Cost Analysis 2018, *Prescribing and Primary Care Services* 2019. [6] Boncheva M et al. *Biochimica et Biophysica Acta* 2008; 1778: 1344-55. [7] Ring a et al. *Skin Research and Technology* 2006; 12: 18-23. 1.

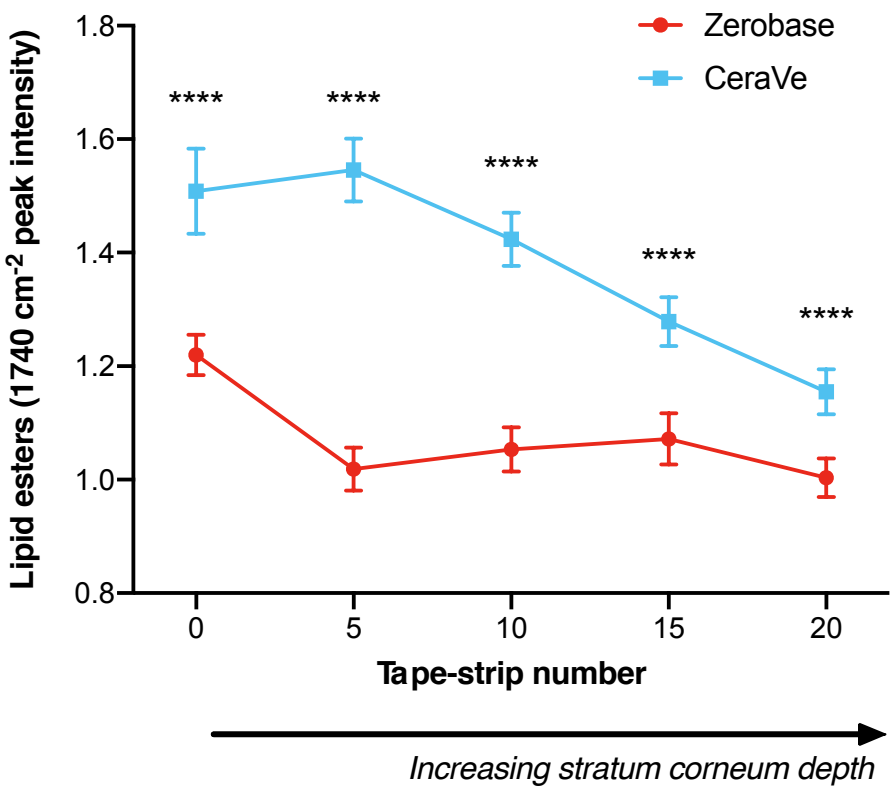
COI DISCLOSURE: SD has received research grants from and/or has consulted with Almirall, Hyphens Pharma, Leo Pharma, L'Oreal, Johnson & Johnson, Perrigo, Pfizer, and Roito. MJC is an investigator and consultant for Astellas, Boots, Galapagos, Galderma, Hyphens, Johnson & Johnson, Leo Pharma, L'Oreal, Menlo, Novartis, Oxagen, Pfizer, Procter & Gamble, Perrigo, Regeneron, and Sanofi Genzyme, and consultant to Abbvie, Galderma, Dermavant, and Reckitt Benckiser. PA, LJS, AP, JC, and KB, and have nothing to declare.

RESTORE: Skin Barrier Integrity





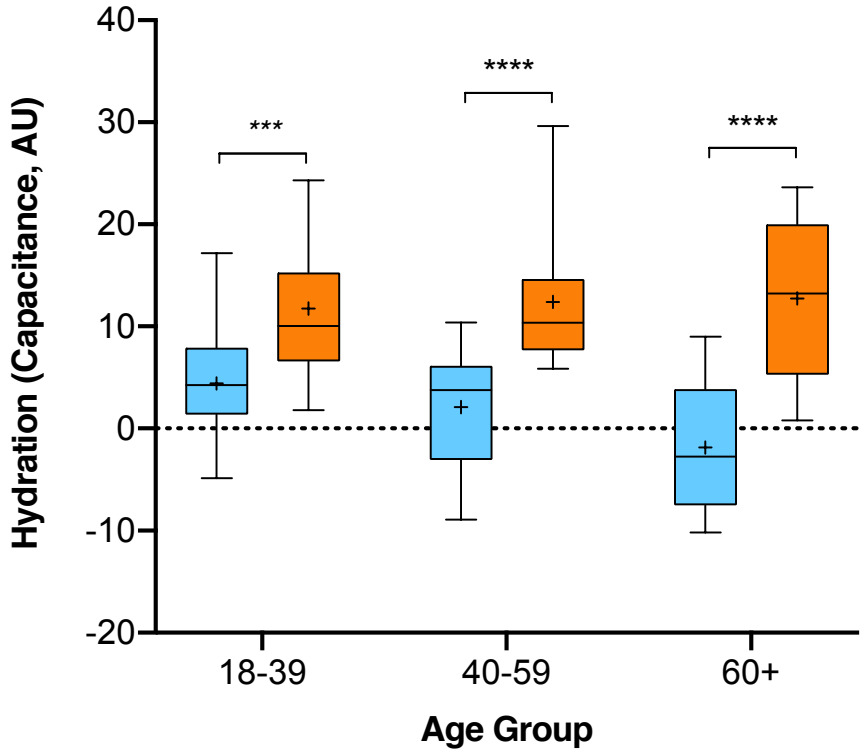
RESTORE phase 2: CeraVe treatment delivers more lipids into the stratum corneum



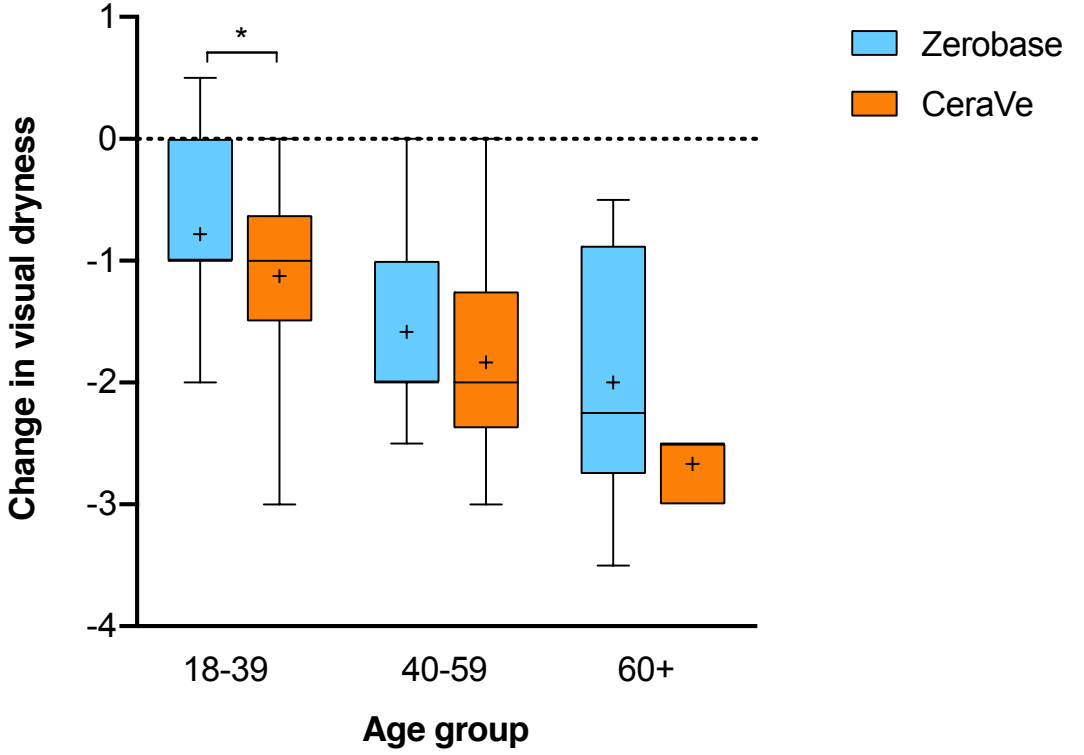
- *CeraVe appears to deliver more lipids into the skin.*
- *The lipid measurement includes fatty acids and hydrocarbons such a paraffin for example*

RESTORE: Skin Moisturization Stratified by Age Group

Stratum corneum hydration



Visual skin dryness

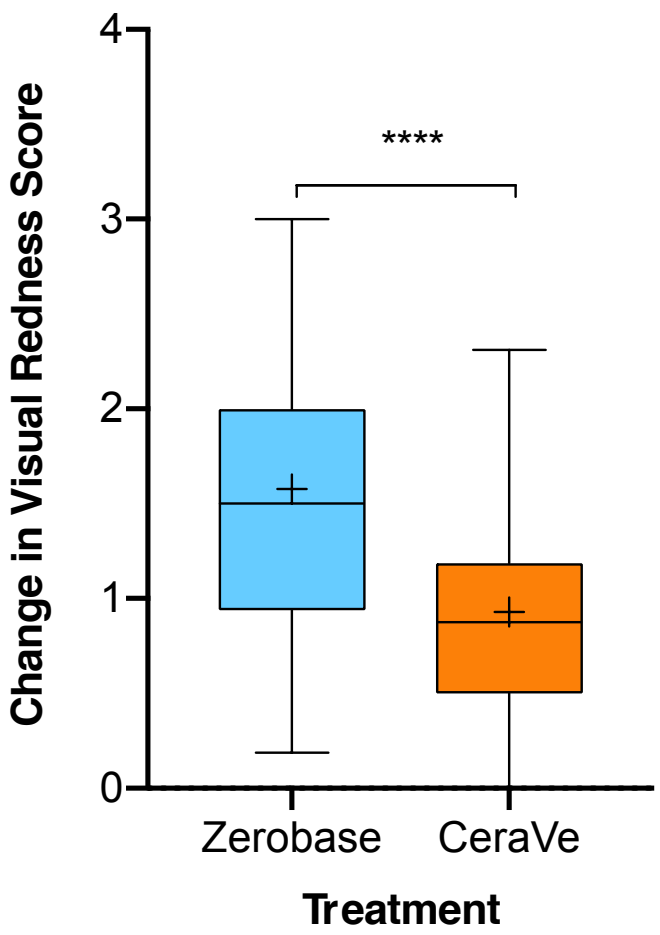


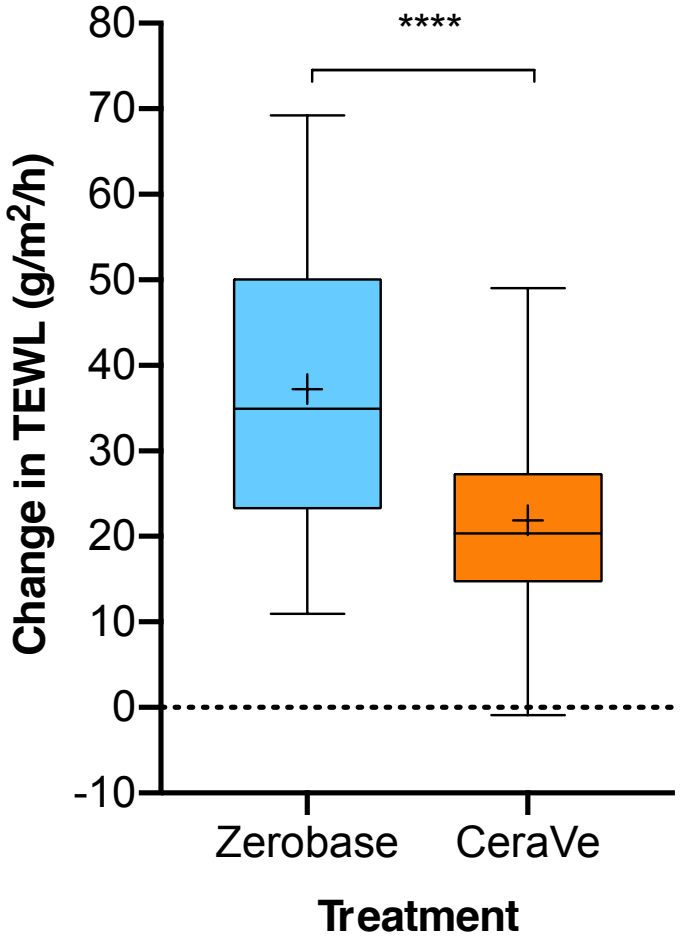
CONFIDENTIAL: Sheffield Dermatology Research, The University of Sheffield.

RESTORE: Skin Sensitivity

Patch testing:

- SLS (1%) patches applied on Day 29.
- Patches removed Day 30
- Reaction quantified at Day 31





What does the RESTORE study shows so far?

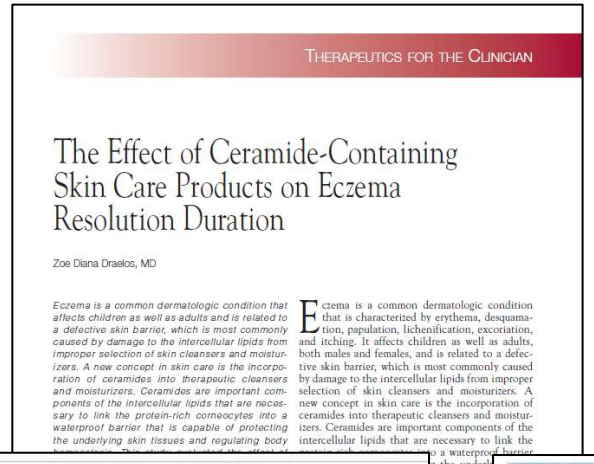
- CeraVe delivers ‘barrier-reinforcement’ compared to Zerobase:
  - Increased skin hydration/water content
  - Decreased skin dryness
  - Increased ‘protection’ from irritants
- CeraVe is more cosmetically acceptable than Zerobase

The headline result

Supported by FTIR, tape strip TEWL and SLS irritation data

The effects that patients can relate to

CeraVe Technology – Backed by Clinical Evidence



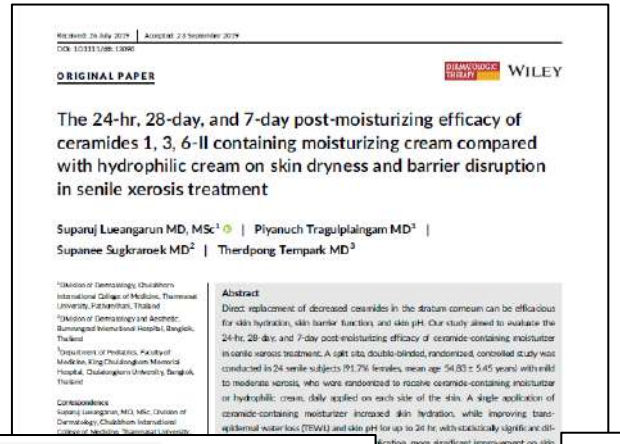
THERAPEUTICS FOR THE CLINICIAN

The Effect of Ceramide-Containing Skin Care Products on Eczema Resolution Duration

Zoe Diana Draelos, MD

Eczema is a common dermatologic condition that affects children as well as adults and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body

Eczema is a common dermatologic condition that is characterized by erythema, desquamation, papulation, lichenification, excoriation, and itching. It affects children as well as adults, both males and females, and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the



ORIGINAL PAPER

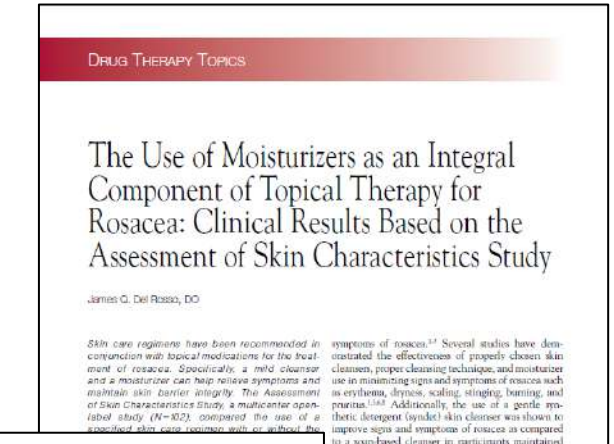
WILEY

The 24-hr, 28-day, and 7-day post-moisturizing efficacy of ceramides 1, 3, 6-II containing moisturizing cream compared with hydrophilic cream on skin dryness and barrier disruption in senile xerosis treatment

Suparuj Lueangarun MD, MSc[1] | Piyanuch Tragulplaingam MD[1] | Supanee Sugkraroek MD[2] | Therdpong Tempark MD[3]

Abstract

Direct replacement of decreased ceramides in the stratum corneum can be efficacious for skin hydration, skin barrier function, and skin pH. Our study aimed to evaluate the 24-hr, 28-day, and 7-day post-moisturizing efficacy of ceramide-containing moisturizer in senile xerosis treatment. A split site, double-blinded, randomized, controlled study was conducted in 24 senile subjects (91.7% females, mean age 54.83 ± 5.45 years) with mild to moderate xerosis, who were randomized to receive ceramide-containing moisturizer or hydrophilic cream, daily applied on each side of the skin. A single application of ceramide-containing moisturizer increased skin hydration, while improving transepidermal water loss (TEWL) and skin pH for up to 24 hr, with statistically significant dif-



DRUG THERAPY TOPICS

The Use of Moisturizers as an Integral Component of Topical Therapy for Rosacea: Clinical Results Based on the Assessment of Skin Characteristics Study

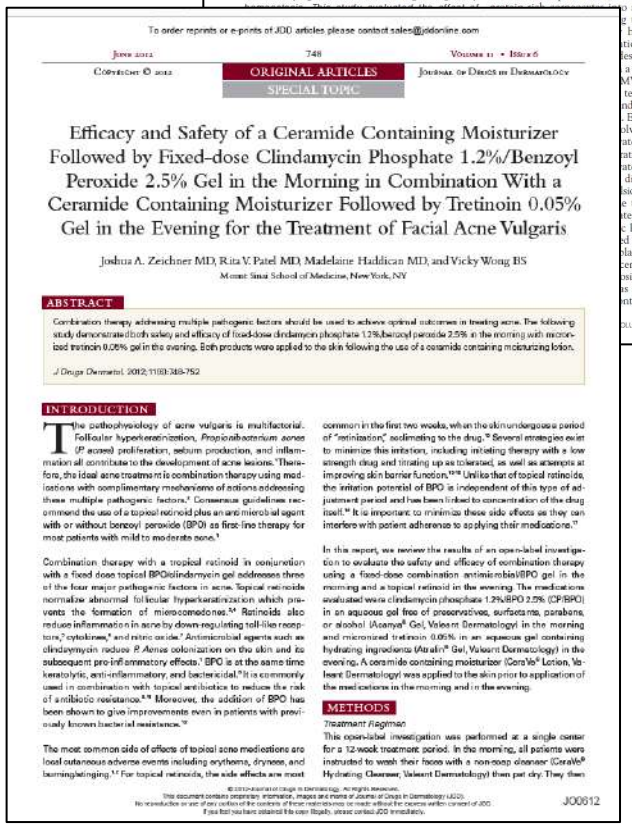
James Q. Del Rosso, DO

Skin care regimens have been recommended in conjunction with topical medications for the treatment of rosacea. Specifically, a mild cleanser and a moisturizer can help relieve symptoms and maintain skin barrier integrity. The Assessment of Skin Characteristics Study, a multicenter open-label study (N=102), compared the use of a specified skin care regimen with or without the

symptoms of rosacea.[1-3] Several studies have demonstrated the effectiveness of properly chosen skin cleansers, proper cleansing technique, and moisturizer use in minimizing signs and symptoms of rosacea such as erythema, dryness, scaling, stinging, burning, and pruritus.[1,2,4,5] Additionally, the use of a gentle synthetic detergent (syndet) skin cleanser was shown to improve signs and symptoms of rosacea as compared to a soap-based cleanser in participants maintained on topical metronidazole.[5]

Dryness of skin and scaling are not infrequent in patients with rosacea, and the utility of moisturizers in these patients is relevant.[7] However, there is evidence that moisturizer use could play an integral adjunctive role in the topical management of rosacea. In one controlled study, use of a niacinamide-containing moisturizer not only improved facial skin hydration in participants with rosacea, as measured by transepidermal water loss, corneometry, and chemical probe measurements, but also was associated with reductions in erythema and inflammatory lesions as well as dryness and scaling.[8]

The hyperirritability of facial skin in rosacea, its susceptibility to external stimuli, including skin care products and the presence of subjective symptoms such as stinging, burning, tingling, and itching are indicative of inherent sensitive skin.[9] Skin sensitivity correlates with impaired epidermal barrier function.[10] Increased transepidermal water loss, reflective of epidermal barrier dysfunction, has been demonstrated predominantly in the central facial region of patients with both erythematotelangiectatic rosacea (subtype 1) and papulopustular rosacea (subtype 2).[11]



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Efficacy and Safety of a Ceramide Containing Moisturizer Followed by Fixed-dose Clindamycin Phosphate 1.2%/Benzoyl Peroxide 2.5% Gel in the Morning in Combination With a Ceramide Containing Moisturizer Followed by Tretinoin 0.05% Gel in the Evening for the Treatment of Facial Acne Vulgaris

Joshua A. Zeichner MD; Rita V. Patel MD; Madelaine Haddican MD; and Vicky Wong BS

Mount Sinai School of Medicine, New York, NY

ABSTRACT

Combination therapy addressing multiple pathogenic factors should be used to achieve optimal outcomes in treating acne. The following study demonstrates both safety and efficacy of fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% in the morning with microsized tretinoin 0.06% gel in the evening. Both products were applied to the skin following the use of a ceramide containing moisturizing lotion.

J Drugs Dermatol. 2012;11(6):748-752

INTRODUCTION

The pathophysiology of acne vulgaris is multifactorial. Follicular hyperkeratinization, *Propionibacterium acnes* (*P. acnes*) proliferation, sebum production, and inflammation all contribute to the development of acne lesions.[1] Therefore, the ideal acne treatment is combination therapy using medications with complimentary mechanisms of actions addressing these multiple pathogenic factors.[2] Consensus guidelines recommend the use of a topical retinoid plus an anti-microbial agent with or without benzoyl peroxide (BPO) as first-line therapy for most patients with mild to moderate acne.[3]

Combination therapy with a topical retinoid in conjunction with a fixed dose topical BPO/clindamycin gel addresses three of the four major pathogenic factors in acne. Topical retinoids normalize abnormal follicular hyperkeratinization which prevents the formation of microcomedones.[3,4] Retinoids also reduce inflammation in acne by down-regulating toll-like receptors,[5] cytokines,[6] and nitric oxide.[7] Antimicrobial agents such as clindamycin reduce *P. Acnes* colonization on the skin and its subsequent pro-inflammatory effects.[1] BPO is at the same time keratolytic, anti-inflammatory, and bactericidal.[8] It is commonly used in combination with topical antibiotics to reduce the risk of antibiotic resistance.[3,9] Moreover, the addition of BPO has been shown to give improvements even in patients with previously known bacterial resistance.[10]

The most common side of effects of topical acne medications are local cutaneous adverse events including erythema, dryness, and burning/stinging.[11] For topical retinoids, the side effects are most common in the first two weeks, when the skin undergoes a period of "retinization," acclimating to the drug.[12] Several strategies exist to minimize this irritation, including initiating therapy with a low strength drug and titrating up as tolerated, as well as attempts at improving skin barrier function.[13,14] Unlike that of topical retinoids, the irritation potential of BPO is independent of this type of adjustment period and has been linked to concentration of the drug itself.[15] It is important to minimize these side effects as they can interfere with patient adherence to applying their medications.[16]

In this report, we review the results of an open-label investigation to evaluate the safety and efficacy of combination therapy using a fixed-dose combination antimicrobial/BPO gel in the morning and a topical retinoid in the evening. The medications evaluated were clindamycin phosphate 1.2%/BPO 2.5% (CP/BPO) in an aqueous gel free of preservatives, surfactants, parabens, or alcohol (Acanya® Gel, Valeant Dermatology) in the morning and micronized tretinoin 0.06% in an aqueous gel containing hydrating ingredients (Atralin® Gel, Valeant Dermatology) in the evening. A ceramide containing moisturizer (CeraVe® Lotion, Valeant Dermatology) was applied to the skin prior to application of the medications in the morning and in the evening.

METHODS

Treatment Regimen

This open-label investigation was performed at a single center for a 12-week treatment period. In the morning, all patients were instructed to wash their faces with a non-soap cleanser (CeraVe® Hydrating Cleanser, Valeant Dermatology) then pat dry. They then

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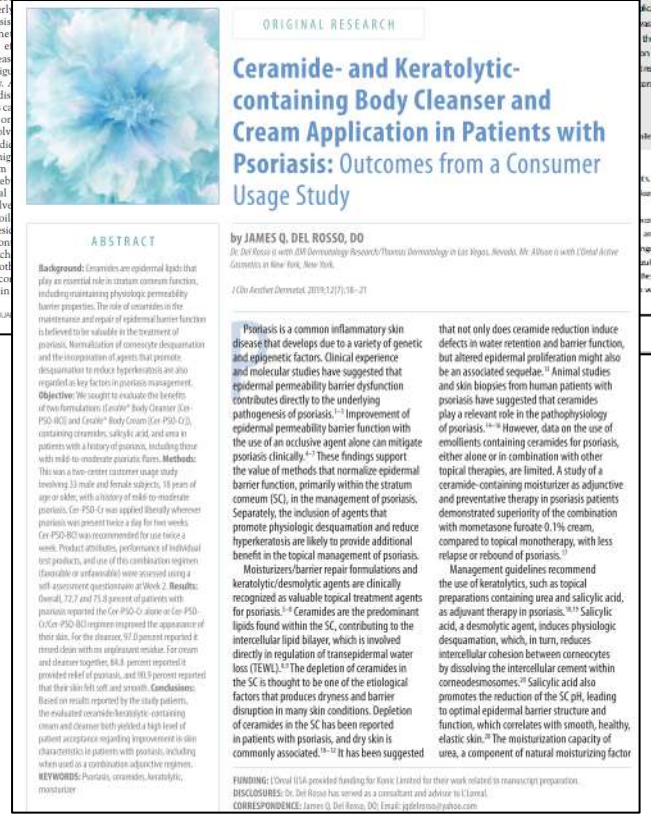


ORIGINAL RESEARCH

Ceramide- and Keratolytic-containing Body Cleanser and Cream Application in Patients with Psoriasis: Outcomes from a Consumer Usage Study

by JAMES Q. DEL ROSSO, DO

Dr. Del Rosso is with JDR Dermatology Research/Thomas Dermatology in Las Vegas, Nevada. Mr. Allouse is with L'Oréal Active Cosmetics in New York, New York.

J Clin Aesthet Dermatol. 2009;2(7):16–21

ABSTRACT

Background: Ceramides are epidermal lipids that play an essential role in stratum corneum function, including maintaining physiologic permeability barrier properties. The role of ceramides in the maintenance and repair of epidermal barrier function is believed to be valuable in the treatment of psoriasis. Normalization of corneocyte desquamation and the incorporation of agents that promote desquamation to reduce hyperkeratosis are also regarded as key factors in psoriasis management. **Objective:** We sought to evaluate the benefits of two formulations (CeraVe® Body Cleanser (Cer-PSO-BCl) and CeraVe® Body Cream (Cer-PSO-Cr)), containing ceramides, salicylic acid, and urea in patients with a history of psoriasis, including those with mild-to-moderate psoriatic flares. **Methods:** This was a two-center customer usage study involving 33 male and female subjects, 18 years of age or older, with a history of mild-to-moderate psoriasis. Cer-PSO-Cr was applied liberally wherever psoriasis was present twice a day for two weeks. Cer-PSO-BCl was recommended for use twice a week. Product attributes, performance of individual test products, and use of this combination regimen (favorable or unfavorable) were assessed using a self-assessment questionnaire at Week 2. **Results:** Overall, 72.7 and 75.8 percent of patients with psoriasis reported the Cer-PSO-Cr alone or Cer-PSO-Cr/Cer-PSO-BCl regimen improved the appearance of their skin. For the cleanser, 97.0 percent reported it rinsed clean with no unpleasant residue. For cream and cleanser together, 84.8 percent reported it provided relief of psoriasis, and 90.9 percent reported that their skin felt soft and smooth. **Conclusions:** Based on results reported by the study patients, the evaluated ceramide/keratolytic-containing cream and cleanser both yielded a high level of patient acceptance regarding improvement in skin characteristics in patients with psoriasis, including when used as a combination adjunctive regimen.

KEYWORDS: Psoriasis, ceramides, keratolytic, moisturizer

Psoriasis is a common inflammatory skin disease that develops due to a variety of genetic and epigenetic factors. Clinical experience and molecular studies have suggested that epidermal permeability barrier dysfunction contributes directly to the underlying pathogenesis of psoriasis.[1-3] Improvement of epidermal permeability barrier function with the use of an occlusive agent alone can mitigate psoriasis clinically.[4-7] These findings support the value of methods that normalize epidermal barrier function, primarily within the stratum corneum (SC), in the management of psoriasis. Separately, the inclusion of agents that promote physiologic desquamation and reduce hyperkeratosis are likely to provide additional benefit in the topical management of psoriasis.

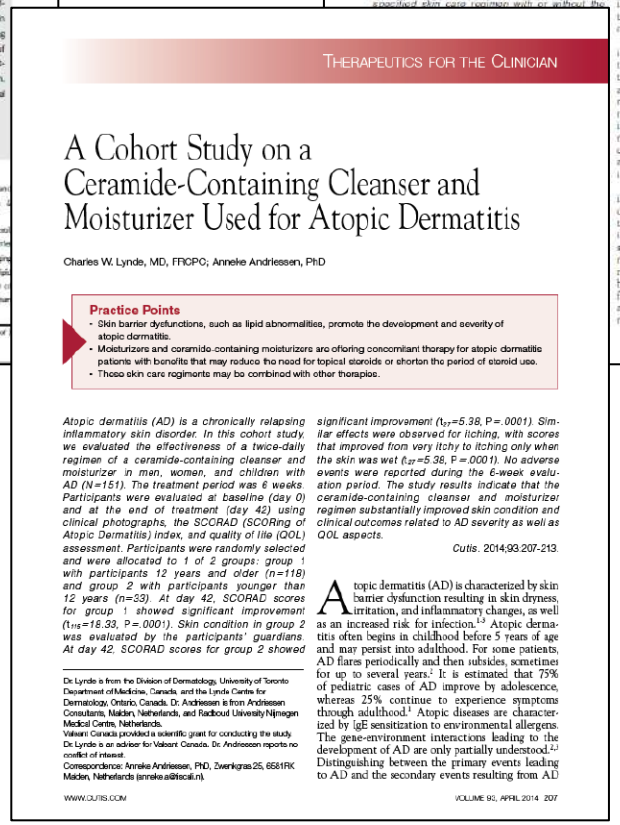
Moisturizers/barrier repair formulations and keratolytic/desmolytic agents are clinically recognized as valuable topical treatment agents for psoriasis.[5-8] Ceramides are the predominant lipids found within the SC, contributing to the intercellular lipid bilayer, which is involved directly in regulation of transepidermal water loss (TEWL).[4,5] The depletion of ceramides in the SC is thought to be one of the etiological factors that produces dryness and barrier disruption in many skin conditions. Depletion of ceramides in the SC has been reported in patients with psoriasis, and dry skin is commonly associated.[9-12] It has been suggested that not only does ceramide reduction induce defects in water retention and barrier function, but altered epidermal proliferation might also be an associated sequelae.[13] Animal studies and skin biopsies from human patients with psoriasis have suggested that ceramides play a relevant role in the pathophysiology of psoriasis.[14-16] However, data on the use of emollients containing ceramides for psoriasis, either alone or in combination with other topical therapies, are limited. A study of a ceramide-containing moisturizer as adjunctive and preventative therapy in psoriasis patients demonstrated superiority of the combination with mometasone furoate 0.1% cream, compared to topical monotherapy, with less relapse or rebound of psoriasis.[17]

Management guidelines recommend the use of keratolytics, such as topical preparations containing urea and salicylic acid, as adjuvant therapy in psoriasis.[18,19] Salicylic acid, a desmolytic agent, induces physiologic desquamation, which, in turn, reduces intercellular cohesion between corneocytes by dissolving the intercellular cement within corneodesmosomes.[20] Salicylic acid also promotes the reduction of the SC pH, leading to optimal epidermal barrier structure and function, which correlates with smooth, healthy, elastic skin.[20] The moisturization capacity of urea, a component of natural moisturizing factor

FUNDING: L'Oreal USA provided funding for Ronic Limited for their work related to manuscript preparation.

DISCLOSURES: Dr. Del Rosso has served as a consultant and advisor to L'Oreal.

CORRESPONDENCE: James Q. Del Rosso, DO; Email: jqdelrosso@yahoo.com



THERAPEUTICS FOR THE CLINICIAN

A Cohort Study on a Ceramide-Containing Cleanser and Moisturizer Used for Atopic Dermatitis

Charles W. Lynde, MD, FRCPC; Anneke Andriessen, PhD

Practice Points

- Skin barrier dysfunctions, such as lipid abnormalities, promote the development and severity of atopic dermatitis.
- Moisturizers and ceramide-containing moisturizers are offering concomitant therapy for atopic dermatitis patients with benefits that may reduce the need for topical steroids or shorten the period of steroid use.
- These skin care regimens may be combined with other therapies.

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disorder. In this cohort study, we evaluated the effectiveness of a twice-daily regimen of a ceramide-containing cleanser and moisturizer in men, women, and children with AD (N=151). The treatment period was 6 weeks. Participants were evaluated at baseline (day 0) and at the end of treatment (day 42) using clinical photographs, the SCORAD (SCORing of Atopic Dermatitis) index, and quality of life (QOL) assessment. Participants were randomly selected and were allocated to 1 of 2 groups: group 1 with participants 12 years and older (n=118) and group 2 with participants younger than 12 years (n=33). At day 42, SCORAD scores for group 1 showed significant improvement (t_{116}=18.33, P=.0001). Skin condition in group 2 was evaluated by the participants' guardians. At day 42, SCORAD scores for group 2 showed significant improvement (t_{32}=5.38, P=.0001). Similar effects were observed for itching, with scores that improved from very itchy to itching only when the skin was wet (t_{32}=5.36, P=.0001). No adverse events were reported during the 6-week evaluation period. The study results indicate that the ceramide-containing cleanser and moisturizer regimen substantially improved skin condition and clinical outcomes related to AD severity as well as QOL aspects.

Cutis. 2014;93:207-213.

Atopic dermatitis (AD) is characterized by skin barrier dysfunction resulting in skin dryness, irritation, and inflammatory changes, as well as an increased risk for infection.[1-3] Atopic dermatitis often begins in childhood before 5 years of age and may persist into adulthood. For some patients, AD flares periodically and then subsides, sometimes for up to several years.[2] It is estimated that 75% of pediatric cases of AD improve by adolescence, whereas 25% continue to experience symptoms through adulthood.[1] Atopic diseases are characterized by IgE sensitization to environmental allergens. The gene-environment interactions leading to the development of AD are only partially understood.[2,3] Distinguishing between the primary events leading to AD and the secondary events resulting from AD

Dr Lynde is from the Division of Dermatology, University of Toronto Department of Medicine, Canada, and the Lynde Centre for Dermatology, Ontario, Canada. Dr. Andriessen is from Andriessen Consultants, Malden, Netherlands, and Radboud University Nijmegen Medical Centre, Netherlands.

Valeant Canada provided a scientific grant for conducting the study. Dr. Lynde is an advisor for Valeant Canada. Dr. Andriessen reports no conflict of interest.

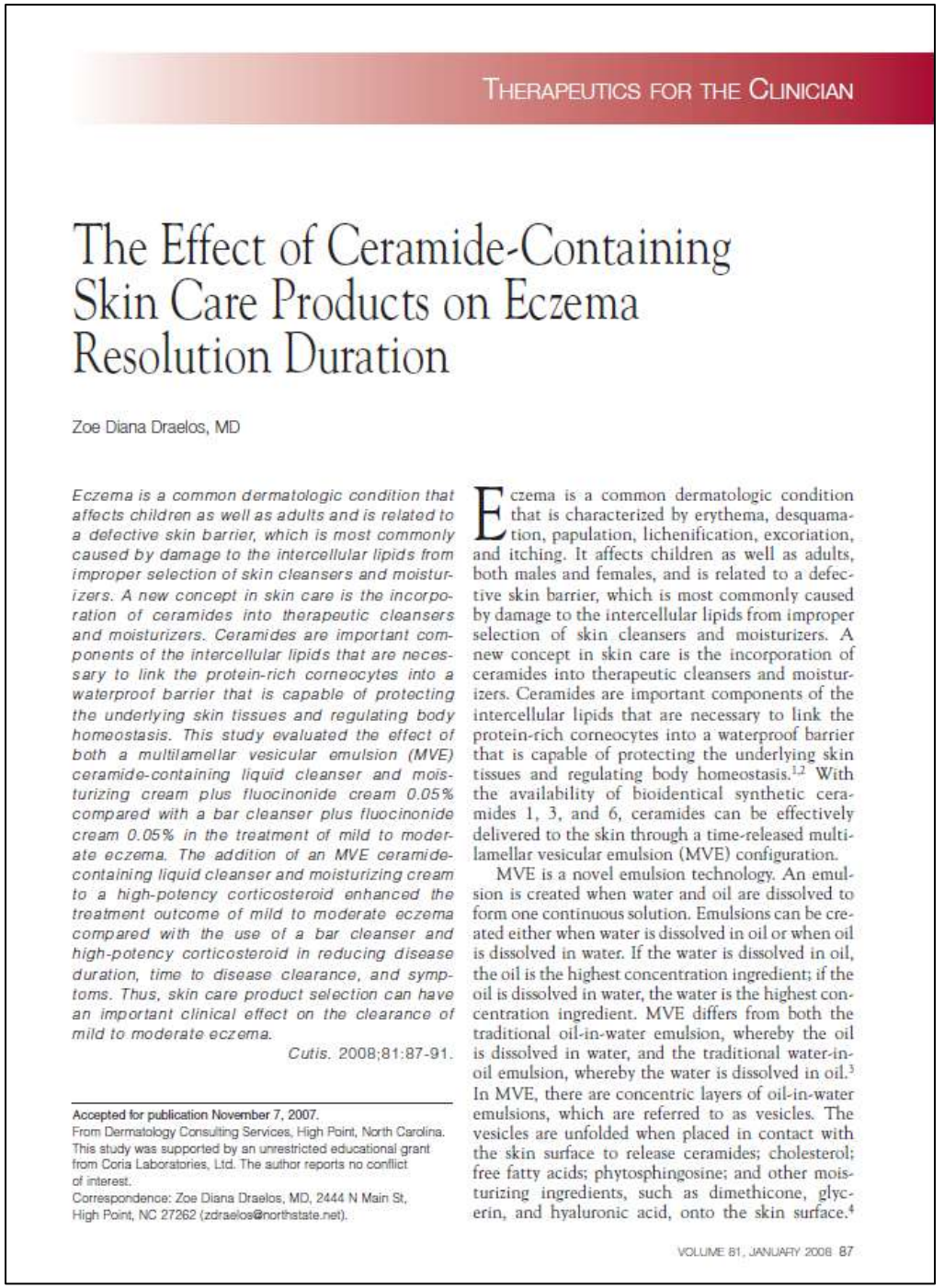
Correspondence: Anneke Andriessen, PhD, Zwenkgras 25, 6581RK Malden, Netherlands (anneke.a@tiscali.nl).

4-Week study

- The 4-week study included 60 subjects aged 5 to 80 years with mild-to-moderate AD
- The study evaluated the effect of
  - Ceramide-containing liquid cleanser and moisturizing cream plus fluocinonide cream 0.05%

compared with

  - Bar cleanser plus fluocinonide cream 0.05%



THERAPEUTICS FOR THE CLINICIAN

The Effect of Ceramide-Containing Skin Care Products on Eczema Resolution Duration

Zoe Diana Draelos, MD

Eczema is a common dermatologic condition that affects children as well as adults and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body homeostasis. This study evaluated the effect of both a multilamellar vesicular emulsion (MVE) ceramide-containing liquid cleanser and moisturizing cream plus fluocinonide cream 0.05% compared with a bar cleanser plus fluocinonide cream 0.05% in the treatment of mild to moderate eczema. The addition of an MVE ceramide-containing liquid cleanser and moisturizing cream to a high-potency corticosteroid enhanced the treatment outcome of mild to moderate eczema compared with the use of a bar cleanser and high-potency corticosteroid in reducing disease duration, time to disease clearance, and symptoms. Thus, skin care product selection can have an important clinical effect on the clearance of mild to moderate eczema.

Cutis. 2008;81:87-91.

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Correspondence: Zoe Diana Draelos, MD, 2444 N Main St, High Point, NC 27262 (zdraelos@northstate.net).

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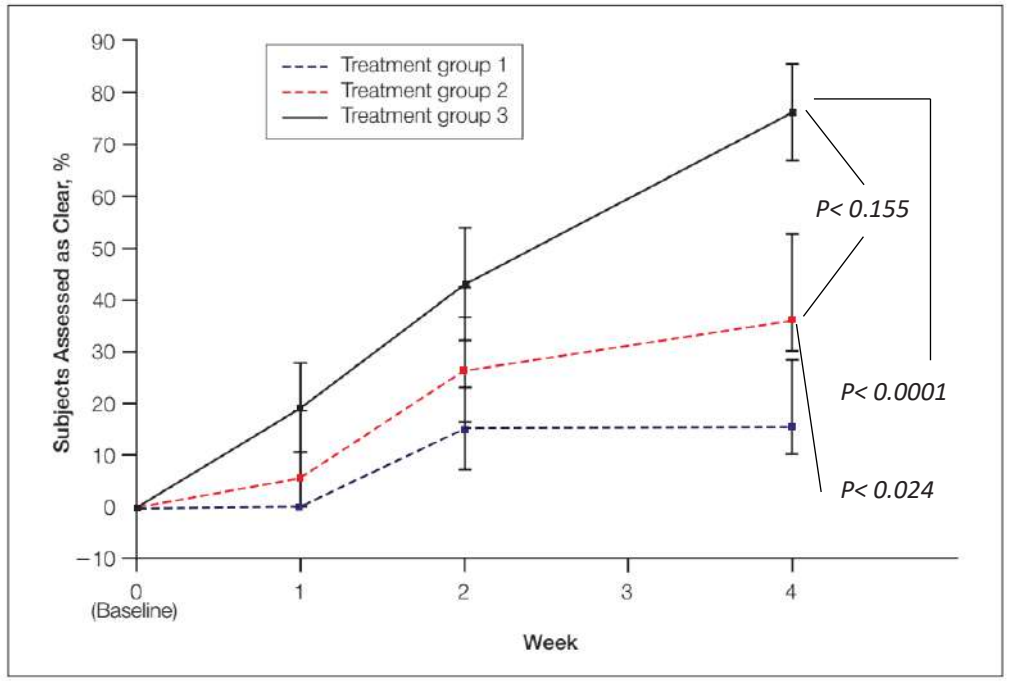
MVE is a novel emulsion technology. An emulsion is created when water and oil are dissolved to form one continuous solution. Emulsions can be created either when water is dissolved in oil or when oil is dissolved in water. If the water is dissolved in oil, the oil is the highest concentration ingredient; if the oil is dissolved in water, the water is the highest concentration ingredient. MVE differs from both the traditional oil-in-water emulsion, whereby the oil is dissolved in water, and the traditional water-in-oil emulsion, whereby the water is dissolved in oil.[3] In MVE, there are concentric layers of oil-in-water emulsions, which are referred to as vesicles. The vesicles are unfolded when placed in contact with the skin surface to release ceramides; cholesterol; free fatty acids; phytosphingosine; and other moisturizing ingredients, such as dimethicone, glycerin, and hyaluronic acid, onto the skin surface.[4]

Drealos ZD, Cutis. 2008;81:87-91.

4-Week study on patients with mild-to-moderate atopic dermatitis, cont.

Percentage of subjects assessed as clear of disease over the duration of the study.



Treatment group 1, fluocinonide cream 0.05% plus mild bar cleanser

Treatment group 2, fluocinonide cream 0.05% plus ceramide-containing liquid cleanser

Treatment group 3, fluocinonide cream 0.05% plus ceramide containing liquid cleanser and moisturizing cream.

At week 4:
P< 0.155 (NS) for treatment group 1 versus treatment group 2
P < 0.0001 for treatment group 1 versus treatment group 3
P< 0.024 for treatment group 2 versus treatment group 3

Drealos ZD, Cutis. 2008;81:87-91.

4-Week study on patients with mild-to-moderate atopic dermatitis, cont.

Global Disease Severity by Treatment Group*

Treatment Group	Baseline Assessment	Treatment Week Assessment	Difference	*P* Value: Group 1 vs Group 2	*P* Value: Group 1 vs Group 3	*P* Value: Group 2 vs Group 3
Week 1						
Group 1	3.0	2.6	0.4	.012	.004	.272
Group 2	3.1	1.9	1.2			
Group 3	3.0	1.6	1.4			
Week 2						
Group 1	3.0	2.0	1.0	.442	.013	.063
Group 2	3.1	1.6	1.5			
Group 3	3.0	0.9	2.1			
Week 4						
Group 1	3.0	1.6	1.4	.0443	<.001	.087
Group 2	3.1	0.9	2.2			
Group 3	3.0	0.3	2.7			

Treatment group 1: Fluocinonide cream 0.05% plus mild bar cleanser

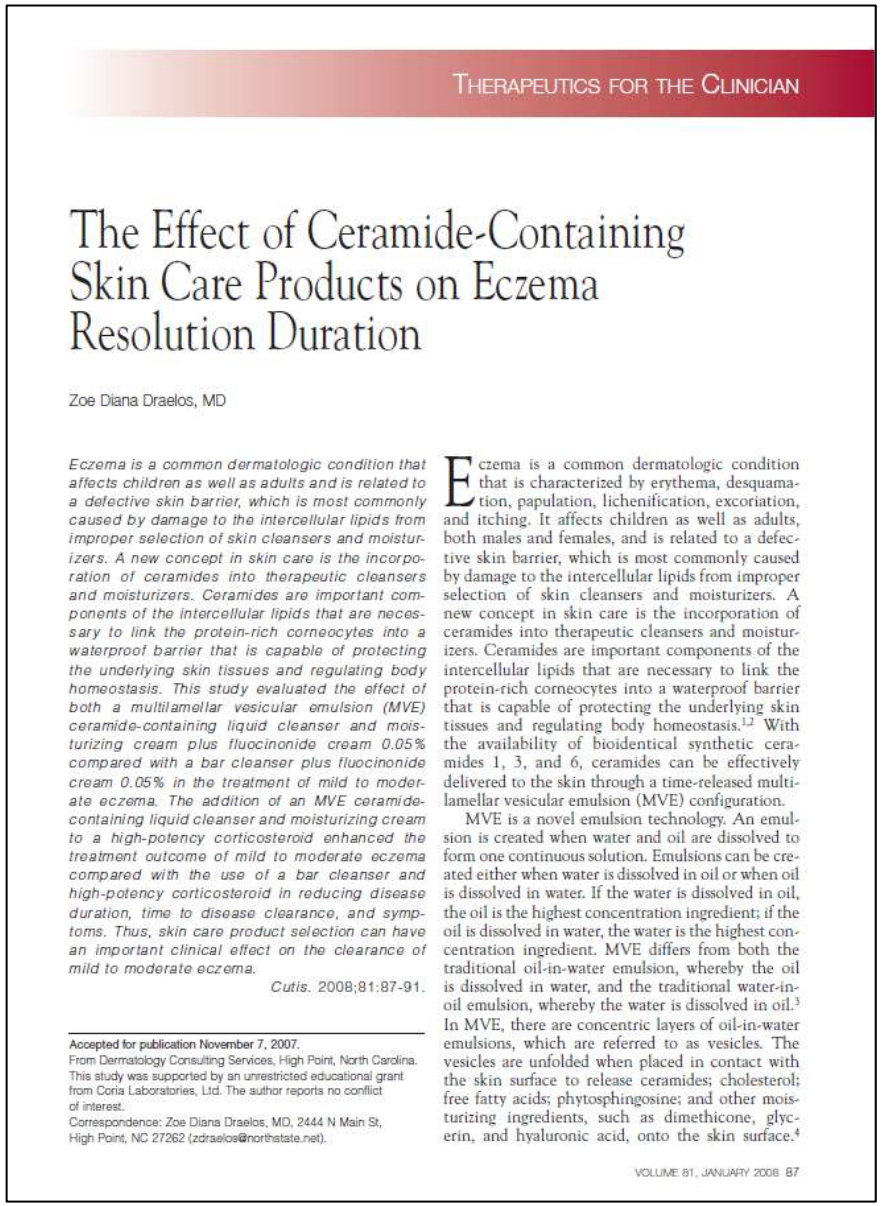
Treatment group 2: Fluocinonide cream 0.05% plus ceramide-containing liquid cleanser

Treatment group 3: Fluocinonide cream 0.05% plus ceramide containing liquid cleanser and moisturizing cream.

Drealos ZD, Cutis. 2008;81:87-91.

Conclusions of the study

- The study 4-week study included 60 subjects aged 5 to 80 years with mild to moderate atopic dermatitis.
- A ceramide-containing liquid cleanser and moisturizing cream plus fluocinonide cream 0.05% was compared to compared the use of a bar cleanser plus fluocinonide cream 0.05%.
- The **addition of the ceramide containing liquid cleanser and moisturizing cream** to a high-potency corticosteroid **enhanced the treatment outcome** of mild to moderate eczema compared with the use of a bar cleanser and high-potency corticosteroid in **reducing disease duration**, **time to disease clearance, and symptoms.**



The Effect of Ceramide-Containing Skin Care Products on Eczema Resolution Duration

Zoe Diana Draelos, MD

Eczema is a common dermatologic condition that affects children as well as adults and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body homeostasis. This study evaluated the effect of both a multilamellar vesicular emulsion (MVE) ceramide-containing liquid cleanser and moisturizing cream plus fluocinonide cream 0.05% compared with a bar cleanser plus fluocinonide cream 0.05% in the treatment of mild to moderate eczema. The addition of an MVE ceramide-containing liquid cleanser and moisturizing cream to a high-potency corticosteroid enhanced the treatment outcome of mild to moderate eczema compared with the use of a bar cleanser and high-potency corticosteroid in reducing disease duration, time to disease clearance, and symptoms. Thus, skin care product selection can have an important clinical effect on the clearance of mild to moderate eczema.

Cutis. 2008;81:87-91.

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Eczema is a common dermatologic condition that is characterized by erythema, desquamation, papulation, lichenification, excoriation, and itching. It affects children as well as adults, both males and females, and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body homeostasis.[1,2] With the availability of bioidentical synthetic ceramides 1, 3, and 6, ceramides can be effectively delivered to the skin through a time-released multilamellar vesicular emulsion (MVE) configuration.

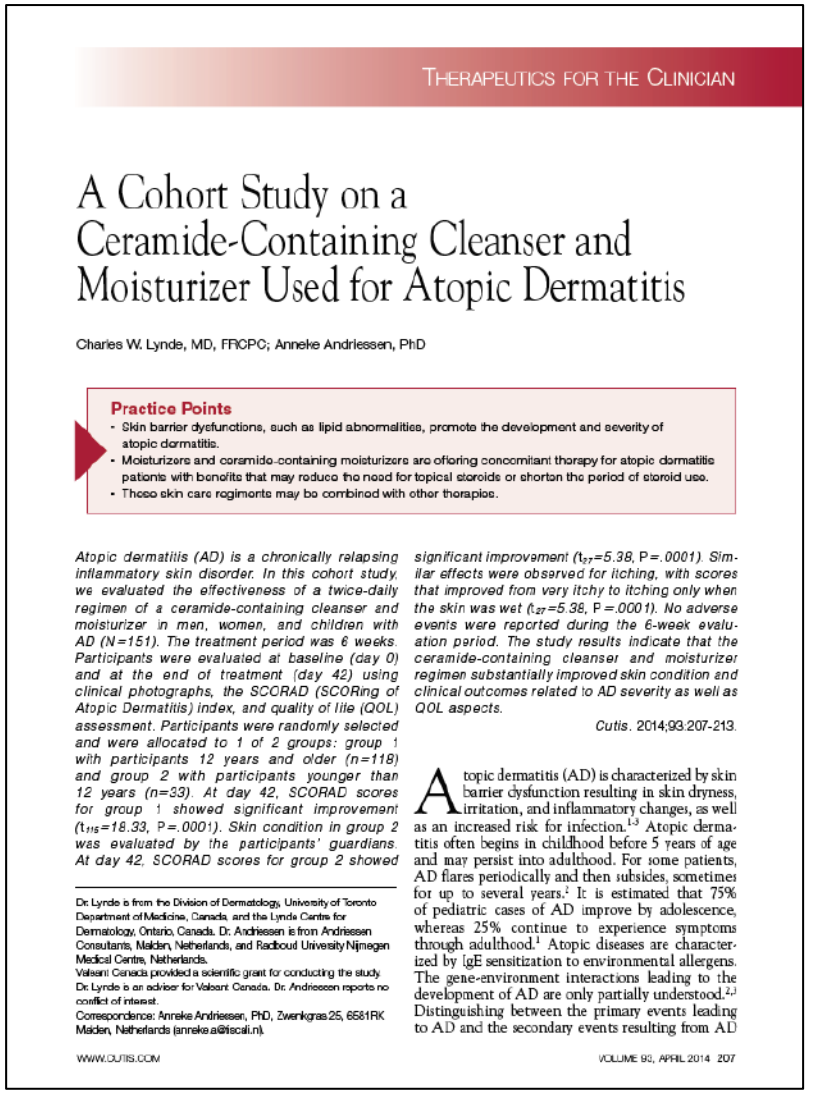
MVE is a novel emulsion technology. An emulsion is created when water and oil are dissolved to form one continuous solution. Emulsions can be created either when water is dissolved in oil or when oil is dissolved in water. If the water is dissolved in oil, the oil is the highest concentration ingredient; if the oil is dissolved in water, the water is the highest concentration ingredient. MVE differs from both the traditional oil-in-water emulsion, whereby the oil is dissolved in water, and the traditional water-in-oil emulsion, whereby the water is dissolved in oil.[3] In MVE, there are concentric layers of oil-in-water emulsions, which are referred to as vesicles. The vesicles are unfolded when placed in contact with the skin surface to release ceramides; cholesterol; free fatty acids; phytosphingosine; and other moisturizing ingredients, such as dimethicone, glycerin, and hyaluronic acid, onto the skin surface.[4]

Drealos ZD, Cutis. 2008;81:87-91.

CeraVe Clinical study on Adults and Children with Atopic Dermatitis

Evaluation of safety and efficacy of 6 weeks CeraVe Hydrating Cleanser followed by CeraVe Moisturizing Cream (twice daily) in 151 subjects (children; n = 33) and adults; n = 118) with mild-to-moderate atopic dermatitis

Atopic dermatitis symptoms and skin condition were evaluated after 42 days (+/- 5 days) of treatment .



THERAPEUTICS FOR THE CLINICIAN

A Cohort Study on a Ceramide-Containing Cleanser and Moisturizer Used for Atopic Dermatitis

Charles W. Lynde, MD, FRCPC; Anneke Andriessen, PhD

Practice Points

- Skin barrier dysfunctions, such as lipid abnormalities, promote the development and severity of atopic dermatitis.
- Moisturizers and ceramide-containing moisturizers are offering concomitant therapy for atopic dermatitis patients with benefits that may reduce the need for topical steroids or shorten the period of steroid use.
- These skin care regimens may be combined with other therapies.

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disorder. In this cohort study, we evaluated the effectiveness of a twice-daily regimen of a ceramide-containing cleanser and moisturizer in men, women, and children with AD (N=151). The treatment period was 6 weeks. Participants were evaluated at baseline (day 0) and at the end of treatment (day 42) using clinical photographs, the SCORAD (SCORing of Atopic Dermatitis) index, and quality of life (QOL) assessment. Participants were randomly selected and were allocated to 1 of 2 groups: group 1 with participants 12 years and older (n=118) and group 2 with participants younger than 12 years (n=33). At day 42, SCORAD scores for group 1 showed significant improvement (t_{117}=18.33, P=.0001). Skin condition in group 2 was evaluated by the participants' guardians. At day 42, SCORAD scores for group 2 showed significant improvement (t_{27}=5.38, P=.0001). Similar effects were observed for itching, with scores that improved from very itchy to itching only when the skin was wet (t_{27}=5.38, P=.0001). No adverse events were reported during the 6-week evaluation period. The study results indicate that the ceramide-containing cleanser and moisturizer regimen substantially improved skin condition and clinical outcomes related to AD severity as well as QOL aspects.

Cutis. 2014;93:207-213.

Atopic dermatitis (AD) is characterized by skin barrier dysfunction resulting in skin dryness, irritation, and inflammatory changes, as well as an increased risk for infection.[1-3] Atopic dermatitis often begins in childhood before 5 years of age and may persist into adulthood. For some patients, AD flares periodically and then subsides, sometimes for up to several years.[1] It is estimated that 75% of pediatric cases of AD improve by adolescence, whereas 25% continue to experience symptoms through adulthood.[1] Atopic diseases are characterized by IgE sensitization to environmental allergens. The gene-environment interactions leading to the development of AD are only partially understood.[2,3] Distinguishing between the primary events leading to AD and the secondary events resulting from AD

Dr Lynde is from the Division of Dermatology, University of Toronto Department of Medicine, Canada, and the Lynde Centre for Dermatology, Ontario, Canada. Dr. Andriessen is from Andriessen Consultants, Malden, Netherlands, and Radboud University Nijmegen Medical Centre, Netherlands.

Valeant Canada provided a scientific grant for conducting the study. Dr Lynde is an advisor for Valeant Canada. Dr. Andriessen reports no conflict of interest.

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Lynde CW, Andriessen A. *Cutis*.2014;93(4)207-2013

Participant Baseline Demographics

Characteristics	Participants, n (%)	
	Group 1 (n=118)	Group 2 (n=33)
Gender		
Male	35 (29.7)	21 (63.6)
Female	83 (70.3)	12 (36.4)
Allergy		
Dairy	6 (5.1)	8 (24.2)
Hay fever/asthma	16 (13.6)	6 (18.2)
Other	0 (0)	4 (12.1)
AD location[a]		
Inner aspect of elbows	64 (54.2)	12 (36.4)
Inner aspect of knees	47 (39.8)	15 (45.5)
Neck/upper chest	4 (3.4)	9 (27.3)
Other	3 (2.5)	1 (3.0)

Abbreviation: AD, atopic dermatitis.
[a]In group 2, AD was present in multiple locations.

N = 151

A Cohort study on a Ceramide-containing Cleanser and Moisturizer used for Atopic Dermatitis.

Lynde CW, Andriessen A. *Cutis*.2014;93(4)207-2013

A Cohort study on a Ceramide-containing Cleanser and Moisturizer used for Atopic Dermatitis, cont.

Skin Condition (SCORAD) at Baseline

Skin Condition	Participants, n (%)		
	Group 1 (n=118)	Group 2 (n=33)	Total N = 151
Dry	77 (65.3)	5 (15.2)	82 (54.3)
Very dry	18 (15.3)	17 (51.5)	35 (23.2)
Crusting/oozing	11 (9.3)	4 (12.1)	15 (9.9)
Very crusting /oozing	51 (43.2)	1 (3.0)	52 (34.4)
Itchy	44 (37.3)	10 (30.3)	54 (35.8)
Very itchy	118 (100)	11 (33.3)	129 (85.4)

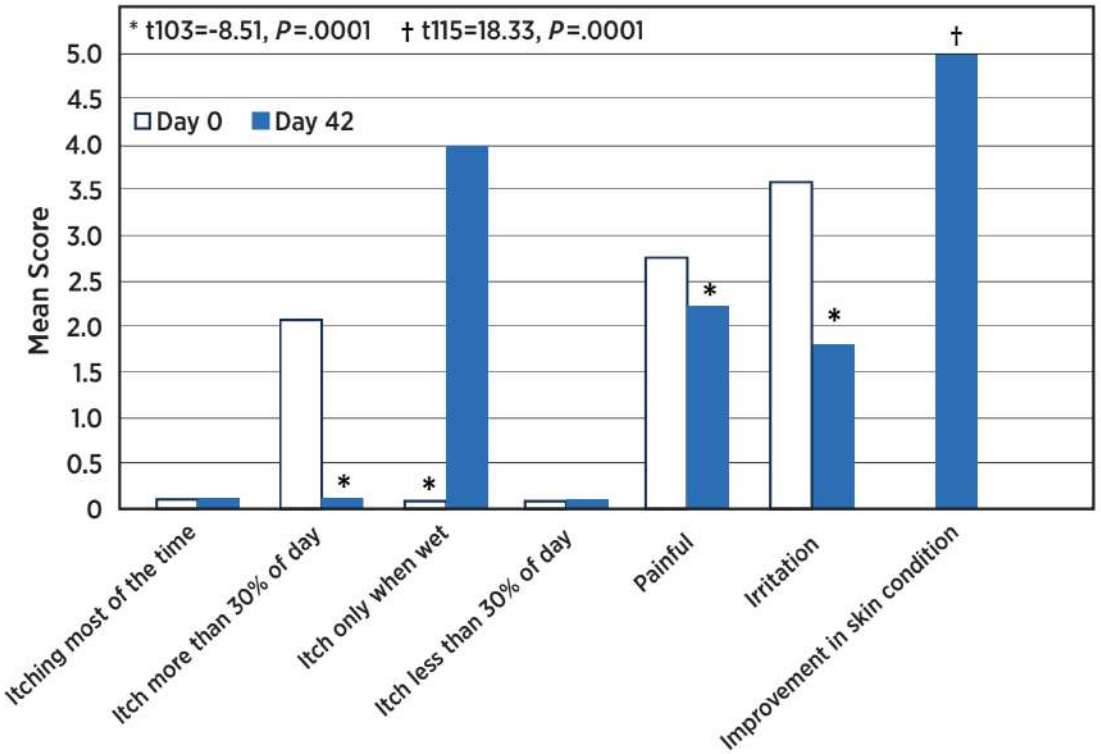
Abbreviation: SCORAD, SCORing of Atopic Dermatitis.

Lynde CW, Andriessen A. *Cutis*.2014;93(4)207-2013

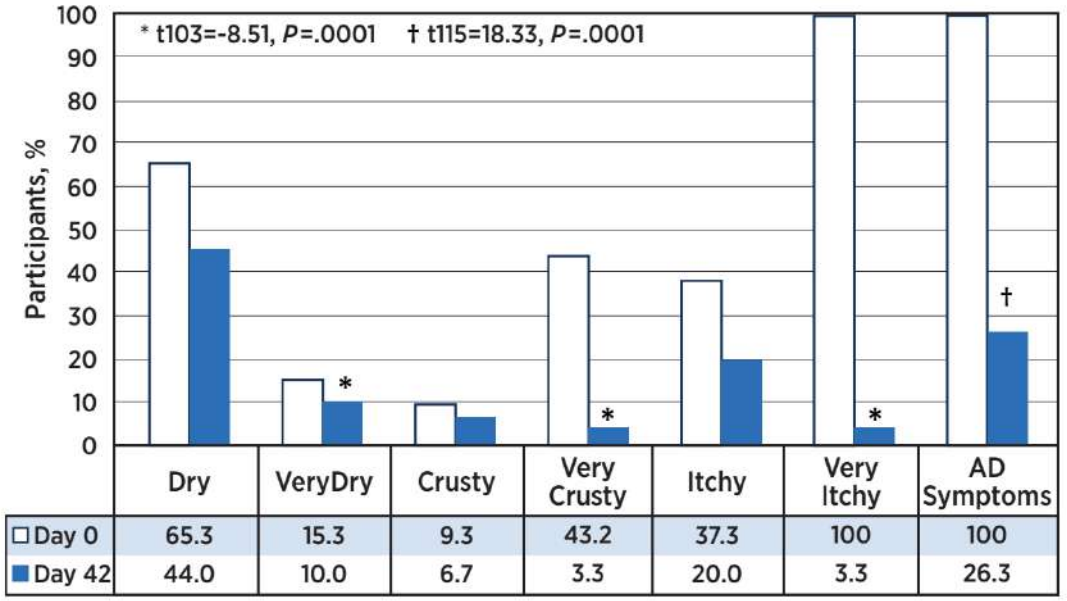
A Cohort study on a Ceramide-containing Cleanser and Moisturizer used for Atopic Dermatitis, cont.

Group 1: PATIENTS >12 years (n=118)

REPORTED AD SYMPTOMS AT BASELINE AND AFTER 42 DAYS (+/- 5 DAYS) OF CLEANSER AND MOISTURIZER USE



REPORTED QUALITY-OF-LIFE PARAMETERS AT DAY 42, SCORED ON A 5-POINT SCALE (1=NOT AGREE TO 5=STRONGLY AGREE).



	Dry	VeryDry	Crusty	Very Crusty	Itchy	Very Itchy	AD Symptoms
Day 0	65.3	15.3	9.3	43.2	37.3	100	100
Day 42	44.0	10.0	6.7	3.3	20.0	3.3	26.3

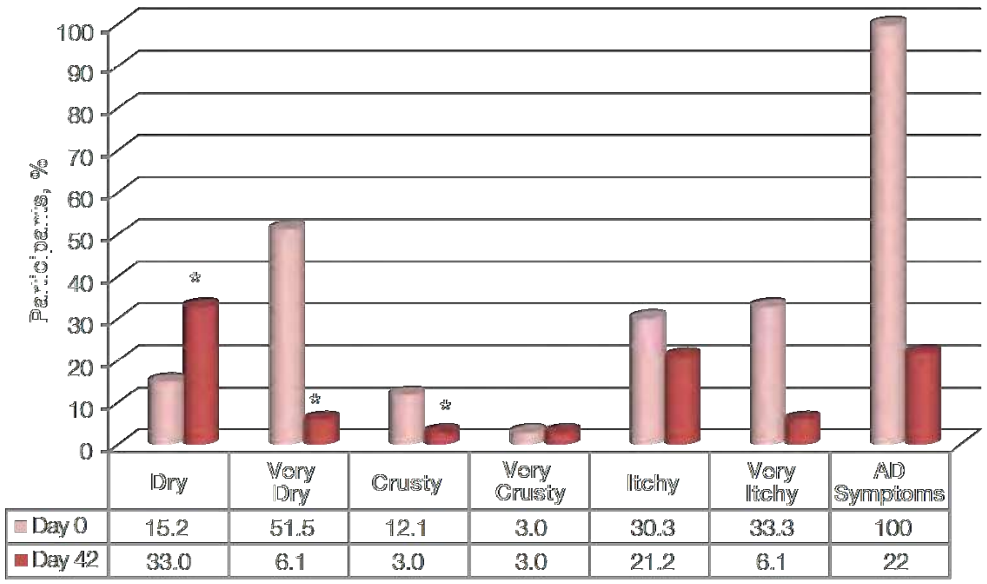
CeraVe Hydrating Cleanser followed by CeraVe Moisturizing Cream twice daily (BID)

Lynde CW, Andriessen A. *Cutis*.2014;93(4)207-2013

A Cohort study on a Ceramide-containing Cleanser and Moisturizer used for Atopic Dermatitis, cont.

Group 2: PATIENTS <12 years (n= 33)

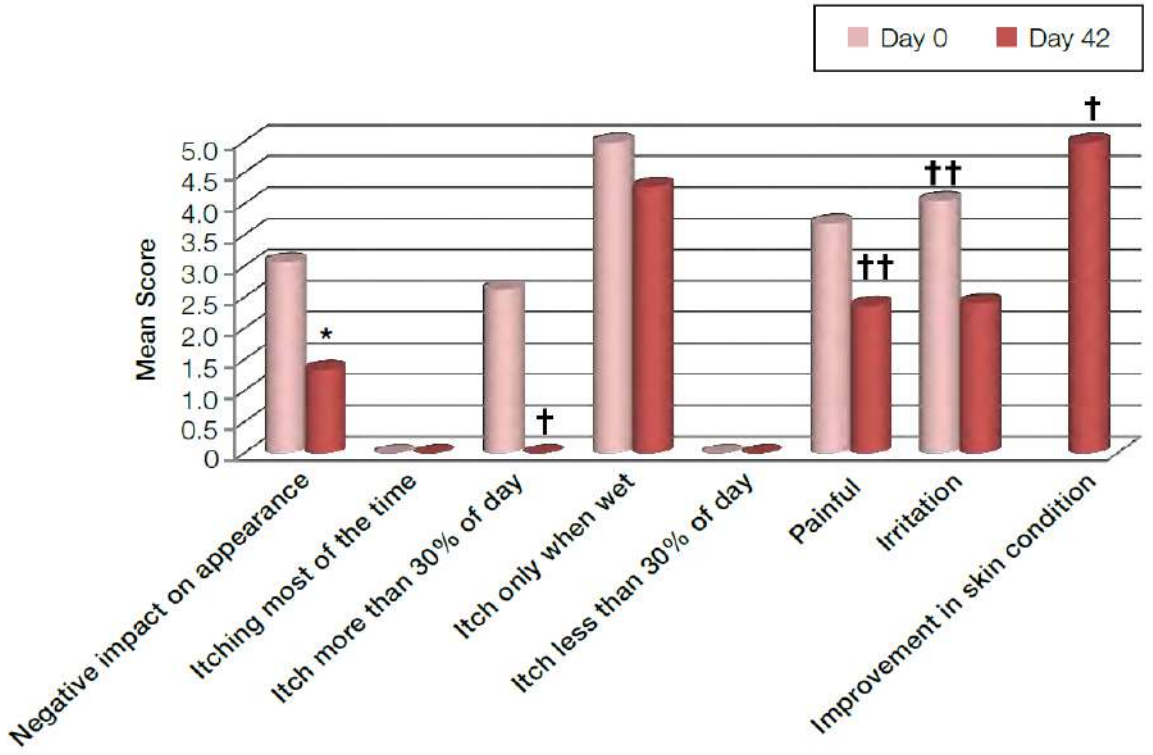
REPORTED AD SYMPTOMS AT BASELINE AND AFTER 42 DAYS (+/- 5 DAYS) OF CLEANSER AND MOISTURIZER USE (BID)



	Dry	Very Dry	Crusty	Very Crusty	Itchy	Very Itchy	AD Symptoms
Day 0	15.2	51.5	12.1	3.0	30.3	33.3	100
Day 42	33.0	6.1	3.0	3.0	21.2	6.1	22

*t_{27}=2.65, P=.001 † t_{27}=5.38, P=.0001

REPORTED QUALITY-OF-LIFE PARAMETERS AT DAY 42, SCORED ON A 5-POINT SCALE (1=NOT AGREE TO 5=STRONGLY AGREE).



*t_{27}=2.65, P=.001 †t_{27}=5.38, P=.0001 †† t_{28}=2.53, P=.02

CeraVe Hydrating Cleanser followed by CeraVe Moisturizing Cream twice daily (BID)

Lynde CW, Andriessen A. *Cutis*.2014;93(4)207-2013

A Cohort study on a Ceramide-containing Cleanser and Moisturizer used for Atopic Dermatitis – A typical Case

- Twice-daily use of a ceramide-containing cleanser and moisturizer combination substantially improved skin condition and clinical outcomes according to the SCORAD index as well as QOL in patients with AD
- The products were shown to be easy to use and were well tolerated in children and adults with AD with no adverse reactions reported

Figure 5. A 20-month-old boy with atopic dermatitis since birth on the right hand (A), right leg (B), and right antecubital fossa (C) at baseline. At day 42, improvement was noted on the right leg (D).

Lynde CW, Andriessen A. *Cutis*.2014;93(4)207-2013

CeraVe Technology – Backed by Clinical Evidence, cont.

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A Consensus About the Importance of Ceramide Containing Skincare for Normal and Sensitive Skin Conditions in Neonates and Infants

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[b]Radboud UMC, Nijmegen and Andriessen Consultants, Malden, The Netherlands
[c]Florida Atlantic University, Boca Raton, FL
[d]Baylor College of Medicine and Texas Children's Hospital, Houston, TX; A Children's House for Pediatric Dermatology, Houston, TX
[e]Northwestern Medical Group, Chicago, IL; Northwestern University Feinberg School of Medicine, Chicago, IL
[f]King Bay Pediatrics, Maimi, FL, General Pediatrics, Nicklaus Children's Hospital, Miami, FL
[g]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY

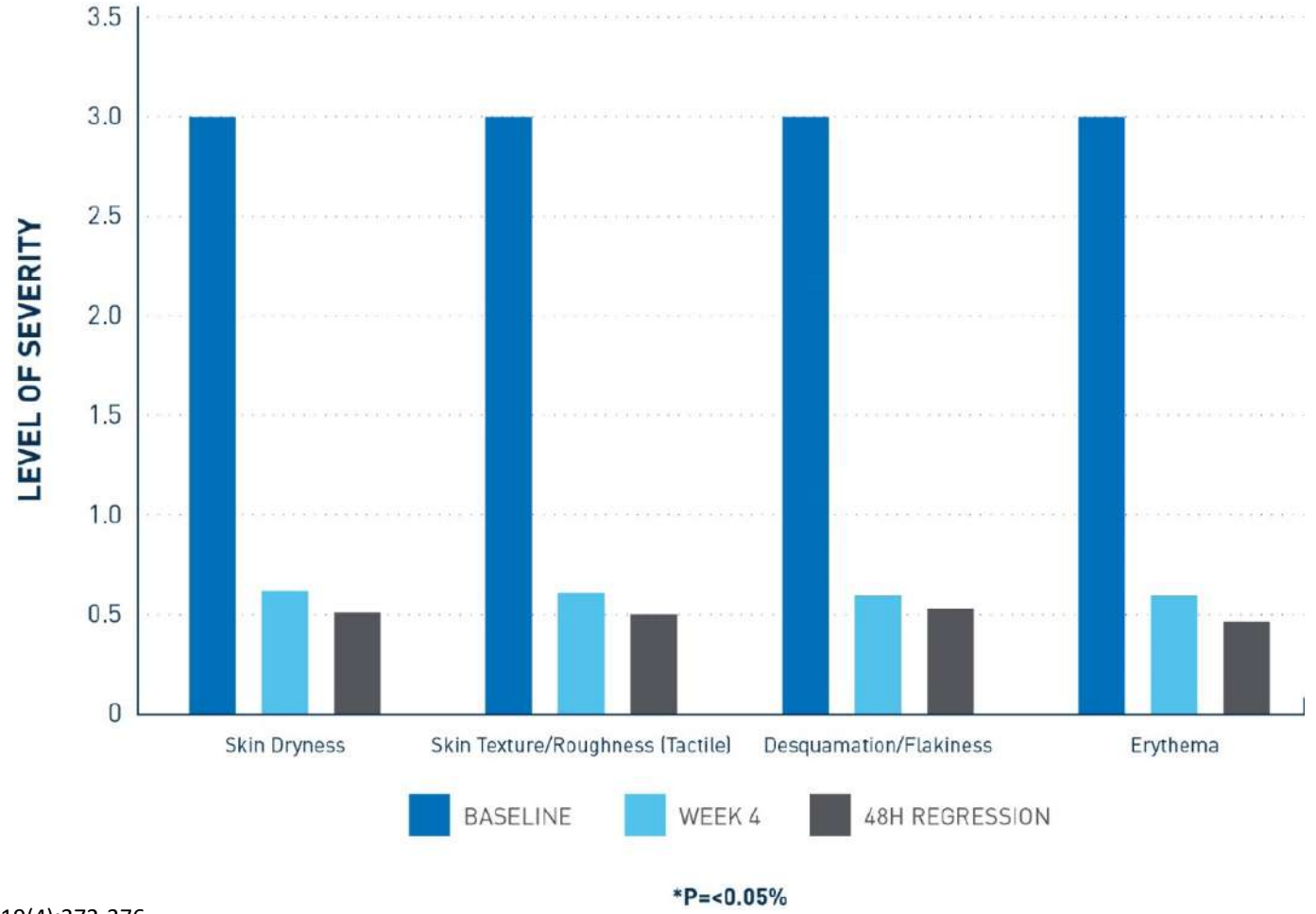
Single-center controlled clin study on 49 women, ages 30 to 65 with dry to very dry skin

- Protocol: 4-week single-center, controlled study.
  - Moisturizing Cream use twice daily on the lower leg; the other leg remained untreated.
  - Home care regimen: Neutrogena Bar Soap, Moisturizing cream
- Assessments were made on both the treated and non-treated areas
  - Efficacy and tolerability evaluation at baseline, immediate, day 3, week 4 and a 48-hour regression.
  - Bio-instrumental measurements and self-assessment questionnaires at baseline, immediate, day 3, week 4 and a 48-hour regression.

Draelos Z. J Drugs Dermatol. 2020; 19(4):372-376

Controlled study - Clinical grading: Continues to maintain the skin barrier

Maintains improvement even **AFTER 48 HOURS** of stopping use



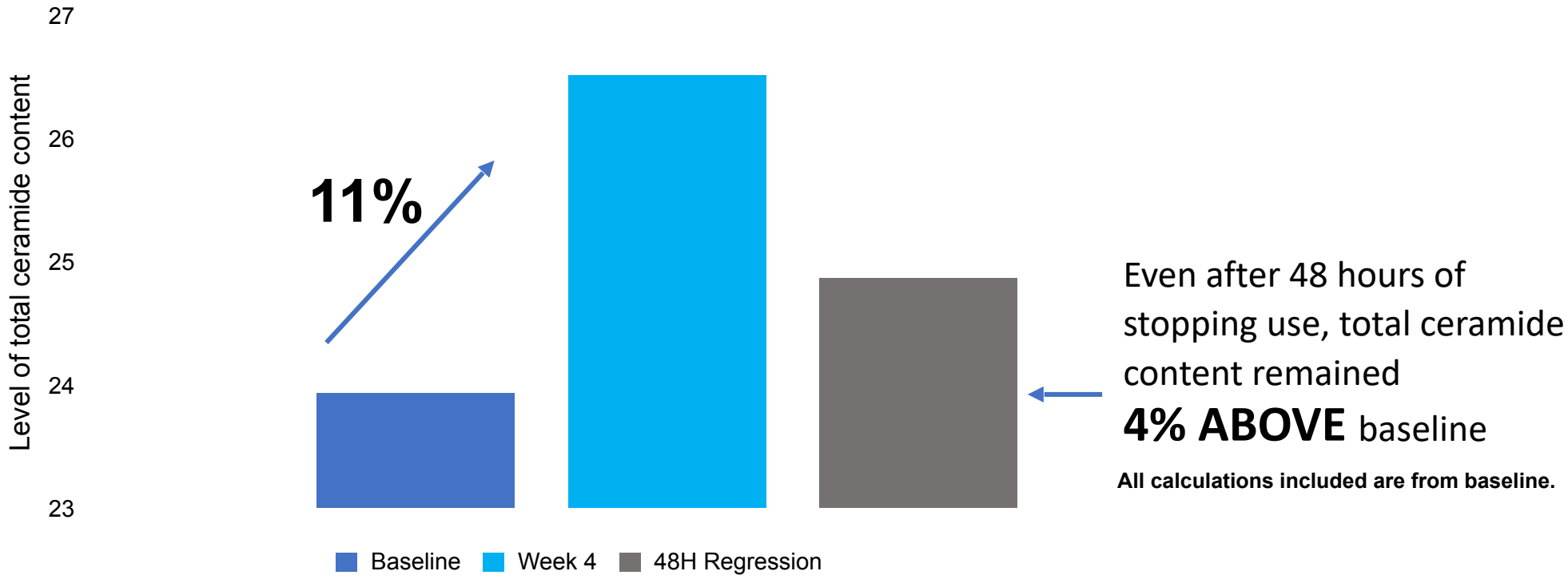
All calculations included are from baseline.

Draelos Z. J Drugs Dermatol. 2020; 19(4):372-376

Controlled study - BIOCHEMICAL EXPLORATION

Increase total ceramide content in the skin

Daily use resulted in a **11% INCREASE** in total ceramide content in 4 weeks



Even after 48 hours of stopping use, total ceramide content remained **4% ABOVE** baseline

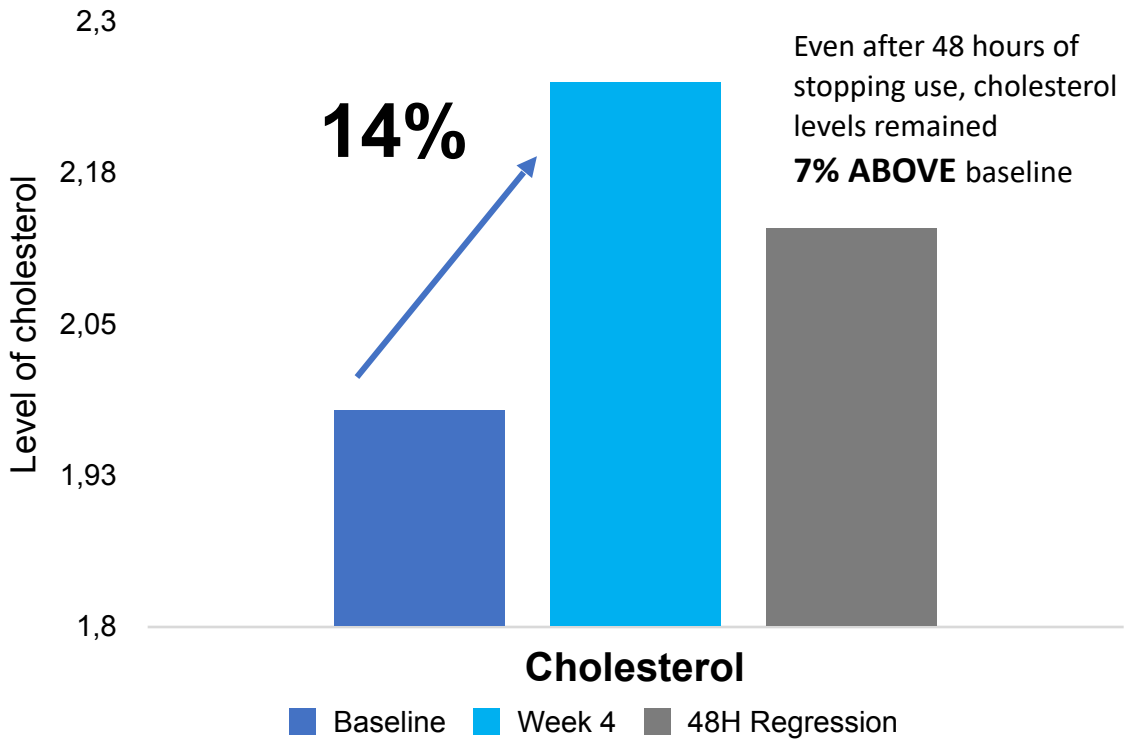
All calculations included are from baseline.

Draelos Z. J Drugs Dermatol. 2020; 19(4):372-376

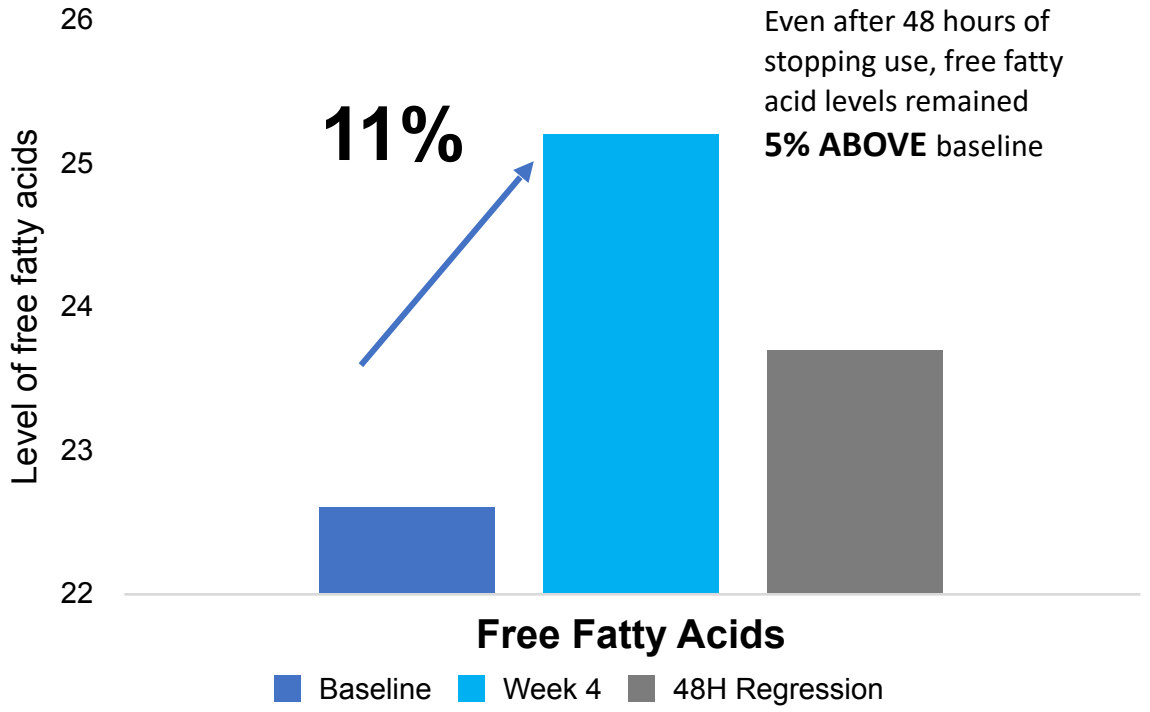
Controlled study - BIOCHEMICAL EXPLORATION, cont.

SHOWN TO INCREASE CHOLESTEROL AND FREE FATTY ACIDS LEVELS

Daily use resulted in a **14% INCREASE** in cholesterol levels in 4 weeks



Daily use resulted in a **11% INCREASE** in free fatty acids levels in 4 weeks



Draelos Z. J Drugs Dermatol. 2020; 19(4):372-376

All calculations included are from baseline.

Controlled study - PHOTOGRAPHIC EVALUATION

VISIBLY MAINTAINS CUTANEOUS MOISTURE

Results apparent even **48 HOURS AFTER** stopping use

Draelos Z. J Drugs Dermatol. 2020; 19(4):372-376

Conclusions

The choice of cleanser/moisturizer is dependent on individual preference

The ideal agent should be:

Safe, effective, inexpensive

Free of additives, fragrances, perfumes, sensitizing agents

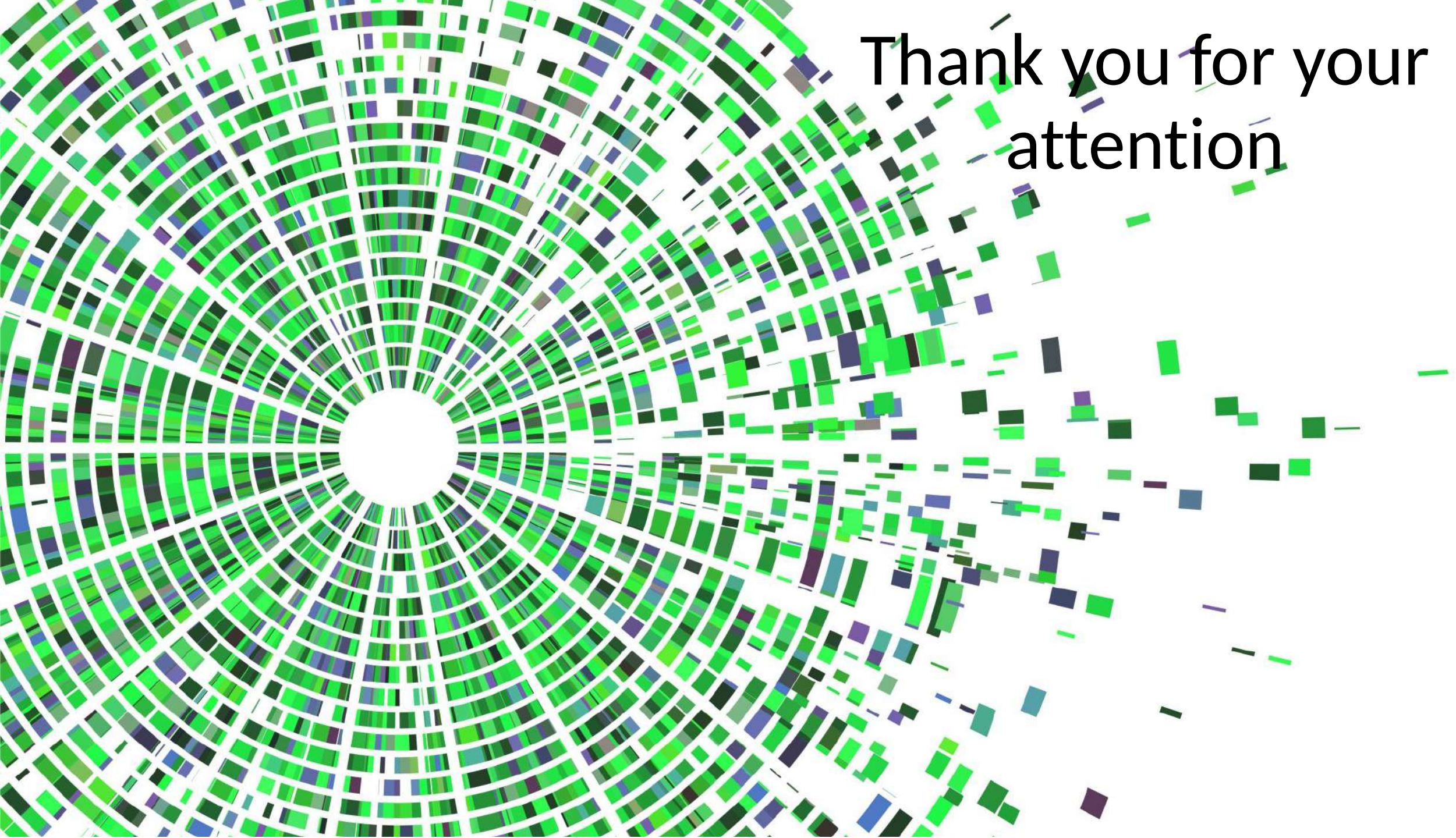
Found pleasant to use by the patient

Use a cleanser and moisturizer with a near-physiologic pH (4 - 6) allow for acid mantle repair and increased antimicrobial defense capacity

Conclusions

CeraVe skincare is supported by clinical evidence and helps restore skin barrier function, which is beneficial for inflammatory skin conditions

Questions?


Thank you for your attention