Review
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Barrier Properties of Atopic Eczema Skin: Supramolecular Structure and Evaluation Method

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Abstract: As a barrier, the skin prevents organisms and xenobiotic substances, including toxins, from entering the body and protects the body from losing essential substances, especially water and electrolytes. This vital barrier function is compromised in diseased skin, particularly atopic eczema (AE), due to significant structural changes in the intercellular lipid of the stratum corneum. Unraveling the complex correlation between three key domains: lipid composition, structural lipid organization, and skin barrier properties, gives a valuable perspective on the prediction of disease severity and product efficacy. In this comprehensive review, the crucial role of the intercellular stratum corneum space on chemical movement across the skin is discussed first, along with the foundational stratum corneum model, as a basis for the lipid organization concept. Subsequently, data from the original articles concerning the direct effect of lipid composition on barrier properties were thoroughly discussed, aided by review articles, to draw the correlation between the three domains as stated previously. The synthesized results showed that in AE, levels of long-chain ceramides and fatty acids decrease. This reduction ostensibly compromises the skin's barrier function by diminishing the formation of essential orthorhombic crystalline structures and long-periodicity phases (LPPs).

Introduction

Atopic eczema (AE, synonym for atopic dermatitis) is a hereditary disease associated with mutations in numerous genes. Among others, the genes directly responsible for the epidermal (skin) barrier function encode profilaggrin and late cornified envelope protein 3A, which are termed *FLG* and *LCE3A*, respectively (1). *FLG* is the most-studied gene associated with the disease. Profilaggrin (phosphorylated filaggrin) is attached to keratohyalin granules of keratinocytes that are located in the stratum granulosum (SG). Dephosphorylation of profilaggrin produces filaggrin monomers that are localized in the deepest layer of the stratum corneum (SC), acting as the glue of keratin filaments for aggregation (2). In the upper layer of SC, filaggrin is further degraded to produce a histidine-rich amino acid matrix, which is converted to produce pyrrolidone carboxylic acid and urocanic acid. These two substances are responsible for acidifying the medium to be fit with the pH needed by β-glucocerebrosidase and acidic sphingomyelinase to synthesize ceramides actively (3). Moreover, filaggrin also plays a role in the secretion of lamellar bodies from keratinocytes, containing the substrates for lipid synthesis (4). Therefore, *FLG* is indirectly correlated with skin intercellular lipid composition, and *FLG* mutations, which are determined by the interaction of a specific individual's *FLG* nature and the environment, result in loss-of-function *FLG* variants associated with AE.

In a review about atopic eczema (AE) in 2015, it is shown that the prevalence of AE in the world is around 3% in adults and 20% in childhood (5). In 2019, the prevalence in adults increased to about 10%, while in children, it was steady (6), indicating that this disease still needs attention. AE patients have social problems related to personal interaction and psychological problems related to individual well-being (7, 8) due to the aesthetic function of the skin, in addition to the physiological problem. Skin, as the body's surface, has several physiological functions, including protection against penetration of chemicals from outside the body and preventing water evaporation. In an AE patient, the barrier property of the skin is modulated, triggering a higher level of transepidermal water loss (TEWL) and penetration of irritants (9), which exacerbates the effect of AE.

The penetration of water and other substances across the skin follows several routes, such as sweat and hair pores, intercellular lipid lamella, and passive diffusion via epidermal cells. Consequently, changes in these three pathways potentially affect the skin barrier properties. However, the second route, i. e., via intercellular lipid,

becomes the most dominant route due to the largest surface area. Therefore, in this review, we focus on how the barrier properties of the AE skin are modulated and correlate the changes with the lipid organization of the intercellular space of the stratum corneum.

Many studies demonstrate that the main lipid as well as the minor lipid of the stratum corneum intercellular matrix change in composition, mainly a decrease in esterified ultra-long-chain ceramide and an increase in unsaturated fatty acids, as elucidated by stripping samples (10). To study the effect of lipid component modification on lipid organization and barrier properties, artificial skins that mimic the compositions are prepared. The methods of lipid stratum corneum (SC) analysis and organization are highlighted. To correlate lipid composition and organization with barrier properties, the drug model permeability and water evaporation across lipid SC membranes should be evaluated. It was unraveled that the decrease in barrier properties of the AE artificial skin correlates with the decrease in Long Periodicity Phase (LPP) and orthorhombic crystalline phase.

On one hand, the collected information is necessary as a perspective to formulate drug products capable of increasing the barrier properties of the AE skin. Increasing the barrier properties means protecting the body from the outside-in movement of toxins and allergens and inside-out water loss. On the other hand, modulation of barrier properties can be exploited in transdermal delivery of systemic drugs for AE itself or for other diseases. Therefore, this work aims to address the underlying reasons for the modification of AE skin barrier properties at the first level of causality. Whereas the higher level of causality, i. e. , the enzymatic alteration that is responsible for lipid composition, is excluded.

Methodology

The present traditional unsystematic narrative review was started by identifying subjects that support the review objective. These subjects were ordered as subsections, which are listed in the Results and Discussion section. The first four subsections are supporting issues, included in the manuscript as reasons concerning the importance of intercellular lipids and as information on the baseline (normal/health condition) of lipid composition and organization. The following subsections are the main focus of this manuscript. The information and data in the subsections were retrieved from scientific databases, including PubMed and Google Scholar, using topic-specific keywords. The collected articles for all subsections were screened using the inclusion criteria, including English-language articles and articles from scientific books or journal articles granted a Digital Object Identifier (DOI). There are no specific exclusion criteria for the types of literature that strengthen the supporting issue subsections. However, references from review articles and book chapters are excluded from the main focus subsections. Therefore, only primary literature, such as research articles and case reports, is accepted in the main focus subsections.

The Limitation of the Methodology

The publication year of the accepted articles is not limited. All articles were analyzed solely based on their content, specifically whether or not they supported the planned subsections. Many of them are not included in the references list because they contain no information that supports the subsections. Unfortunately, the number of these excluded articles is not documented well. Due to the limited number of suitable articles, the specific keywords for searching in PubMed or Google Scholar were progressive to focus on specific information supporting the subsection idea. Therefore, documentation for these specific keywords is unavailable. Since the number of searched articles and the process of article selection are not documented well, the presented knowledge synthesis is only based on the literature listed in the References section. Therefore, dissenting opinions derived from other references may be possible.

Anatomy of Skin as a Barrier Function

Structurally, human skin is composed of 3 layers: epidermis, dermis, and hypodermis (subcutis), with the epidermis being the outermost layer. The top layer of the epidermis is the stratum corneum, the dead outermost layer, followed by the viable layers, namely stratum granulosum, stratum spinosum, and stratum basale. On some of the body sites, such as the palm and sole, the dead stratum lucidum also occurs under the stratum corneum (SC). The total thickness of the epidermis ranges from 31 to 637 µm, varying between body site, sex, age, and race (11–15), whereas the thickness of SC is estimated to be only about 6-20 nm, depending on the body site, with about 20 layers (16, 17). However, SC has a unique composition and configuration that produces an excellent barrier property. In addition to the main skin barrier, the whole epidermis also has a barrier function (18).

Viable epidermis is constructed by cells known as keratinocytes, the most abundant cell type, together with melanocytes and Langerhans cells, which originate in the stratum basale. This undifferentiated cell attaches to the basement membrane, a membrane that separates the epidermis and dermis layers. While moving up to the upper layer of the epidermis, the keratinocyte differentiates and desquamates as the final step. This process takes 40-56 days for healthy skin and is faster in diseased skin (19–21). Another choice for the keratinocyte instead of differentiating is to undergo apoptosis, which is ended by being phagocytosed, which occurs in the stratum basale (20, 22).

Differentiation of keratinocytes is important, as this process is mandatory for stratum corneum formation. The differentiation of keratinocytes starts with the detachment from the basal membrane, followed by the movement of free keratinocytes to the higher layer (stratum spinosum). Subsequently, the keratinocytes become flat, increasing cell contact, and desmosomes are produced. At the same time, the new subclasses of protein keratin are produced, namely keratin 1 and keratin 10. A keratohyalin granule is produced in the cell, which is now in the stratum granulosum layer. In this layer, many processes occur, e. g., the crosslinking of keratin filaments to produce cytoskeletons and the degradation of DNA, the nucleus, and the organelles of the cell, followed by the occurrence of the lamellar bodies. The process of cornified envelope formation also starts here. Actually, cornification is a replacement process of the keratinocyte membrane. The

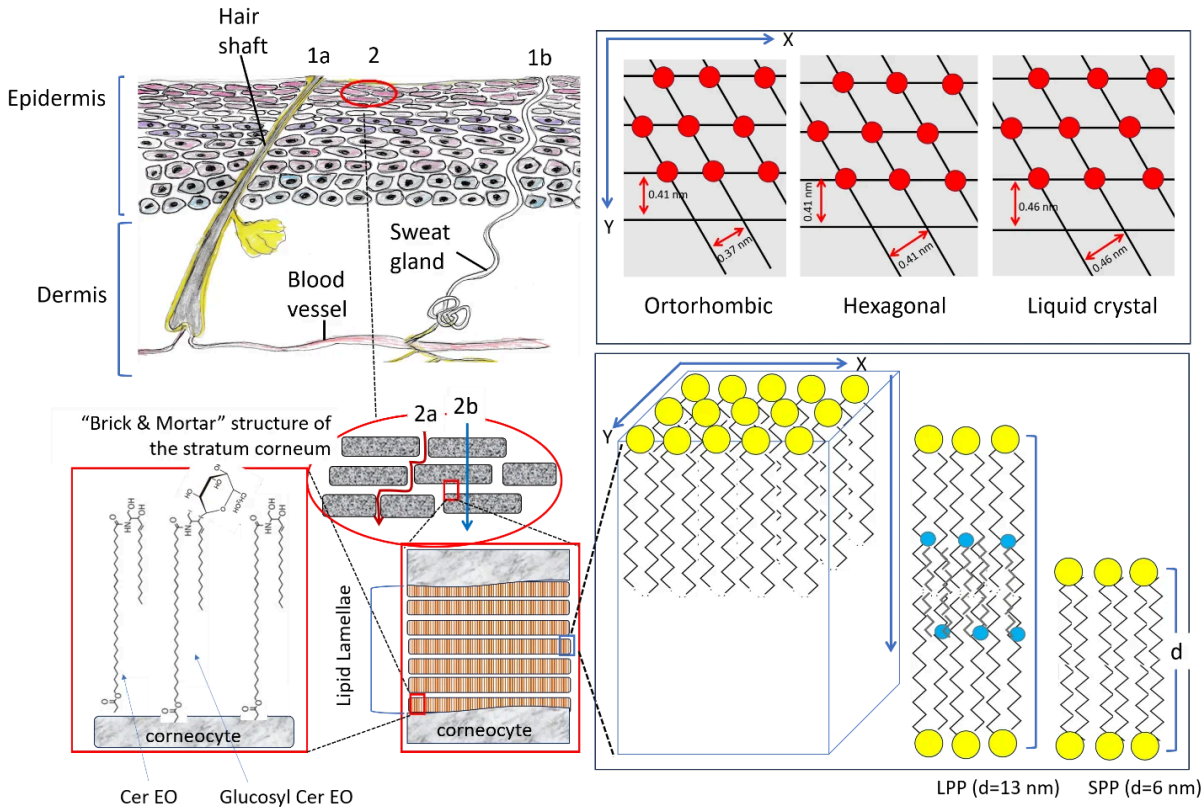


Figure 1. Structure of the skin and lipid organization. Left-hand side: The skin contains the dermis and epidermis layers. The substance enters the body by the transappendageal route via follicle hair (1a) and sweat pore (1b), or the transepithelial route via intercellular (2a) and transcellular (2b) regions. Out of these four routes, the intercellular route is the major way in which the substance follows the lipid lamellae. Lower right-hand side: The long periodicity phase (LPP, 3 lipid layers) and Short Periodicity Phase (SPP, lipid bilayer) occur as lateral organization of lipid lamellae (z axis, blue and yellow circles are the head groups of ceramides and/or FFAs), which show the repeat distance (d) of about 13 nm and 6 nm, respectively. Upper right-hand side: Laterally (view perpendicular to the z-axis to address the x and y-axes), the lipid is organized as orthorhombic at the skin temperature, but as the temperature increases, this packing turns to hexagonal before transforming to liquid crystal. The red circles represent the perpendicular view of lipid tails, i.e., the methylene group. The figure was created by the authors. The references are provided in the manuscript body.

cornified envelope is formed by various proteins, such as loricrin, filaggrin, keratin, involucrin, and small proline-rich (SPRs) proteins, which are highly transglutaminase-crosslinked (20, 23, 24).

Where are the other components of the epidermis membrane, such as phospholipids? In the previous paragraph, it is mentioned that lamellar bodies occur in the keratinocytes of the stratum granulosum. Lamellar bodies contain phospholipids, glucosylceramides, sphingomyelin, cholesterol, and numerous lipid hydrolases, including β-glucocerebrosidase, acidic sphingomyelinase, secretory phospholipase A2 (sPLA2), and acidic/neutral lipases. In the terminal process of cornification, lamellar bodies secrete their contents. Glucosylceramides and sphingomyelin are transformed into ceramides, and phospholipids are hydrolyzed to free fatty acids. Ceramides, free fatty acids, and cholesterol are the main components of lipid lamellae, which fill in the intercellular space of the "brick" cornified envelope (corneocyte) as a "mortar"(25–27), as shown in the stratum corneum structure. The lamellar structure of the intercellular is started with the lipid section attached to the protein cornified envelope by a covalent bond to the glutamate residue of involucrin, known as the lipid envelope (28, 29). The physicochemical properties of skin cells and intercellular matrices, as well as the skin pores and hair, determine the preferred route for material to permeate.

Substances Permeation Through the Skin

Figure 1 shows that the process of substances entering the blood through the skin takes place in two ways. First, following the route of sweat pores and hair follicles (both of which are referred to as the transappendageal route), and second, permeate across the epidermis, namely the transepidermal route. Concerning the first route, the sweat pore is ideal for hydrophilic material due to the components filling the pore, aqueous sweat. These include hydrophilic molecules (such as caffeine) and nano-sized materials (such as hydropolymer nanoparticles, liposomes, and micelles). The surface of lipophilic nanocarriers, such as nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN), is also hydrophilic; thus, these lipid nanocarriers are also compatible with this route. Additionally, these lipid nanocarriers are able to undergo phase inversion, making them compatible with sebum, the

component filling the hair follicles'pores (30 – 35). However, the area of sweat and hair skin pores is only around 0.1-1.2 percent of the total surface area of the skin, depending on the body site (36), making them the minor route of transport through the skin.

The second route is the major pathway, particularly for the lipophilic substances of molecular size, since this route occupies around 90-99 % of the skin surface (36). However, it is difficult for substances to pass through the epidermal layer by entering epidermal cells (referred to as transcellular transport), even though this route is shorter than following the meandering intercellular pathway. The corneocytes contain very dense proteins surrounded by a cornified envelope and a lipid envelope that is highly impermeable. This condition affects the intercellular space as the main route of substance permeation, known as

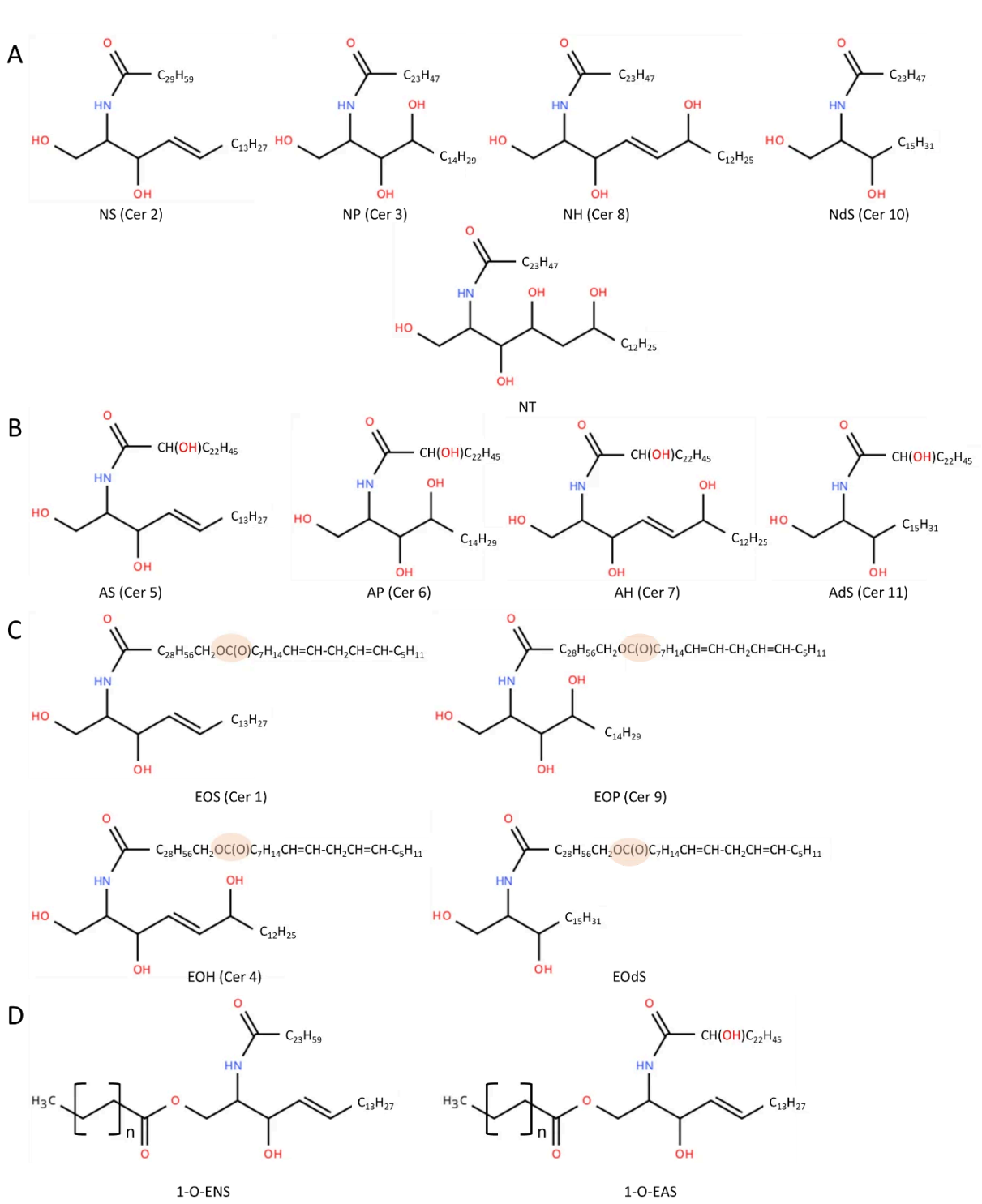


Figure 2. Molecular structure of ceramide subclasses showing the most abundant chain length. Three types of fatty acids are denoted: non-hydroxy (A), α-hydroxy (B), and ω-esterified by mostly linoleic acid (C, the ester groups are highlighted in red). Esterification is also possible in the sphingoid backbone by saturated fatty acid (D). The figure was created by the authors. The references are provided in the manuscript body.

intercellular transport (37, 38). Therefore, the composition of the material filling this pathway determines the permeability of transported substances.

Intercellular Composition of the Stratum Corneum Layer in Healthy Skin

The transcellular route is very limited by the impermeability of the corneocyte, while the transappendageal route is limited by its surface area. This condition causes the intercellular space to become the most possible transdermal route, and the changes in its composition and organization are expected to alter the whole skin barrier function. It is interesting to unravel the composition of the intercellular spaces of corneocytes comprising lipid, in relation to their function.

The lipids lie between corneocytes in lamellar formation, meaning that the lipid sequence and water sequence arise one-to-one (39, 40). The main components of the lipid region are ceramides, free fatty acids (FFA), and cholesterol, in an approximately equimolar ratio (41). Some traces of free sphingoid base also occur in a small amount, about 0, 44% by weight of stratum corneum lipids (42, 43). In addition, cholesterol sulfate and triglycerides are also found in the stratum corneum lipid (44–48).

While the cholesterol and FFAs of stratum corneum lipid are quite simple, ceramide, a class of lipid formed by a sphingoid base linked to a fatty acid via an amide bond, varies in molecular structure. This type of substance plays a critical role in determining the barrier properties of the stratum corneum (49). The structure of ceramide subclasses is provided in **Figure 2** (50). Four sphingoid bases coexist, e. g. , sphingosine (abbreviation: S, which has an unsaturated covalent bond in C4 and C5 of sphingoid base), dihydrosphingosine (dS, saturation of C4 and C5 with two hydrogen atoms), phytosphingosine (P, hydroxylation of C5 and hydrogenation of C4), and 6-hydroxysphingosine (H, hydroxylation of C6). The fatty acid bound to these sphingoid bases can be a non-hydroxy fatty acid (N), an α-hydroxy fatty acid (A), or an esterified ω-hydroxy fatty acid (EO). The combination of 4 sphingoid bases and 3 free fatty acids produces 12 subclasses of ceramides (42, 51–54). It should be noted that dihydroxy dihydrosphingosine linked to a non-hydroxy fatty acid was also recently detected. This new sphingoid base skeleton is symbolized by T, as there are "two" dihydroxy. Besides that, unesterified ω-hydroxy fatty acid (symbolized as O) linked to phytosphingosine was also found (55). However, it is suspected as a residue of ceramide covalently bound to the cornified envelope protein, involucrin (28, 56). In addition, 2 subclasses of ceramide were very recently identified. The modification is esterification of the 1-OH of Sphingosine (S) bonded to hydroxy and non-hydroxy fatty acids, namely 1-O-EAS and 1-O-ENS, respectively (57). Excluding the OP (i.e., a ceramide subclass constructed by an omega-hydroxy fatty acid bonded to phytosphingosine), **Figure 2** shows the structure of all 15 ceramide subclasses, with the most abundant carbon chain length of sphingoid base, fatty acid, and acyl ester.

The combination of 3 fatty acid types (N, A, EO, and O) with 6 sphingoid bases (S, P, H, dS, T, and 1-O-esterified S) should produce 24 subclasses. However, there is no single research for the determination of ceramide subclasses, resulting in all the subclasses. Suzuki and co-workers proved the existence of an additional sphingoid base, the 4, 14-Sphingadiene (SD), bonded to all fatty acid types. Missing 1-O-esterified Sphingosine and T Sphingoid bases, the existence of 20 (i. e. , 4x5) subclasses of ceramide was evidenced (58). The ceramide subclasses situation is more complex due to the discovery of a new sphingoid base, the 1-O esterified Phytosphingosine, and a new fatty acid, the β-hydroxy fatty acid (59, 60).

Molecularly, the ceramide compound in stratum corneum is very heterogeneous, since the carbon chain length of sphingoid bases as well as fatty acids is widely varied. It is reported that more than 1300 species of ceramide exist in the human stratum corneum (58). The most abundant and well-known chain length of sphingoid base is C18 (61). In fact, it varies between C12 and C28 (62, 63). It has been found that the total chain length of ceramide ranges between C32 and C74, suggesting that the sphingoid base is probably varied (63, 64). The fatty acid linked to the sphingoid base is also heterogeneous in length, with the even chain length being more dominant than the odd one. The saturated fatty acid is much greater than the unsaturated one. The most abundant acyl moieties are 24, 26, and 28-carbon chain lengths, excluding ω-esterified ceramide and NS ceramide that show more than 30-carbon chain length domination (52, 54, 65–68). Another researcher suggested that ω-esterified ceramide has an acyl carbon chain length of 28 to 34 (55). More than 90% molar ratio of the fatty acid bond to the ω-hydroxy fatty acid of ceramide is linoleic acid (C18: 2), and others are C20: 2, C22: 2, and C16: 2, respectively, from the higher fraction (55). The various lipid components, as described here, are orchestrated to form a structured lipid lamella showing a specific organization in the lamellar direction and perpendicular view. This supramolecular organization of the material filling the intercellular pathway determines the permeability of transported substances.

Intercellular Lipid Organization of the Stratum Corneum in Healthy Skin

It is mentioned previously that lipids in the intercellular space of SC are arranged as lamellae (69). The lamellae were modelled, first, as a "stacked monolayer model" (70), then modified by a "domain mosaic model" (71). The second-generation models of lipid stratum corneum are the "sandwich model" (72) and "single gel phase model"(73), which were debatable mainly about the existence of a liquid phase in the lipid region of lamellae (74). The "sandwich model" suggests that a lipid unit of lamellae is constructed by a liquid narrow sequence gripped by 2 broad solid-state sequences, known as "broad-narrow-broad", whereas the "single gel phase model" suggests that the lipid region of lamellae is homogeneous (72, 73, 75, 76). Later, no evidence proves the "single gel phase model". Moreover, Iwai and coworkers proposed the new model, the "stacked bilayer model" (77), although it needs much more evidence. Research by Radhakrishnan and coworkers that prepared a lipid membrane composing ceramides, fatty acids, and cholesterol is likely to support this stacked bilayer model (78). However, the membrane lacked a specific ceramide, i. e., esterified ceramide, which plays a critical role in the layer formation of lamellar lipid skin, namely Long

Periodicity Phase (LPP) according to the sandwich model.

Based on the sandwich model, as shown in **Figure 1**, two repeat distances coexist: 13.4 nm and 6.4 nm. In the latter, they are referred to as the Long Periodicity Phase (LPP) and the Short Periodicity Phase (SPP), respectively (75, 79). The LPP is always found in the stratum corneum of healthy skin, so it is believed that this phase has a prominent role in the barrier function (75). It is also evidenced that decreasing the proportion of LPP in the stratum corneum model, as well as in the native stratum corneum from diseased skin, reduces the barrier properties (80–83). Perpendicular to the plane of lamellae, the intercellular stratum corneum lipids of healthy skin are organized dominantly as an orthorhombic-dense-ordered crystalline at room temperature. Increasing the temperature, this lateral packing comes to a hexagonal-less-dense-ordered crystalline, and at temperatures above 80 °C, the lipids disorder to form a crystalline liquid phase (84, 85). This lipid organization is displayed in **Figure 1**. Showing the denser lipid packing, the fraction of orthorhombic organization correlates with skin resistance against penetration.

Many studies have been conducted to elucidate the position of each component of lipids in a unit of lamellae. Measurement using neutron diffraction along the LPP proves a repeatable distance of a high electron density every about 13 nm, which is the length of the LPP (86). This result agrees with the measurement using small-angle X-ray diffraction (SAXD) on human stratum corneum (87), artificial stratum corneum (88), and an epidermal cell culture model (89). Around the center of LPP are also found two regions with high electron density, spaced about 2.5 nm (90, 91). These four high-electron-density positions mark the boundary of the broad-narrow-broad construction, as stated previously. The high density of electrons suggests that the heads of ceramides and fatty acids are resting. The long carbon chain of ceramide and free fatty acid puts their heads on both sides of LPP, and some of them meet tail to tail in the center, especially the acyl chains of CER EO (91). The head of the short-chain ceramide and free fatty acid can be kept in the interphase of liquid and crystalline sequence, around the center of LPP, and beside the head of long-chain ceramide and free fatty acid, and meet tail to tail in the broad region of LPP (92). Alternatively, the short-chain ceramide and free fatty acid arrange the SPP with the head group kept on both sites and meet tail-to-tail (93). In the SPP, the head group of cholesterol is slightly deeper from both sites, and the tail is in the inner part of the LPP (93). The position of cholesterol in the LPP is still debatable. It can be attached head-to-head with ceramide in the center of the LPP, the fluid region (90), or in the inner part of the broad sequence of LPP (94, 95).

The existence of CER EO, especially CER 1 (CER EOS), is a requisite in the formation of LPP. The CER EOS-deficient stratum corneum model is unable to develop LPP. Generalizing this data to the subclass level, CER EO reduction gives a significant decrease in the LPP domain (93, 96, 97), and correlates with the permeability enhancement (98). Moreover, the application of saturated acyl ω-esterified instead of unsaturated ones, e. g. , CER EOS-stearate instead of CER EOS-oleate (oleyl-EOS ceramide) or CER EOS-linoleate (linoleyl-EOS ceramide), also fails to form the LPP (80). The chain length of FFA and the ratio of total FFA to the total lipid play a prominent role in the orthorhombic lattice domain. Increasing the chain length of FFA improves the formation of the LPP domain (99) and additionally promotes the lipid crystal to the more orthorhombic system (97, 100). Comparing the role of the LPP domain and the orthorhombic crystal form on the SC permeability, it is noted that the role of lamellar organization on SC barrier properties is dominant over the lateral organization (101, 102).

The effect of the epidermal microenvironment on the lamellar and lateral organization of SC has been studied. The LPP formation is sensitive to pH. This process is upregulated upon changing pH from 5 to 7, 4 (46, 103), while the lateral packing of the lipid is not affected by pH (103). The level of hydration has little effect on lateral packing (104). The intensity of LPP is very affected by the temperature. It starts to decrease slowly within the temperature range of 20 °C to 32 °C. Increasing the temperature above 32 °C, the intensity of the LPP signal gradually decreased, and the LPP disappeared at about 55 °C. Consequently, the lamellae showed high permeability (105, 106). A similar trend is also observed in lateral organization. An increase in temperature reduces the orthorhombic phase. At normal skin temperature, i. e. , 32 °C, the lipid lamella constructed from an *ex vivo* epidermal lipid contains an orthorhombic-to-hexagonal phase ratio of about 5: 1. Introduction of sebum components, such as a case of lipid lamellae from an *in vivo* epidermal sample, decreases the orthorhombic phase to a 1: 1 phase ratio (60). The effect of sebum contaminating SC lipids on supramolecular organization additionally confirms that lipid composition is more dominant in determining the SC organization. Therefore, lipid isolation from the stratum corneum and analytical methods for lipid species determination are crucial steps in SC lipid composition assessment.

Method and Sample for SC Lipid Profiling

The lipid composition of SC can be analyzed using various methods. Norlan and co-workers developed a high-performance liquid chromatography (HPLC) method to reveal the lipid composition of the inner stratum corneum. A subsequent gas liquid chromatography/mass spectroscopy (GLC/MS) method was needed to separate the subclasses of ceramide and free fatty acid, which were not accomplished using HPLC, and gas liquid chromatography/flame ionization detector (GLC/FID) was used to complete the quantitative analysis of each component (107). In another study, Weerheim and Ponect used an HPTLC method to study the fraction of three major components, namely cholesterol, free fatty acid, and ceramide, in the depth variation of the SC regardless of the subclasses of each component (41). Moreover, Masukawa and coworkers used normal-phase liquid chromatography-electrospray ionization-mass spectrometry (NPLC-ESI-MS) to measure the ceramide composition in SC (108). A new method of analysis for lipid SC profiling has been validated and used in various studies. This one-step LC/MS method has been successfully used to determine the change in lipid composition at the subclass level in healthy as well as atopic eczema and Netherton syndrome SC (81, 83, 109 –

Table 1. The change of SC lipid composition and SC properties in atopic eczema (AE) skin. The permeability data (marked by *) resulted from an artificial SC model that mimics the AE lipid composition.

Parameters	Modification	Reference
Mass fraction of total lipid in SC	Reduce	(118)
Mass fraction of total ceramide in SC	Reduce	(118, 119, 124)
Ratio of ceramide to cholesterol	Reduce	(121)
Mass fraction of CER EO in total ceramide	Reduce	(124–126)
Ratio of CER EOS-oleate to CER EOS linoleate	Increase	(125, 127)
Ratio of CER EO with unsaturated to saturated one	Increase	(128)
Ratio of α-hydroxyl ceramides to non-α-hydroxyl ceramides	Increase	(81, 124)
Chain length of non-esterified ceramides	Reduce	(126, 129)
Mass fraction of long-chain FFA, i. e. , more than 23, in FFA	Reduce	(64, 130)
Mass fraction of unsaturated FFA in FFA	Increase	(64)
Mass fraction of cholesterol sulphate in SC lipid	Increase/decrease**	(121, 125, 131)
Free sphingoid base	Unconcluded	(132, 133)
Glucocylsphingosine and sphingosilphosphorylcholine	Increase	(134, 135)
Triglyceride content in SC	Reduce	(136)
LPP length	Reduce	(81, 109)
LPP formation	Reduce	(81, 109)
Orthorhombic formation	Reduce	(81, 137)
Barrier properties	Reduce	(128, 138)
Permeability* and TEWL	Increase	(128, 138)

** Yamamoto *et al*. (1991) and Tokoro *et al*. (2025) state that cholesterol sulphate increases. In contrast, Di Nardo *et al*. (1998) reported that cholesterol sulphate decreases. Based on authors' evaluation, it was identified that **Figure 1** of Di Nardo article suggests that the cholesterol sulphate increased, different with the statement in the text body.

111). At a higher level of analysis, an LC/MS-based method has been successfully developed by setting up a high-resolution MS/MS fragmentation in the instrumentation to determine the ceramide species of healthy skin (55).

Lipid samples for SC profiling can be collected from various resources. Such as SC isolated from human skin (biopsy), tape-stripped *in vivo* skin, and full-thickness skin explant (41, 81, 83, 107, 110). An epidermis biopsy specimen can be deproteinized without collapsing the lipid lamellae organization. Therefore, it is best to study the natural supramolecular organization, for instance, to determine the SPP/LPP and Hexagonal/Orthorhombic packing, in addition to lipid composition analysis. However, due to an ethical issue, it is intolerable to take the full stratum corneum sample (by biopsy) from the diseased skin, such as atopic eczema, to be used in a lipid profiling study. Usually, the strip sample is used instead of the full stratum corneum biopsy specimen.

The advantage of using SC striped samples is the flexibility in selecting the SC depth. Therefore, the data on the depth-course lipid composition can be revealed; i. e. , each layer of SC (differences in depths) has a different composition of ceramide, free fatty acid, and cholesterol (41). However, critical steps should be performed to prepare lipid lamellae from strip samples, including lipid extraction from the strip, spraying lipid solution in extracting solvent, solvent evaporation, annealing the embedded lipid at a higher temperature, cooling to form lamellae, and hydration. Conducting these steps on a depth-based group of strip samples, the correlation of SC depth on lipid organization is revealed, i. e. , the more hexagonal formation in the upper layer of SC represents the shorter-chain ceramide and free fatty acid in the strip sample (84, 112). This is in line with a postulation that the increase in chain length of free fatty acids and/or ceramides triggers a more orthorhombic crystalline morphology of lipid, showing higher barrier properties (61, 64, 81). Since lipid components in diseased skin change, the lipid organization is also altered, as discussed in the following subsection.

Stratum Corneum Lipid Composition and Organization in Diseased Skin

The alteration of skin barrier properties can be caused by either non-skin diseases or skin diseases. The most famous non-skin disease that affects skin barrier properties is diabetes mellitus (113). Even the diabetic effect on the skin can be evaluated by the naked eye, such as diabetic dermopathy (114) and necrobiosis lipoidica (115). Some studies on diabetic patients have shown enhancements in skin dryness and lipid content (116). Moreover, the ceramides, including N (normal), A (hydroxy), and esterified, see **Figure 2**, increase significantly (117). However, information on the modification of the chain length of ceramides and free fatty acids is lacking, let alone data on lipid organization. In skin diseases such as atopic dermatitis (atopic eczema), psoriasis, and Netherton syndrome, information on lipid composition and organization is well known. In the following paragraph, only atopic eczema will be discussed.

The skin of an atopic eczema patient shows several modulations in lipid composition as listed in **Table 1**. A significant decrease in total ceramide and total lipid per mass of stratum corneum was identified using thin-layer chromatography. In the lesional part of AE skin, as well as in older patients, a higher decrease was evaluated. While the total lipid and total ceramide percentages in SC are decreased, the ceramide-to-lipid ratio remains constant (118). Further research confirms the decrease in ceramide, with additional information indicating that, in AE skin, the

recovery of ceramide levels after stripping is slow, whereas in healthy skin it is fast (119). The lack of activity of sphingomyelinase in atopic eczema skin causes a decrease in ceramide content (120). Moreover, the cholesterol-to-ceramide ratio increases from 1.53 in healthy skin to 2.24 in AE skin (121). At a certain level, enhancing the cholesterol-to-ceramide ratio does not affect permeability. Conversely, when the cholesterol level decreases by 40% from normal (which is not the case in AE), the barrier properties increase (121 – 123).

Ceramide decrease can be broken down into each class. The most pronounced ceramide class that shows a significant decrease is esterified ceramide (CER EO), particularly CER EOS (118, 125, 126). Moreover, the ratio of CER EOS-oleate to CER EOS-linoleate is higher than normal (healthy SC) (125). The cis structure of the oleyl chain determines the bulky lamella, which is responsible for the drop in SC barrier properties. Further studies revealed that the other subclass of CER EO, namely CER EOH, was also decreased in the non-lesional site of the non-filaggrin mutation AE, in addition to CER EOS declining. The decrease in CER EO is predicted as a result of increasing activity of glucosylceramide deacylase in AE skin (124, 139). It is predicted that the decrease in CER EO is the main cause of the shortening in the repeat distance of LPP, which is responsible for permeability enhancement (109). Furthermore, the ratio of esterified ceramide with unsaturated fatty acids (particularly C30: 1, C32: 1, and C34: 1) and saturated fatty acids in AE skin is higher than in normal skin and positively correlates with TEWL (128). The reduction in barrier properties was further evidenced by a finding showing that the TEWL value of lesional skin in AE patients was higher than that of normal skin and the non-lesional site of *FLG* mutation patients. Here, TEWL enhancement was positively correlated with CER EOH decrease and CER AH enhancement, while the levels of CER AS, AP, NS, and NP had no significant effect (122, 136, 140).

Concerning the alteration of non-esterified ceramides, Janssens and coworkers reported that the α-hydroxyl ceramides (AS, AP, AH, and AdS) were increasing, while non-hydroxyl ceramides (NP, NH, NdS) were decreasing. The increasing of NS level was an exception to this trend. This research also showed that in AE patients, the magnitude of the orthorhombic lateral packing is decreasing (81, 124). In-line results were exhibited in a later article, completed with an explanation of the issue. The addition of a hydroxyl group to the head of ceramide enlarges the occupied surface, presumably resulting in difficulty in the formation of dense lipid, i. e. , an orthorhombic domain, resulting in a higher TEWL (141). However, although the hydrogen group addition likely decreases in the orthorhombic domain, which should trigger lower barrier properties, the permeability declined, explaining that the alpha-hydroxy ceramide presumably increases the barrier properties due to the additional hydrogen bond (142). Additionally, the non-esterified ceramides of eczema skin are also shorter than those in normal skin due to down-regulation of Elongation of Very Long-Chain Fatty Acids (*ELOVL*) (81, 126, 129). This also possibly contributes to barrier properties deterioration in eczema SC since the short-chain ceramide insertion into lipid lamellae likely decreases the interlocking of lipid tails.

The new findings on lipid changes in atopic dermatitis suggest classifying ceramides into two groups: long-chain ceramides (carbon chain length> 50) and short-chain ceramides (carbon chain length < 40). In atopic eczema patients, the long-chain ceramides are decreasing while the short-chain ceramides are increasing (124, 126). This finding is in agreement with the clinical study concerning the non-lesional site of *FLG* mutation patients, which additionally reveals that the ceramide alteration is a cause of LPP reduction on lamellar organization and orthorhombic decline on lateral packing, triggering the decrease in stratum corneum barrier properties (81). On the lesional site, the decrease in long-chain ceramides is significantly higher. Adding the information to the previous study, the *FLG* mutation does not have any significant effect on the alteration of ceramide composition (64, 143), in line with the study on reconstructed human skin equivalent (144). In an animal study using mice, it is shown that the decreasing level of long-chain ceramide and the increasing level of short-chain ceramide are due to the mutations in Elongation of very long-chain fatty acid-4 (*ELOVL4*) (145).

Concerning the FFA, only a little information is available. Some reports show that in AE patients, either on the lesional or non-lesional site, the long-chain free fatty acids with more than 23 carbon chain-length decrease significantly, leading to a modification of the lateral packing to a less orthorhombic. Moreover, the unsaturated free fatty acid is also present at a higher level, while the hydroxy free fatty acid is decreasing (64, 130). The new finding also suggests that the ratio of FFA with the carbon chain of at least 22 to cholesterol is decreasing for the non-lesional AE, and the decreasing value is higher in the lesional site (122). Modelling this condition and assessing barrier properties reveals that FFA shortening also contributes to deterioration in barrier properties (64, 146–148).

The minor components of the stratum corneum lipid are also changed. While cholesterol, one of the three major components of lipid SC, is increased, its derivative, namely cholesterol ester, remains constant in AE with and without *FLG* mutation (136). Concerning cholesterol sulphate, while Yamamoto and co-workers (1991) stated that cholesterol sulphate enhancement in AE skin was not significantly different (125), Di Nardo and coworkers (1998) reported that cholesterol sulphate decreased (121). The updated studies revealed its enhancement, completed with knowledge that cholesterol sulphate in the healthy epidermal layer is higher in the stratum granulosum part, while in AE skin it concentrates in the stratum corneum (131). Due to this conflicting statement, a deeper check was conducted. A statement in the body of the article showing the cholesterol sulphate decline disagrees with **Figure 1**, which explains the cholesterol sulphate enhancement (121). Concerning the decrease in triglyceride levels of SC, it exists in lesional and non-lesional parts of AE skin (136). The decrease is not related to triglyceride hydrolysis since free fatty acid and ceramide are also decreased. Likely, triglycerides are concentrated for sebum production, as atopic dermatitis skin secretes more sebum than normal skin (149).

Glucosylsphingosine and sphingosilphosphorylcholine are the other minor components of SC that are also

affected by eczema. These substances are hydrolysis products of ceramide precursor, glucosyl ceramide and sphingomyelin by sphingomyelin deacylase (150). This argues that in AE stratum corneum, the upregulation of these lysosphingolipid substances correlates with the decreasing value of ceramide (134, 135). The conversion of glucosyl ceramide to ceramide is also decreased due to the decreased activity or expression of lysosomal glucosyl ceramide beta-glucosidase (GBA) (133). This leads to the more pronounced upregulation of glucosylsphingosine.

Concerning the free sphingoid bases, the alteration in eczema skin remains a topic of debate. Arikawa and coworkers reported a decrease in sphingosine, the most abundant sphingoid base with antimicrobial activity, and correlated this with an enhancement of microbial colony growth in AE skin. The sample for sphingosine quantification is a stripped sample reflecting the upper layer of stratum corneum (132). Interestingly, Loiseau and coworkers revealed that the concentration of stratum corneum-free sphingosine is elevated in a mouse model of AE skin, while free sphinganine base is decreased. The sum of these two most abundant sphingoid bases is increased. It should be noted that Loiseau and coworkers could use full SC in quantifying sphingosine and sphinganine since the eczema is induced in mouse models (151). Since the samples in the above research differ across individual species and stratum corneum depth layers, they cannot be considered contradictory. However, recent studies reveal that stripped samples of eczema skin in humans show a significant increase in sphingosine and sphinganine in the lesional, but not in the non-lesional, part (133). The increasing level of free sphingoid base is a result of the activity of the enzymes sphingomyelin deacylase and glucosylceramide sphingomyelin deacylase (152, 153).

Similar to changes in major components of SC, i. e. , ceramide, free fatty acid, and cholesterol, which trigger modifications in barrier properties, adjustments in minor components in AE skin also induce barrier changes. Unfortunately, only a limited number of studies correlating the specific change and TEWL are available. The cholesterol sulphate level in AE skin significantly correlates with the enhancement of TEWL due to the disturbance of SC lamellae (154). Toncic and coworkers determined the TEWL value of normal and dermatitis skin, and correlated the value with sphingosine and sphingonine. A positive correlation with r^2 of about 0.43 indicates that the enhancement of free sphingoid bases decreases the barrier properties (133). Concerning substance permeability and lamellar organization, *in situ* measurement is not possible. Therefore, a stratum corneum model is developed to study the effect of lipid changes in AE skin.

Application of the Stratum Corneum Model to Study Lipid Changes in AE Skin

Modeling changes in the clinical data of AE skin made it possible to identify the critical modulation, owing to the ease of modifying lipid composition in the stratum corneum model, designated as stratum corneum substitute. The "artificial" stratum corneum can be prepared by modifying specific substance changes, while maintaining a constant magnitude of non-studied components. However, it should be noted that the preparation of this SC model, as described in the previous section, plays a critical role in lipid lamella formation, leading to the possibility of different lipid organization from the similar lipid composition, commonly termed as crystal polymorphism if only a single substance is involved. This limitation can be minimized by following the detailed steps of stratum corneum substitute preparation, which is available elsewhere (155). Depending on the subsequent experiment, the stratum corneum substitute can be embedded in specific material, for instance, a porous membrane for permeability studies or a potassium bromide plate for infrared measurement to determine lateral organization.

Research on lamellar organization using the stratum corneum model showed that CER EO is a prerequisite for LPP formation at a proper length. CER EOS has a better ability to initiate LPP formation than CER EOP (90, 93, 156, 157). The disturbance of LPP formation results in a lack of appropriate barrier properties (59). It is demonstrated that a membrane prepared by pig ceramide added by CER EOS has a better barrier property against hydrocortisone permeation. Moreover, the lipid organization is more orthorhombic than the original pig ceramide (61). Concerning non-esterified ceramide, the decreasing level of CER NdS C24 at the expense of CER NS C24 was modeled by Skolova and coworkers by constructing a simple synthetic stratum corneum using equimolar lignoceric acid (C24: 0), cholesterol, and ceramide. Cholesterol sulphate is added at a concentration of 5%. It is revealed that this aberration has no significant change in membrane permeability, as shown by indomethacin and theophylline permeation flux, and lateral packing, as shown by FTIR (158). In disagreement with this report, Stahlberg and coworkers showed that at skin temperature (32 °C), a lipid mixture of equimolar CER NS, Cholesterol, and lignoceric acid has a more orthorhombic lattice than one containing CER NdS (159). It means that a significant increase in the level of CER NS in atopic eczema patients (81) has not yet been concluded as a critical modulation of the stratum corneum barrier property.

The next major component of the stratum corneum which is modified in AE is cholesterol. The effect of the cholesterol-to-ceramide ratio enhancement as in AE skin (122, 136), was studied using the SC model composed of only three major components of SC. Unfortunately, the cholesterol was separated, and the artificial SC failed to mimic the barrier properties reduction, as indicated by the lower value of benzoic acid flux transport (160).

A stratum corneum model membrane developed by Ramos and Lafleur tried to confirm the relation between the length of FFA and the lateral packing of stratum corneum from clinical data. This stratum corneum model membrane compares the lipid organization of two ternary mixtures of FFA/Cholesterol/Ceramide. The lipid containing palmitic acid (C16) as short-chain FFA showed phase separation, while the usage of lignoceric acid (C24) produced a homogeneous lipid mixture (64, 148). This mixing property result is in line with a previous study conducted by FTIR. The membrane composed of FFA C24 showed a higher orthorhombic-hexagonal temperature transition, as an indication of better barrier properties (161).

The effect of unsaturated free fatty acids

enhancement in AE skin was mimicked by Lee and coworkers. They used water permeability as a parameter of barrier properties. It was shown that an increasing amount of unsaturated free fatty acid in AE stratum corneum is a critical modulation of decreasing its barrier properties. The stratum corneum model membrane, which contained oleic acid, linoleic acid, and petroselinic acid, has higher water permeability compared to its saturated counterpart (162). In line with the previous report, Mojumdar and coworkers studied using a stratum corneum model membrane, which resulted in a more hexagonal packing as well as an increase in permeability of hydrocortisone in a membrane containing monounsaturated free fatty acid (163).

Concerning the changes in minor components, an increase in the level of sphingoid base was assessed by preparing the lamellar vesicle (niosome) with and without sphingoid base containing the dye 2, 5-carboxyfluorescein (CFC). The lamellar vesicle with sphingosine in Ceramide/FFA/Cholesterol mimicking normal skin, as well as AE skin, shows higher permeability of dye. Moreover, the enhancement of the sphingosine-to-sphinganine ratio, which is a condition in AE skin, increases the flux of the dye. Unfortunately, there is no information regarding the lamella organization (151). The effect of cholesterol sulphate on barrier properties of stratum corneum substitute was studied using theophylline and indomethacin as drug models. The decrease in barrier properties, as indicated by the higher permeation flux of both drugs and water loss, was in line with the increase in cholesterol sulphate-to-cholesterol ratio. However, the orthorhombic packing was adopted by all formulations representing three levels of cholesterol sulphate (164). Several methods are exploited for the determination of these lamellar organizations.

Identification of Lipid Lamellae Organization in the Stratum Corneum

The main purposes of lipid organization identification are to reveal the repeat distance of the lamellar phase, e. g. , LPP and SPP, and the lipid lateral packing perpendicular to the lamellar body, e. g. , orthorhombic and hexagonal crystalline structures. The repeat distance of LPP and SPP might be measured using small-angle X-ray diffraction (SAXD), as well as electron diffraction (163, 165–167). The crystalline structure of the lipid stratum corneum might be elucidated using Fourier transform infrared (FTIR), electron diffraction, and wide-angle X-ray diffraction (WAXD) (84, 87, 143, 163, 168, 169). Only the FTIR and SAXD methods will be discussed as follows.

Utilizing FTIR, the information about stratum corneum lipid lateral organization is revealed by the attitude of the CH_2 group resulting from the infrared (IR) wave, as shown in **Figure 3**. Thetwo hydrogen atoms bonded to a carbon atom can vibrate in at least three modes, e. g. , rocking, scissoring, and symmetric stretching, with wavenumbers around 700-750, 1460-1480, and 2845-2860 cm^{-1}, respectively. In general, the orthorhombic lateral packing of hydrocarbon chains allows CH_2 coupling, resulting in the doublet peaks in the rocking and scissoring wavenumber regions, and decreasing the wavelength of symmetric stretching. The magnitude of the orthorhombic lattice is linear with the distance between the two peaks or the bandwidth of the CH_2 scissoring (84, 104, 105, 170).

To unravel the question of what the molecule participates in the CH_2 group determining the vibration, the lipid mixture applying perdeuterated fatty acid (DFFA) to substitute the FFA gives the desirable information. Recording the IR spectrum of such a mixture reveals the CD_2 vibrations at wavenumbers of 1080-1100 cm^{-1} and 2088-2100 cm^{-1} for scissoring and symmetric stretching, respectively. The decoupling of CH_2 rocking in the orthorhombic lattice by CH_2 indicates that both ceramide and FFA contribute to this crystalline organization. The behavior of rocking and scissoring related to the lateral packing organization of lipids in the stratum corneum and the information taken from it are listed in **Table 2**. The wavelength change in CH_2 symmetric stretching as a result of temperature informs the transition of lipid organization, in particular from hexagonal ordering to disordering (liquid crystal). This wavelength is relatively constant at low position, demonstrating the orthorhombic packing, followed by a slight enhancement due to the process of solid-state transformation from orthorhombic to hexagonal packing, and constant again as an indication of completely hexagonal packing, then a quick enhancement and constant. The last two phases are the

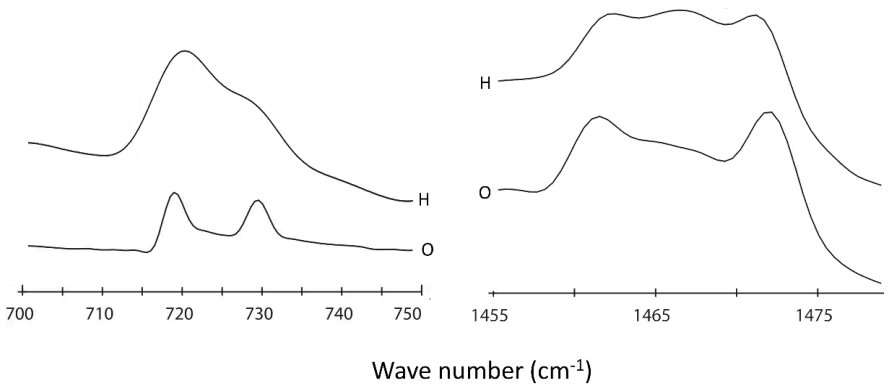


Figure 3. FTIR spectrum in absorbance mode of stratum corneum lipid showing a rocking (left-hand side) and scissoring (right-hand side) vibration of the CH_2 group of FFA and ceramide tail. The upper spectrum shows more hexagonal (H) crystals, while the bottom shows more orthorhombic (O) ones. The figure was generated based on an experiment by the authors.

Table 2. Significant wavelength numbers and their information about the lateral organization of the lipid stratum corneum.

Wave number and mode of vibration	Behavior	Note on lateral organization
700-750 cm-1 (CH_2 rocking) and 1455-1480 cm-1 (CH_2 scissoring)	In the Cer/Chol/FFA mixture: doublet due to CH_2 coupling	Orthorhombic
	In the Cer/Chol/FFA mixture: pure single peak	Hexagonal
	In the Cer/Chol/FFA mixture: triplet or single peak with two shoulders	Hexagonal, phase separation of FFA forms orthorhombic
	In the Cer/Chol/DFFA mixture: pure single peak; adjacent position of ceramides and DFFA decouples the CH_2 vibration	The organization follows the data of the Cer/Chol/FFA mixture.
1080-1100 cm-1 CD_2 scissoring	Only in the Cer/Chol/DFFA mixture	
	Double peak	DFFA phase separation forms orthorhombic and dominates the packing of the mixture (lateral organization follows the Cer/Chol/FFA data)
	Single peak with two shoulders	Hexagonal/Orthorhombic packing of mixture (lateral organization follows the Cer/Chol/FFA data) dominates the DFFA phase separation
	Pure single peak, complete miscibility of ceramides and DFFA decouples the CD_2 scissoring	The organization follows the data of the Cer/Chol/FFA mixture.

signal of the hexagonal to the liquid crystal transition, followed by full disordering. In the lipid mixture containing DFFA, a similar profile of CD_2 symmetric stretching is occurred start from the hexagonal phase to the disordering phase, but the orthorhombic phase and the transition from orthorhombic to hexagonal phase are not shown. This is a consequence of an insensitive change due to the higher atomic weight of deuterium than that of hydrogen. The CH_2 symmetric stretching profile at varying temperatures is shown in **Figure 4** (148, 171 – 174).

As mentioned previously, the lateral packing of SC lamellae is possibly in orthorhombic or hexagonal form, depending on the temperature. Decreasing the wavelength (increasing the wavenumber) of CH_2 symmetric stretching is used to trace the phase transition, as exemplified in **Figure 4**. At low temperature, the system forms an orthorhombic phase. Temperature enhancement from 30 °C to about 40 °C triggers a change in crystal formation from orthorhombic to hexagonal, a less dense ordered crystalline form. Between 60 °C and 70 °C, disordering occurs until the hexagonal crystalline form is completely melted at about 90 °C (84, 104, 105, 170). This data is consistent with the DSC recording, which shows a phase transition from 35 °C to 69 °C (175). The exact transition temperature depends on lipid composition and hydration level. The phase transition temperature decreases slightly with increased hydration (104).

In SAXD pattern measurement, the X-ray beam

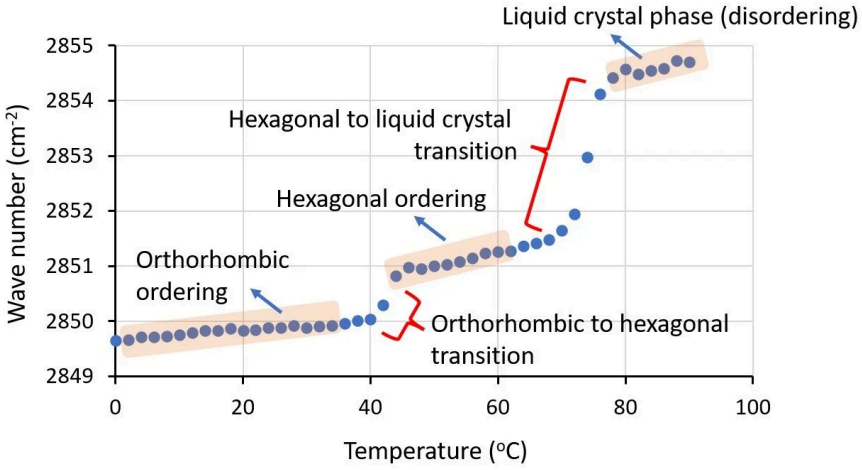


Figure 4. The shifting of the CH_2 symmetric stretching wavenumber as a result of temperature. At the skin temperature (32 °C), the lipid organization is dominated by an orthorhombic crystalline structure. The figure was generated based on an experiment by the authors.

impinges on the sample, resulting in light scattering that is determined by the material's crystal structure. The intensity (I) of scattered X-rays is recorded as a function of the scattering vector (Q), defined by $Q = 4\pi \sin\theta/\lambda$, where λ is the fixed wavelength of the X-ray beam and θ is the scattering angle, which varies with the repeat distance (d) of the crystal in the material. A series of peaks in the Q vs I curve is arranged at a constant repetition. The closer the peaks'positions, the larger the repeat distance is. Recording the Q at a low scattering angle (known as SAXD, less than 5 degrees) will characterize the repetition of the z-axis of lipid lamellae (see **Figure 2** to consider the z-axis), while at a higher angle, referred to as WAXD, information about lateral packing can be revealed. The repeat distance can be calculated by $d=2n\pi/Q_n$, in which n is the order of the peak. If the sample of material has more than 1 mode of repetition, the intensity will be additive (79, 91, 169, 170). A schematic drawing of the 1-dimensional SAXD recording results is shown in the graph in **Figure 5**. Once the lipid organization has been characterized, the barrier properties of the stratum corneum layer, either artificial or original, can be addressed.

Assessing the Barrier Properties of the Stratum Corneum

As a barrier, the stratum corneum blocks the permeation of substances from the surface of the skin into the body (outside-in diffusion) as well as from the body to the surface of the skin (inside-out). Outside-in diffusion is a very interesting process related to the transdermal drug delivery system and toxin (irritant) introducing the skin to trigger or aggravate diseased skin. Inside-out diffusion is a normal process to control the amount of water and electrolytes in the body. These two important processes are determined by the barrier properties of the stratum

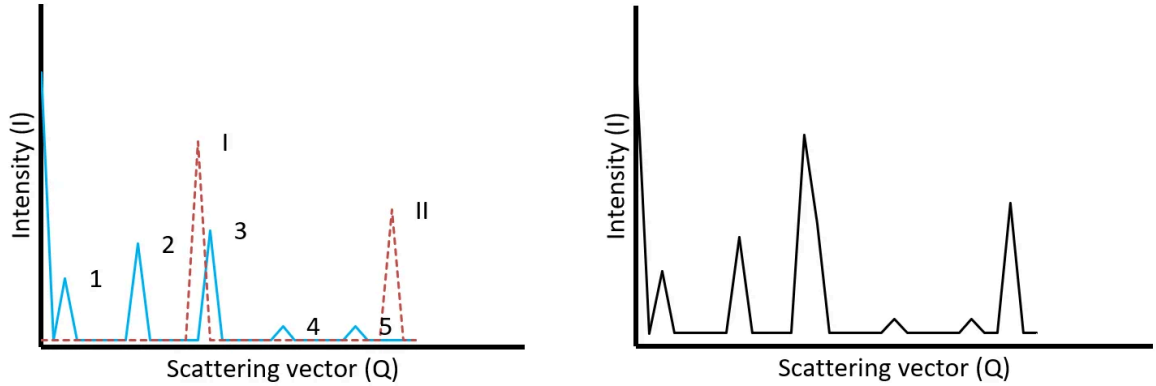


Figure 5. Schematic drawing of 1-dimensional SAXD detection of stratum corneum lamellar organization. Because of the existence of 2 repeating units of lipid lamellae, the peak also repeats in 2 series (left). The solid-line series shows the information on LPP length, while the dashed series demonstrates the SPP length. The orders of the peaks are displayed in Arabic and Roman numerals for LPP and SPP, respectively. Because of the additive character of intensity, the graph exhibits a typical pattern as in the right-hand. The figure was created by the authors.

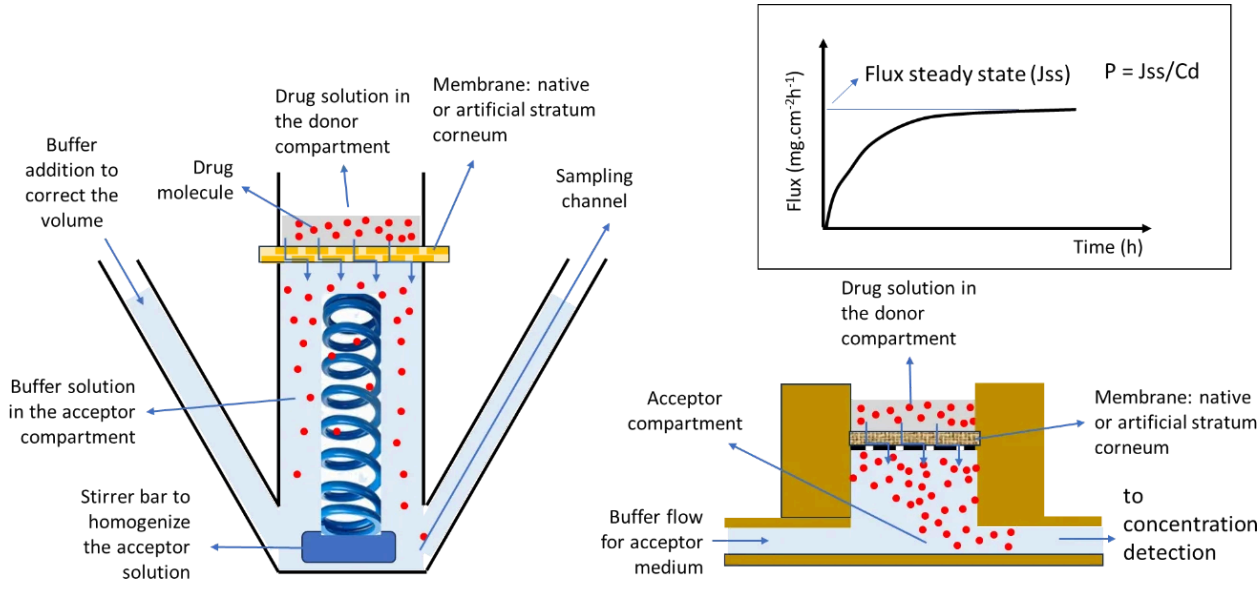


Figure 6. Schematic presentation of diffusion studies using a Franz-like diffusion cell (left-hand side) and flow diffusion cell (right-hand side) to assess outside-in barrier properties of the stratum corneum substitute. The insert is an example of the diffusion study results and permeability calculation. The figures were created by the authors.

corneum. Assessing the barrier properties of the stratum corneum can be performed by permeability determination of a drug model, as well as measuring the TEWL (Trans Epidermal Water Loss) value.

Controllable diffusion study of a drug model (176) can be performed *in vitro* to eliminate the variability of pharmacokinetic factors out of the skin, such as distribution volume and half-time elimination, which occurs in an *in vivo* experiment. Here, human or animal skin, as well as artificial skin, is set up in the diffusion cell as shown in **Figure 6**. Subsequently, the drug in solution is put on the skin in the donor compartment, and the buffer solution is flowed through (or filled into) the acceptor compartment. The plot of the amount (M) of drug that diffuses through the membrane (skin/artificial skin) per unit area (A) as a function of time (t) is analyzed to calculate the flux (J) of drug permeation. The permeability of the drug in the membrane is calculated by dividing J by the drug concentration in the donor compartment (Cd) (61, 177). The barrier property of skin is the inverse of permeability.

TEWL is a characteristic of skin related to the inside-out barrier properties. TEWL measurement can be conducted on the whole skin *in vivo*. In the case of an artificial membrane, it is assumed that the membrane is epidermal skin, and TEWL can be determined *in vitro*. To perform this measurement, the cell diffusion and evaporimeter are combined. The evaporimeter works based on the relative humidity differences between two adjacent regions above the skin, as shown in **Figure 7** (178, 179). The high TEWL indicates poor barrier properties of skin. From an ethical perspective, this method of assessing barrier properties is preferred for use in the clinical application of a drug formulation for dermatitis management. While structural organization assessment needs to break the skin, and *in vivo* permeability studies are possibly affected by various pharmacokinetics events, TEWL measurement is relatively fast and can be applied in dermatitis patients conveniently without defeating the skin barrier.

Topical Drug Formulation Related to Lipid Change in Stratum Corneum of AE Skin

The most pronounced change in lipid composition of AE skin is a decrease in ceramide, which affects the barrier properties and lipid lamella organization. This triggers the preparation of ceramide-rich topical dosage forms. Several clinical trials were conducted to evaluate the efficacy of topical ceramide preparations in various formulations, including emulsions, nanoemulsions, multilamellar vesicles, and creams. The successful results were indicated by the improvement of clinical parameters, such as Eczema Area and Severity Index (EASI), skin hydration, skin dryness, redness, and pruritus, whereas some results showed that the decrease in TEWL value was not significant (180 – 183). While clinical studies with AE patients are prohibited from removing skin samples for lipid composition analysis and lamellar organization for ethical reasons, experiments using dermatitis models are conducted to unravel lipid changes in AE skin due to application of drug formulation. Gwon and coworkers conducted tape stripping on healthy skin to produce skin with decreased barrier properties mimicking the AE condition, as indicated by TEWL value. Topical formulations containing varied chain lengths of NP ceramides were applied on the "diseased" skin for 28 days. It was revealed that the applied ceramides were intercalated into the lipid lamella of SC as indicated by

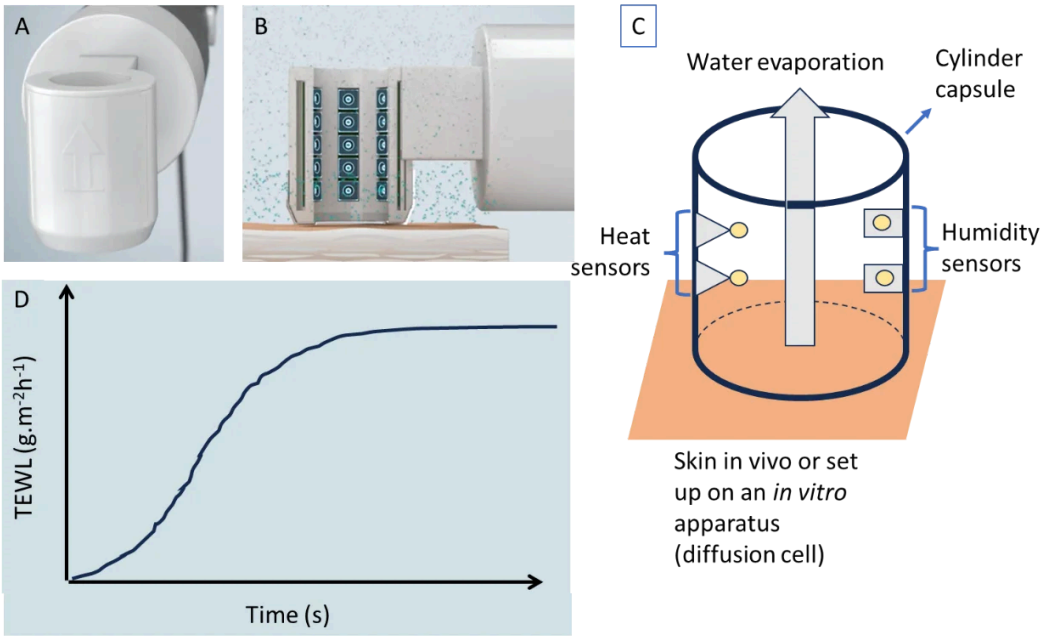


Figure 7. Instrumentation to monitor the barrier property of native/artificial stratum corneum against water, the TEWL: A: Front view of Tewameter®, B: Cross-sectional side view of Tewameter®, C: Schematic representation of TEWL measurement apparatus, D: Typical graph of TEWL measurement. Images A and B were reproduced from https://www.youtube.com/watch?v=wlwJstCwFfU with written permission of Courage + Khazaka Electronic GmbH, Germany. Images C and D were created by the authors.

chain-length-based NP profiles. Moreover, the improvement in barrier properties was greater in the recovery skin controlled by the higher chain length of NP ceramide formulation (184). These results strengthen previous studies using the second AE model, i. e., *ex vivo* dermatitis skin models, concluding that applied ceramides, varied in ceramide types including CER EOS and CER NS, interact with the stratum corneum lamella of the regenerated SC. Moreover, the regenerated SC without application of ceramide formulation showed less orthorhombic packing than the applied ones (185).

The intercalation of the components of the topical formulation was also evidenced for free fatty acids. Using *ex vivo* damaged skin models, Nip and coworkers proved that skin recovery was improved by application of marketed drugs containing free fatty acids, which is not the case in the application of ceramide-containing moisturizing lotion. The repair improvement was shown by an increased number of lamellar bodies and stratum corneum layers (186). Moreover, before intercalation, the free fatty acid was elongated by *ex vivo* damaged skin (187). The intercalation of applied major components of SC into the damaged skin is likely to occur in dermatitis skin. Thus, a decrease in specific SC components of AE skin, as in **Table 1** above, may be corrected by applying respective components to improve the barrier properties of skin AE patients.

Conclusion

The reduction in the barrier properties of atopic eczema (AE) skin has been determined by direct measurement of TEWL in the patients. Isolating the stratum corneum layer from the skin biopsy of healthy and AE patients makes it possible to evaluate changes in the lipid organization, including the reduction in the level of LPP and orthorhombic crystal. Collecting the lipid of AE skin by the stripping method as well as skin biopsy, followed by analyzing the lipid composition mainly using an LC-MS-based method at the class or subclass level, yields a dataset of changes in stratum corneum (SC) lipids compared to healthy skin. To identify the changes in lipid components that are responsible for lipid organization (and barrier properties) modulation, SC artificial membranes that mimic the specific lipid changes in diseased skin are prepared. The ability to control the lipid components of artificial SC makes it possible to analyze specific lipid alterations that significantly affect lipid organization. Moreover, the artificial SC is also used to study drug permeation and transepidermal water loss (TEWL), two parameters that are inversely related to SC barrier properties. Based on such a series of works, it is presumed that the reduction in atopic eczema skin barrier properties is due to the decrease in the fraction of esterified ceramide, long-chain free fatty acid, non-esterified ceramide, and saturation of free fatty acid and fatty acid part of ceramide. It is predicted that these changes reduce the long periodicity phase (LPP) and orthorhombic lateral packing formations. Meanwhile, the change in cholesterol sulphate level is still debatable, whether it decrease or increase. In literature stating the cholesterol sulphate enhancement, a hypothesis is suggested that an increase in cholesterol sulphate increases TEWL (decreases in barrier properties). However, research about the effect of cholesterol sulphate enhancement on the structural organization of lamellae is still needed. More research on the change in free sphingoid base, which is still debatable, needs to be conducted with a more sensitive and selective method, such as UPLC MS/MS; subsequently, the lipid organization and barrier properties concerning the changes need to be characterized. Since applied ceramides and free fatty acids intercalate with lamellar lipid organization, formulation of topical drug for eczema can be developed in a tailored model adjusted to the patient status of eczema. To this end, correlation between specific clinical appearance of eczema and significant reduction of specific lipid components should be first identified.

The limitations of this narrative review are the undefined publication year of included articles and the lack of a systematic strategy for article searching. Moreover, there is no independent screening for article selection. Therefore, the authors declare that this conclusion section was built up based on a selective narrative synthesis. These limitations are subject to improvement on further review, which could be a systematic review.

Abbreviations

AE = atopic eczema, SC = stratum corneum, SG = stratum granulosum, LPP = long-periodicity phase, SPP = short-periodicity phase, TEWL = transepidermal water loss, FFA = free fatty acid, and FTIR = Fourier transform infrared, HPLC = high-performance liquid chromatography, GLC/MS = gas liquid chromatography/mass spectroscopy, GLC/FID = gas liquid chromatography/flame ionization detector, SAXD = small-angle X-ray diffraction, WAXD = wide-angle X-ray diffraction.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

All data generated or analyzed during this study are

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Additional Information

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