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Dry Skin in Atopic Dermatitis

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Atopic dermatitis (AD) is a common, chronically recurring skin disorder. Dry skin is a common finding in patients with AD, apart from the dermatitis. Although there are obvious clinical signs of an impaired barrier function of the skin, few investigators have studied this aspect of AD. The stratum corneum, where the barrier is located, has been studied with different techniques in patients with AD, and the results are now presented. The water-binding capacity of dry atopic skin was found to be reduced when measured with an in vitro microbalance technique. TEWL (transepidermal water loss) measured with and Evaporimeter Ep1®, was increased in dry skin and in clinically normal skin of atopics on predilection areas. Water content was decreased in dry atopic skin, when measured with the Corneometer CM 420®. In a quantitative electron microscopic study, the lamellar bodies were found to have an increased relative volume in dry atopic skin. When using chromatographic analysis, preliminary data suggested reduced amounts of extractable stratum corneum lipids in patients with AD. In a clinical study, 80% of the patients with AD regarded their skin as being dry. Fifty percent were found to have areas of dry skin, on clinical examination. By scanning electron microscopy (SEM), the surface pattern of dry atopic skin was found to be coarse and irregular. When using profilometry, quantitative differences in roughness parameters were found in dry atopic vis-à-vis to normal skin.

The following hypothesis is presented: in patients with AD, the stratum corneum lipids are changed qualitatively and/or quantitatively, resulting in a defective barrier function. The dry fell of skin of atopic patients is due to its rough surface pattern.

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Atopic dermatitis (AD) is a common, chronic and recurrent skin disorder, affecting especially children and young adults.

A common finding in patients with AD is the occurrence of dry skin, often on non-predilection areas for dermatitis, such as the back. When present, this dry skin has quite a uniform appearance, with a finely scaling non-erythematous, non-inflamed skin surface which feels rough to the touch, often with a perifollicular accentuation (1).

Another common finding in patients with AD is the high incidence of non-allergic contact dermatitis (2,3), especially on the hands indicating a defect barrier function of the atopic skin.

In 1952, Blanck (4) showed in his classical experiments that the only plasticiser of dry skin is water. By using an in vitro technique, he dehydrated pieces of stratum corneum from the sole and showed that these pieces became brittle and dry when the water content falls below 10%. However, it is doubtful if this kind of experiment can be applied to clinical conditions of dry skin. It has now been shown that clinically occuring dry skin does not always lack water. Studies on 'physiological dry' skin, defined as dry skin without any concomitant skin disorder, have shown a normal water content in the stratum corneum (5,6). Ståhle-Bäckdahl (7) has shown that patients with uraemia and dry skin have a normal water content of stratum corneum.

It is conceivable that the common feature of different kinds of dry skin is a structural abnormality of the skin surface, expressed as a feeling of roughness to the touch. The pathogenesis of such a roughness is not known and probably differs in various disorders. It is conceivable that disorders where dry skin is one of the symptoms may be due to some 'intrinsic' factor, whereas 'physiological dry' skin may be due to more extrinsic factors and is thus more variable.

The water-binding capacity of dry atopic skin

The amount of water in the stratum corneum is one factor of importance for barrier properties. In the dynamic relation of water flux through the stratum corneum and the water content within the stratum corneum, both the ability to bind water (hygroscopicity) and the ability to retain water (water-holding capacity) are of importance (8).

To study these properties in patients with atopic dermatitis, an in vitro experiment was used. Pieces of stratum corneum were prepared from the dry skin of the back in 12 patients with AD and from 12 controls. After full hydration, the gradual loss of water in open air was determined by weighing specimens at intervals during a 40 min. period.

The investigations showed that the stratum corneum from dry atopic skin had a significantly reduced ability to bind water, compared with normals.

The ability to retain water was the same in both groups (9).

Transepidermal water loss

The transepidermal water loss (TEWL) is considered to reflect the functional state of the epidermal diffusion barrier. Different investigators (10,11) have found an increased TEWL in patients with AD. However, the results vary according to the technique used an it is difficult to accomplish a direct comparison (12). It is obviously important to define clearly the degree of skin involvement and the location on the body of the area measured.

The Evaporimeter Ep1®, which is by now the most frequently used apparatus for in vivo studies of the barrier (13), was used to measure TEWL. TEWL vas determined after 30 s on three body locations: the hand and the forearm, regarded as predilection areas for AD, and the back, regarded as a non-predilection area. Sixteen atopic patients with dry skin and 16 atopic patients with normal skin on these areas were compared with 16 non-atopics. A significant increase in TEWL was found on all three body locations in atopic patients with dry skin as well as on the back of the hand and on the

forearm of the atopic patients with normal skin. This may indicate an early defect in the barrier function. The highest TEWL was found on the back of the hand in all three groups. This may in part be explained by the fact that the hands are often exposed to water and chemicals which impair the skin barrier (14).

In a recent study (15) the accuracy of the Evaporimeter was tested and found to be a highly accurate device. The was considerable interindividual variation, while the intra-individual variation was of minor degree. TEWL has no clear correlation to the water content of stratum corneum. In normal skin, a high water content is accompanied by a high TEWL, but in abnormal skin a high TEWL can be seen together with a low or normal water content. Thus it only gives information on the water diffusion barrier of the skin.

Water content

The water content of stratum corneum is one factor of importance for its barrier properties. An increased water content, induced by occlusion of the skin surface for example, is well known to promote percutaneous absorption, a fact often used in clinical practice. A normal content of about 10% water within the stratum corneum is regarded as necessary to keep the skin soft an pliable (4). Various methods have been developed to measure the water content of the stratum corneum in vivo (16,17,18). In the present study a newly developed commercial instrument, the Corneometer CM 420®, was used. The Corneometer CM 420® has a probe which works as a condensor, whose capacitance is influenced by a change in the dielectrical constant of any material with which it comes into contact. Water has a high dielectrical constant that influences the capacitance which will rise with an increased water content. The measurement data are expressed as non-dimensional units (AE = arbeits-einheiten).

The measurements were made on the back of 20 atopic patients with dry skin and of 20 atopic patients with normal skin. The data were compared with those of 20 non-atopics with normal skin. An in vitro experiment with pieces of stratum corneum, hydrated in the open air, was performed in an attempt to correlate the values of the Corneometer to absolute amounts of water.

As measured with the Corneometer CM 420® the water content of the stratum corneum of dry skin in patients with AD was significantly lower than that of clinically normal skin both of patients with AD and of controls.

In the in vitro study the water content was found to be about 24% of the wet weight of the stratum corneum of dry atopic skin, 37% in normal atopics, and 41% of the stratum corneum of normal skin (19).

Different methods for estimating the water content of the stratum corneum will record values at different depths, and important fact since there is a gradient of water through the corneum with gives a higher water content in the deeper layers, and a lower water content in the outermost layers due to surface evaporation. With the Corneometer CM 420® which measures the deep layers of the stratum corneum, dry atopic skin was found to have a decreased water content. In a recent study, Blichmann & Serup (16) compared the Skicon 100®, which measures conductance, expressed as the reciprocal impedance, with the Corneometer CM 420®. The Conclusion was that the Skicon 100® measures the water content of most superficial layers of the corneum and that this method is probably sensitive to fluctuations in water diffusion between the skin surface and the ambient atmosphere. Skicon 100® is more sensitive to increased hydration, while the Corneometer CM 420® is better suited to measure reduced hydration. Finley et al. (20) found an increased water content in the stratum corneum, measured with an impedance recording instrument. Floor et al. (17) came to the same conclusion, using infrared spectroscopy. The level of measurement with this method is regarded to be the outer strata, although no increase was recorded in the water content after stripping. Methodological differences may account for the conflicting results regarding the water content of dry atopic skin.

Due to the water gradient existing in the stratum corneum in vivo, estimation of true water content from in vitro studies is difficult. Recently, using a sophisticated method of electron probe analysis, Warner et al. (21) have estimated the water content to be 15–40% in an almost linear profile through the stratum corneum.

The barrier of the skin

One of the main functions of the skin is to maintain the diffusion barrier between the internal and external milieu environment of the organism. This barrier function is located exclusively in the stratum corneum, which may be regarded as a 15–20 μm thick, densely packed 'membrane'. The obvious function of the lower epidermal strata would thus seem to be to formation of the outermost sheet.

Research over the last 15 years has shown that the intercellular lipids of the stratum corneum play a key role in establishing the barrier.

The stratum corneum can be compared to a brick wall, with the corneocytes as the bricks and the intercellular lipids as the mortar (22). During the process of keratinization, the lipid composition of the epidermis changes dramatically, to a large degree reflecting the formation and transformation of the barrier. The cells of stratum basale and stratum spinosum show a complex lipid composition, characteristic of cells containing a whole range of subcellular organelles. Phospholipids are thus the major constituent (about 60%) at this level. The phospholipids are successively catabolized to give both the energy and material needed to synthesize more non-polar lipids in the anaerobic environment of higher strata in the epidermis.

In this context, the lamellar bodies (LB) (synonyms: membrane-coating granules (MCG), Odland's bodies) play a central role. These structures first appear in the upper stratum spinosum and are seen most abundantly in the stratum granulosum. They have an orderly internal structure of parallel lipid lamellae, and contain glycosphingolipids, free sterols, and hydrolytic enzymes (23). In the upper stratum granulosum, these bodies fuse with the plasma membrane, extruding their content into the intercellular spaces of stratum corneum. Here the lamellar disks are reorganized into the broad bilayers of the stratum corneum interstices. Histochemically, these morphological changes correspond to substantial alterations in the

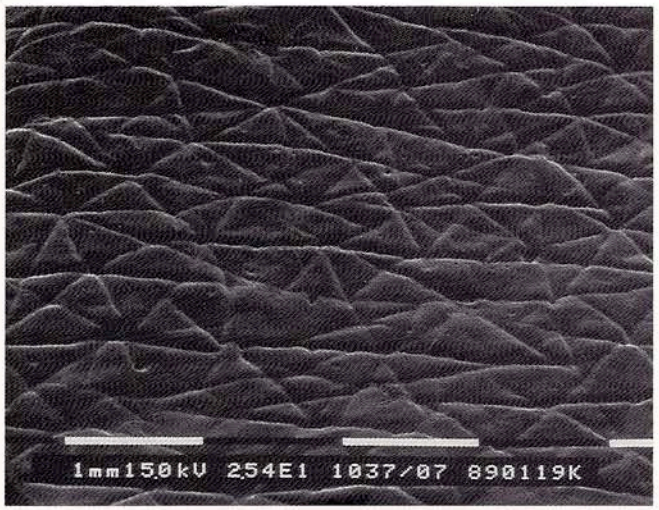

Fig. 1. SEM micrograph of a replica from normal skin (bar 1 mm).

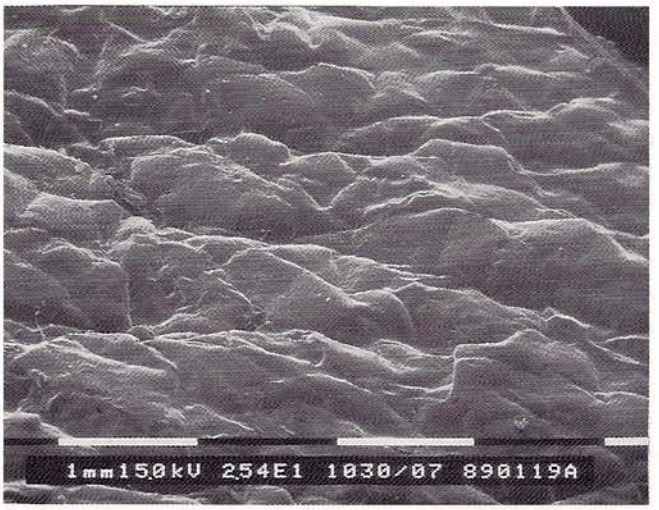

Fig. 2. SEM micrograph of a replica from dry atopic skin (bar 1 mm).

composition of lipids. The quantity of non-polar lipids such as free sterols, free fatty acids, triglycerides, and sterolesters increases, as do the sphingolipids, including the ceramides.

A subgroup of the sphingolipids, the ceramides, constitute about 40% of the stratum corneum lipids in human skin. Structurally, they are a heterogeneous and complex group of lipids (24). Each has both a polar head and a prominent non-polar tail. The hydrophobic tail makes up the interior of the bilayer, ranging between 14 and 30 carbon atoms in length. These long hydrocarbon chains are almost entirely saturated and straight and thus allow bilayers to form in which the lipid units are closely packed, thus being ideally suited for water impermeability.

Whole stratum corneum contains approximately 10% lipid, while the membrane complexes contain 50% lipid. In contrast to previous opinion, i.e. that the intercellular space volume is minute, it was recently shown that it constitutes 10–30% of the whole stratum corneum volume (25). Thus it constitutes a significant hydrophobic (lipophilic) transport channel through the skin.

Lamellar bodies in atopic dermatitis

Owing to the fact that patients with AD have a defective barrier, the question was raised whether the LB were in some way changed in atopic patients. Biopsies were taken from dry dorsal skin in 9 patients with AD and from normal dorsal skin in 9 non-atopics. A quantitative morphometric electronmicroscopic study was then performed on this material. To obtain a quantitative estimate of the number of the lamellar bodies ten consecutive fields of the border area between the stratum corneum and the stratum granulosum were photographed at a magnification of × 10.000. The evaluation of the relative volumes of keratohyalin granules, filaments and granular material was based on five micrographs of the stratum granulosum in the same section as was used for the LB analysis. There was a significant increase in the relative volume of LB in dry atopic vis-à-vis to normal skin.

The results, showing an increased relative volume of LB in dry atopic skin, may indicate a disturbance in the lipid metabolism. Markers of differentiation were not significantly changed, which may indicate that there is no major disturbance of the keratinization process (26).

The lipids of the stratum corneum in AD

3-mm punch biopsies were obtained from 11 atopic patients and 12 controls and prepared so as to retain only the stratum corneum, from which the lipids were extracted. These lipid extracts were spotted on to silica-coated quartz rods, run in the 3 different lipid solvents to separate the different lipid classes. Then the chromatograms were fixed with the flame ionization detector of an Iatroscan TH-10®. All peaks were identified by comparison with known standards (22).

The total content of extractable lipids was small. One way of assessing the amount is to relate it to the total area unit of the chromatogram. The data suggest that the total lipid content of atopic skin was substantially smaller than that of control skin. Due to technical problems related to the small amounts extracted, no data on the absolute amounts of lipids were obtained. The distribution of the lipid classes was about the same in both groups (27).

The distribution of the lipids tallied with earlier reports (23,28). Reports in the literature on the lipid content of stratum corneum in AD are sparse. Melnick et al. (29) found a decrease in the ceramide fraction in stratum corneum from plantar skin in atopics. In contrast, Lavrijsen et al. (30) reported an increase in the content of ceramides in the stratum corneum in normal skin of patients with AD, using an 'in vivo' extraction technique.

Clinical studies on the frequency of dry skin in AD

Dry skin is a common complaint by patients with AD, but few studies on the actual occurrence of this symptom have been published (1,31). In a long-term follow-up study by Rystedt (32) of almost 1.000 atopic patients, the subjective opinion of having 'dry/itchy' skin turned out to be one of the most unfavourable factors in the long-term prognosis for AD. A clinical evaluation of the frequency and distribution of dry skin was performed in 50 patients with AD, compared with 50 non-atopics.

The results showed that 82% of the patients with AD regarded their skin as being dry. On clinical examination, 48% objectively had patches of dry skin. Uehara & Harumitsu (1) found a frequency of 63% of dry skin among children with AD in Japan. In China, Kang & Runmei (31) reported that 71% of adult atopics had xerosis. Svensson et al. (33) found a frequency as high as 98% of both subjectively and objectively dry skin in atopic patients. The disparity between different investigations may in part be due to racial and/or geographical differences ad well as to differing opinions about the criteria for assessment of the clinical appearance of dry skin.

In a study of sweat pore density, the topography of the fingertips of atopic patients was shown to be different from that of normal individuals and to give a poor fingerprints quality (34). To my knowledge, no examination of the surface of dry atopic skin has yet been performed in SEM. In order to correlate the clinical impression of 'dryness' to skin surface morphology, a non-invasive replica technique was used to visualize the skin surface in the scanning electron microscope (SEM).

SEM replicas of normal skin from the back revealed a regular pattern, with major furrows running parallel, between which, triangles were formed by minor furrows. In replicas from dry atopic skin (see Figs. 1 and 2) the major furrows were seen to be less regular and the minor furrows had almost disappeared (35).

Surface profilometry

The SEM micrographs give a visual impression of the differences between atopic and normal skin but offer no possibility to compare the differences objectively. Surface profilometry, originating from mechanical engineering makes it possible to quantify the topography of a skin surface (36).

Replicas of the dry skin from the back of 10 patients with AD were compared with replicas of the normal skin from 10 controls. The analysis was performed using a computer-controlled three-dimensional stylus-instrument system (Perthometer C5D). The parameters used for mathematical calculations were constructed from a total of 76,800 points for each replica.

There was a significant increase in roughness parameters, while those describing the shape of the profile did not differ between the two groups. In dry atopic skin the peaks were higher but fewer. The *shape* of the skin surface profile seemed to be approximately the same in both groups. The dry skin in patients with AD really does appear to be rough (37).

DISCUSSION

The aim of these studies has been to examine the barrier function of the skin of patients with atopic dermatitis, and to define more objectively the descriptive term 'dry skin', so often used in clinical work. To achieve these goals the stratum corneum, where the barrier is located, has been studied by using techniques for the determination for water-binding capacity, TEWL, and of water content. In addition, the ultrastructural morphology in TEM and the surface morphology in SEM have been studied, as also has the lipid composition of the stratum corneum in atopic skin.

To date, the crucial function of the stratum corneum lipids in the barrier function is well established. This has been shown in a number of experimental works and also confirmed in clinical experience. In experimentally induced deficiency of essential fatty acids (EFA) in rats, their skin becomes 'dry' and 'scaly' and the barrier function becomes impaired. If linoleic acid is added to the diet or applied topically, the skin returns to normal (38). In patients with EFA deficiency due to long-term parenteral nutrition or malabsorption, the skin became dry and hyperpigmented, after topical application of linoleic acid, the skin returned to normal (39). Renewed interest in lipids for treatment of patients with AD has also been reported. Fish oil extract, rich in eicosapentanoic acid has been give perorally to atopic patients by Bjorneboe et al. (40). This resulted in a significant decrease in the amount of scaling and itch, although the eczematous changes were not significantly improved. Oral treatment with evening primrose oil, rich in gammalinoleic acid, gave a statistically significant improvement compared with placebo in patients with AD, as regards both severity of inflammation and dryness and itching (41,42).

Finley et al. (20) have shown that in dry atopic skin the corneocytes have a tendency to 'clump' together, with the result that they break away from the surface in large clusters. This may play a certain role, but the main reason for the feeling of roughness to the touch is assumed to be found in the topographical changes. The mechanism behind the formation of the surface pattern is not clearly understood. The major furrows can be seen to be projected down to the dermal surface, whereas the minor furrows have only been recorded to a level corresponding to the stratum granulosum. This means that some interaction between the basal cells and the dermis is involved in forming of the major furrows, while the minor furrows, on the other hand, probably represent interactions of the keratinocytes with their environment. In this context, changes in the stratum corneum of dry atopic skin, such as a reduced ability to bind water and a decreased water content, probably play some part.

There are several sites for water binding within the stratum corneum. The keratin molecules characteristically bind water, but water also bind to various structures within the lipid phase. This is shown by the fact that the water-binding ability of the stratum corneum is reduced after extraction with lipid solvent. Whether the 'natural moisturizing factors' (NMF), such as amino acids, urea, and inorganic salts are 'hidden' behind a lipid structure and are thus extracted, and/or whether the water binds directly to hydrophillic regions in the lipid bilayers is not fully understood.

The following hypothesis is presented: in patients with AD, the stratum corneum lipids are changed quantitatively and/or qualitatively, resulting in a defective barrier function, both in dry and in clinically normal skin on predilection areas. The decrease in water-binding capacity of the stratum corneum and the small amount of water within the corneum may partly be regarded as a consequence of the lipid alterations. The impression of dryness is due to the rough surface pattern of the atopic skin.

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