Cutaneous Barrier, Innate Immunity and Diabetes

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Cutaneous Barrier

CB is defined as a dynamic, functional and morphological structure made up of cells and non-cellular components of the skin which provides an effective isolation of the individual from his environment. It prevents infections, maintains body temperature and electrolyte balance, avoids water loss and limits the damage of oxidative stress and effects of ultraviolet radiation (Table 5.1).

The complex lipid structure that makes up the CB is regulated to keep homeostasis in the skin.

A disturbance of the epidermal barrier function induces a rapid response from the keratinocytes that involves upregulation of the inflammatory signal cytokines, adhesion molecules and growth factors. This leads to epidermal hyperplasia and an increase in lipid synthesis in order to restore normal function.

Several diseases a variety of drugs and therapeutic options may delay repair or alter the healthy barrier's kinetics [1].

The physical barrier localized primarily in the stratum corneum (SC) is crucial in the activity of the epidermal permeability barrier. The viable epidermis and outer nucleated layers also contribute to this skin function. On other hand, the SC is more than just an inert brick wall. In the presence of physiologic stress, it can regulate the rate of corneocytes shedding or desquamation.

In the SC, the corneocytes produced from terminal keratinocyte differentiation build a platform of protein-enriched cells, the cornified envelope, formed through

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Table 5.1 Cutaneous barrier functions

Barrier	Role	Effector
Permeability	Prevent excess water loss Protects from harmful chemicals, allergens and microbial pathogens Maintains body temperature	Components of skin structure
Antimicrobial	Protects against multiple pathogens (bacteria fungi and some viruses)	Acidic pH Sphingoid bases Innate immune (antimicrobial peptides)
Antioxidant	Protects skin from oxidative stress	Tocopherol Vitamin C-E Glutathione Ubiquinol Uric acid Small proline rich region proteins (SPRR) Superoxide dismutase
UV	Protects skin from UV DNA damage Protects skin from oxidative stress	Urocanic acid Structure components

specific precursor proteins crosslinking, including involucrin, loricrin, small proline-rich regions proteins (SPRR), transglutaminase, filagrin and corneodesmosomes, surrounded by an enriched neutral lipid, covalently binded into the extracellular space.

Fillagrin, the principal water ligand compound, is a component of the natural moisturizing factor (NMF) cross-linked to the cornified envelope and aggregates keratin filaments into macrofibrils.

The enriched neutral lipid-lamellar membranes localized in the extracellular spaces of the SC are synthesized in the keratinocytes as lamellar bodies (LB) during epidermal differentiation.

LB are secretory organelles 0.2 Å~ 0.3 μ with a predominant role in the maintenance of cutaneous permeability and other activities such as antimicrobial, chemical defense and movement of molecules and proteins from intra to extracellular space.

LB are first observed in the upper stratum spinosum layer of the epidermis, with increasing numbers found in the stratum granulosum layer. This organelles contain phospholipids, glucosylceramides, sphingomyelin, cholesterol and several enzymes. These precursor lipids are converted into non-polar lipid products by enzymes (Fig. 5.1).

Beta-glucocerebrosidase converts glucosylceramides into ceramides, phospholipases convert phospholipids into free fatty acids and glycerol acidic sphingomyelinase converts sphingomyelin into ceramides.

In addition, others enzymes, proteases such as chemotryptic enzymes (kallikreins) and cathepsins, are present in LBs. Enzyme inhibitors, such as the serine protease inhibitor, elafin, are packaged into LBs.

Moreover, antimicrobial peptides (AMP), such as human β-defensin 2 and the cathelicidin LL-37 are also present in LBs [2–5].

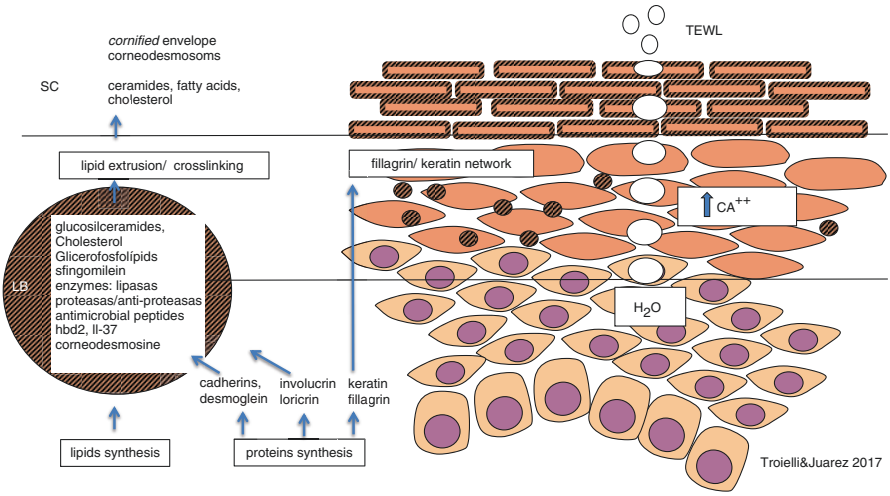

Fig. 5.1 Cutaneous barrier. *LB* lamellar bodies, *SC* stratum corneum, *TEWL* transepidermal water loss (reproduced from Cutaneous Manifestations of Diabetes. Cohen Sabban E.N. 2017)

The SC contains an abundance of cholesterol from the LB, and cholesterol sulfate, that is converted into cholesterol by the Cholesterol Sulfatase enzyme which plays an important role in regulating SC cohesion and desquamation.

Lipids, cholesterol, ceramides and fatty acids must be present in appropriate distribution in stratum granulosum cells in order to synthesize structurally normal LB. Altered metabolism, either in excess or a deficiency of a particular lipid can result in abnormal lamellar bilayer formation and affect normal skin function.

The extracellular processing of lipids leads to a balance of 50% ceramides, 25% cholesterol, and 15% free fatty acids with very little phospholipid.

Topically applied lipids may interfere with the skin barrier function and treatment with formulations containing physiological lipids such as cholesterol, ceramide 3, oleic acid and palmitic acid are suggested as strategy to recover dry skin and inflammatory disorders [2, 6–8].

Lipids required for LB formation are derived from de novo synthesis by keratinocytes and from extra-cutaneous sources not as yet completely identified.

Impaired nutritional status may alter the structural integrity of the skin, as well as a proper nutritional intake. The intake of Ca^{++} and vitamin C complements endogenous factors in regulating skin barrier function [9].

The pH of the skin surface and outer layers is acidic with a pH range from 5 to 5.5 leading to a defense environment against invading organisms and it is necessary for the activity of several enzymes in the SC.

The acidic PH stimulates sphingomyelinase and beta-glucocerebrosidase activity, allowing a normal regulation of ceramides level but also blocks other enzymes such as proteases that need an optimum PH 7 or higher to increase proteolytic activity and induce corneocyte desquamation.

The increase in serine protease activity with pH 7 or higher leads to the activation of protease activated receptor 2 (PAR-2) which can increase the differentiation of keratinocytes into corneocytes and inhibit LB secretion, with severe effect in the homeostasis of the skin.

The importance of preserving an acidic skin PH remains an under recognized topic.

Elderly patients have skin PH increased and ceramide deficit [10]. This is explained by high levels of alkaline enzymes activity, like alkaline ceramidases which are involved in barrier lipid degradation in aged human skin.

Changes in PH predispose to infections. Candidal intertrigo is more frequent in flexural areas with higher PH than in other skin sites.

Diabetics are prone to develop Candidal intertrigo and it has been reported that PH was significantly higher in the intertriginous zones of non-insulin dependent diabetics compared to healthy individuals [11, 12].

Permeability Barrier

Skin hydration level depends on four factors:

1. Presence of natural hygroscopic agents, the NMF within the corneocytes.
2. Presence of endogenous glycerol as a natural moisturizer and hyaluronic acid in the epidermis and dermis.
3. Ordered lamellar arrangement of intercellular lipids in the SC that form a barrier to transepidermal water loss (TEWL).
4. Presence of tight junctions within the stratum granulosum to further impede water loss.

Dry skin can be a symptom in a number of systemic diseases such as psoriasis, diabetes and renal transplantation. The mechanism of xerosis in these disorders is not yet fully understood.

Amino acids (AAs) play important roles in maintaining an optimal hydration state of SC as a component of the natural moisturizing factor (NMF).

These groups of small hydrophilic compounds account for 5–30% of the total dry weight of SC and are the main components to which water binds directly. Small amounts of bound water are associated with the hydrophilic polar groups of intercellular lipids such as sphingomyelin and corneocytes.

The upper SC works like a “sponge” where solutes, ions and antimicrobial peptides contained in the sweat, flow in-out and some are retained.

It has been suggested, that skin hydration depends of arginine, the major component of fillagrin-derived natural moisturizing factors, that is concentrated in the middle layer of the SC.

The low arginine levels in the upper SC are probably due to further metabolic modification, i.e., citrullination, or direct loss to the external environment [13].

Watabe et al., have demonstrated that also sweat contains several NMF, lactate, urea, sodium, and potassium. Lactate and potassium significantly affect the hydration

state of SC and reduced sweat delivery to the SC may cause xerosis in several chronic diseases [14].

A case control study found no difference in SC hydration and transepidermal water loss between diabetics and controls [15].

On the other hand, studies suggest that patients with diabetes mellitus tend to show a normal hydration state with decreased sebaceous and sweat gland activity and impaired skin elasticity without impairment of the SC barrier function [16].

It has been proven that hydration state of SC and lipids on the diabetics skin surface decreases with glycemic index over 110 mg/dl.

A long-standing hyperglycemia condition impairs skin barrier by accelerating skin ageing process.

Insulin plays a decisive role in the skin homeostasis. Epidermis constitutes a glycolytic tissue. Keratinocytes insulin receptors make up the system of insulin uptake which regulates the glycemic level in epidermal cells inducing transitory states of hyperglycemia [17].

The properties of the SC in patients with diabetes mellitus have similarities to senile xerosis. Studies show that diabetic rats have normal levels of ceramides and aminoacids but show low levels of triglycerides in SC [18].

The epidermal barrier retains moisture, regulates water flux, and modifies the rate and magnitude of TEWL.

Nowadays, cutaneous barrier recovery and inflammation are instrumentally monitored as TEWL and skin blood flow using the Evaporimeter and Laser Doppler Flowmeter, respectively.

Pathological states of the skin may be detected by measuring the TEWL rate.

The barrier has the ability to detect homeostatic abnormalities at an early stage through mild TEWL increase. The alteration of the Ca^{+2} gradient, the loss of elevated Ca^{+2} in the granular layer is the signal that induces in a few minutes the physiological self-repair mechanism by releasing the lipid stored in the SC. This lipid movement increases the production of fillagrin and fillagrin degradation products like free aminoacids. These pyrrolidone carboxylic acid and urocanic acid with sugar ions form the NMF to restore hydration.

Dermatologic conditions or metabolic diseases with permeability barrier impairment diminish the capacity to adapt to different exogenous physical, infectious and chemical insults. The repair mechanisms are not able to keep up with the magnitude or velocity to restore normal function and without therapeutic intervention the progression of xerosis leads to dry skin with different signs and symptoms of inflammation and infection.

Antioxidant Barrier

Reactive oxygen species (ROS) contribute to the processes of skin ageing and impaired skin barrier function. ROS are particularly harmful in that they destabilize other molecules and promote chain reactions that damage biomolecules rapidly, such as telomere shortening and deterioration, mitochondrial damage, membrane degradation and oxidation of structural and enzymatic proteins [19, 20].

The CB disturbance decreased antioxidant capacity and alters its functions.

The quantity of ROS in the skin is higher than in any other organ and in many cases a clear correlation between ROS (from internal and external origen) and a proaging state can be found.

The skin is at the interface between the body and the environment and is therefore in constant contact with pollutants, xenobiotics, and UV irradiation. These exogenous factors represent the main contributor to ROS production in human skin, therefore being very specific for this organ. Additionally, alcohol intake, nutritional factors and physiological and mechanical stress are believed to contribute to this kind of ROS production. In addition, the skin is also one of the very few organs that are in direct contact with atmospheric oxygen which can contribute to ROS.

Enzymes that are ROS producing, on purpose or as a byproduct, include the mitochondrial electron transport chain, NADPH oxidases, xanthine oxidoreductase (XOR), several peroxisomal oxidases, enzymes of the cytochrome P450 family, cyclooxygenases, and lipoxygenases.

To deal with ROS production, there are specific antioxidant mechanisms in the skin present at an intra and extracellular level. Most of the antioxidants are at higher concentration in the epidermis than in the dermis. This correlates well with the fact that ROS load is higher in the epidermis than in the dermis. Vitamin C, vitamin E, glutathione, ubiquinol, and uric acid are detectable in the SC but their concentration increases steeply towards deeper cell-layers of the SC. These comparably low concentrations of non-enzymatic and lipophilic anti-oxidants in the outer layers of the SC are possible because the cornified envelope itself has anti-oxidative capabilities. These antioxidant capabilities of the cornified envelope rely on the small proline rich region proteins (SPRR).

The highest concentrations of enzymes and antioxidants are found in the stratum granulosum constantly declining towards the stratum basale. In this way, the suprabasal cells have lower ROS levels and are protected against UVB-induced apoptosis. The importance of the SC as an anti-oxidant/UV barrier is also stressed by the fact that UV can completely deplete the stratum corneum of antioxidants/vitamins. Therefore, only the remaining SC proteins (mainly SPRR2 subfamily) can exert their antioxidant properties and protect the epidermal cells.

The formation of structures known as advanced glycation end products (AGEs) can be significantly accelerated by oxidative stress. AGEs originate from the non-enzymatic glycation reaction between sugars and proteins, nucleic acids or lipids. AGEs are a heterogeneous group of molecules and can either be ingested through food consumption or formed inside the cell. Diabetic patients have higher concentrations of AGEs (see Chap. 15).

UV Barrier

Photon energy carried in UV (particularly UVB at 280–315 nm, and UVA at 315–400 nm) induces alterations that accumulate and promote the majority of the typical manifestations of skin ageing and cancer. UVB makes up only 5% of the UV

radiation that reaches the earth's surface and has little penetrance but it displays great biological activity. UVA makes up the remaining 95% of incident light and is more penetrating, promoting photo aging. However, UVA carries less energy and therefore promotes carcinogenesis to a lower extent than UVB.

The main effects of acute and chronic exposure to UV radiation are DNA damage, inflammation and immunosuppression. These effects are direct as well as indirect due to ROS production [20].

It has recently been established that ultraviolet (UV) irradiation activates the inflammasome in human keratinocytes [21].

Skin Innate Immune System

The innate immune system employs cells of different tissues, organs and molecules to protect the body from a variety of pathogenic microbes and toxins present in the environment.

The skin innate immune system has numerous functions, including:

1. Action as antimicrobial barrier
2. Activation of the complement cascade
3. Recruitment of innate immune cells.

Controlling the extent of an immune response is thus a major challenge for maintaining skin integrity, which is of paramount importance for host survival [22, 23].

The skin innate immune system can detect and respond to the insults of microbes and danger signals from the environment and from inside the body.

The skin, can sense pathogens and mediate immune response by different types of cell receptors present in keratinocytes, macrophages, mast cells, fibroblasts and nerve-related cell types and in many specialized immune cells, including DCs, $CD4^+$ T helper (T_H) cells, γδ T cells and natural killer T (NKT) cells.

The Pattern Recognition Receptors (PRRs) including membrane bound Toll Like Receptors (TLRs) and C-type lectin receptors (CLRs), detect Pathogen Associated Molecular Patterns (PAMPs) sensing byproduct microorganisms, such as lipopolysaccharides (LPS), lipopeptides, flagellin, bacterial DNA, double stranded viral RNA, *Candida sp.* wall, components β-Glucans mannans, phospholipomannans of fungus.

The intracellular PRRs are TLRs of the endosomal compartment and Nucleotide-binding Oligomerization Domain proteins (NOD- Like receptors NOD1 and NOD2) that sense Danger Associated Molecular Pattern (DAMPs).

DAMPS are derived from dying cells, small molecules from damaged cell nuclei, ATP, DNA, β Defensins, HMGB1, exogenous particles like asbestos, endogenous like crystals of uric acid, ultraviolet radiation.

NOD1 and NOD2 are intracellular PRRs that recognize bacterial molecules produced during the breakdown of peptidoglycan (PGN), N0D1 recognizes products of gram negative PGN and NOD 2 products of both gram negative and positive PGN.

The differential activation of these receptors results in various complex signaling pathways, NF-KB, MAPK, inflammasomes and leads to the release of regulatory factors and multiple cytokines (IL-1β, IL6, IL8, IL-18, and IL-33) and chemokines.

IL-33, a newly discovered member of the IL-1 family, has been identified as a potent inducer of Th2 type immunity. Emerging evidence implies that IL-33 may also act as an alarm to alert the immune system when released by epithelial barrier tissues during trauma or infection [24].

Wound healing is impaired in diabetic patients owing to overproduction of inflammatory cytokines, and IL-33 has been involved in modulation of uncontrolled inflammatory responses.

Even though the pathology of diabetic wound healing is not totally explained, recent scientific evidence shows that IL-33 supplement may promote induction of M2 macrophages in diabetic mice and accelerate wound closure.

Macrophages are implicated in all stages of wound healing stimulating angiogenesis, fibrosis and reepithelization. Their polarization state (M1 inflammatory type and M2 proliferative type) depends on the microenvironment present in the wound and is essential for tissue repair.

The functional/phenotypic switch Macrophage M1 to M2 does not readily occur in diabetic wounds and the macrophages remain predominantly in a pro-inflammatory M1-activation state and continue the chronic inflammation [25].

Manipulation of IL-33-mediated signal might be a potential therapeutic approach for diabetic skin wounds.

Keratinocytes participate in the innate immune response of the skin. They can sense danger and infections, toxins, irritants via expressing TLRs and inflammasome activation.

They produce lipids, chemokines, cytokines and peptides with antimicrobial activity, antimicrobial peptides (AMPs). Several AMPs are extruded from the LBs to the extracellular space in the SC [3].

The AMPs lead to pores in the microbial membrane with subsequent osmotic lysis and microbial cell death while cationic antimicrobial peptides associate with negatively charged bacterial membrane, many of which have chemotactic properties. There are others AMPs skin sources (Table 5.2).

Human β-defensins (HBD) are generally short and positively charged, and have hydrophobic or amphipathic domains in their folded structure. They are recognized as HBD 1, 2, 3, 4. HBD 3, 4 are predominantly expressed in the skin and have potent

Table 5.2 AMPs skin sources

AMPs	Sources
α defensins	Azurophilic granules of infiltrating neutrophils
β defensins	Keratinocytes and macrophages
Cathelicidin LL37	Keratinocytes, ductal epithelium, eccrine glands, mast cells
Granulysin	Infiltrating T cells
Psoriasin	Keratinocytes, follicular epithelium, sebocytes
Dermcidin	Eccrine glands
RNase	Keratinocytes

antimicrobial activity against gram-positive. Almost all of HBD have activity against gram-negative bacteria and HBD 2, 3, 4 against yeast and viruses.

Cathelicidins antimicrobial peptides (CAMPs) represent another AMPs family. Human cathelicidin hCAP-18 is constitutively expressed by neutrophils and squamous epithelium in response to inflammatory challenge; it is processed by proteinase 3 to generate the active peptide LL-37.

Recent studies demonstrated that ceramide metabolites, ceramide-1-phosphate and sphingosine-1-phosphate produced in human keratinocytes in response to subtoxic levels of endoplasmic reticulum (ER) stress stimulate production of these major epidermal innate immune elements, β defensins and cathelicidin antimicrobial peptides, via STAT1/3- or NF-κB-dependent mechanisms, respectively.

However, patients with T2DM have lower levels of CAMP (LL-37) and DEFB4 (HBD-2) gene expression in peripheral blood cells which probably makes them susceptible to infectious diseases. Furthermore, it has been reported that the expression of DEFB4 is lower in diabetic foot ulcers in comparison with healthy skin suggesting that low levels of this peptide contribute to poor wound healing in diabetic patients [26, 27].

On the other hand, hyperglycemia, both acute and chronic, has a profound effect on host defense response, innate and adaptative immune systems.

High concentration of glucose activates mitogen-activated protein kinases which influence transcription activity in the nucleus, upregulates TLR4 with increased NK-kappa β activation and IL-8 expression, and stimulates p62/PKC interaction which also results in NF-kappa β activation. These events regulate inflammatory responses and can alter both neutrophil and endothelial function.

Studies using both in vitro and in vivo methods have demonstrated defective neutrophil function in prolonged hyperglycemic states. Diabetic patients have higher susceptibility to infection and increased severity of infections compared to non-diabetic patients.

Chronic Hyperglycemic state negatively affects neutrophil respiratory burst capacity and monocytes proliferation irrespective of the phenotype of diabetes, the duration of the disease or insulin use.

Also produces changes in endothelial function that may be secondary to reduced nitric oxide. In vitro studies, high concentrations of glucose and AGEs decrease constitutive nitric oxide synthases.

Complement activation promotes the opsonization and phagocytosis of pathogens by macrophages and neutrophils. It can also cause direct lysis of microbes and the release of mediators (e.g., C3a and C5a), which direct neutrophil migration and chemotaxis.

Several studies have shown that elevated glucose levels affect the complement cascade system, blocking the complement fixation and reducing opsonization delay bacterial clearance [28].

The impact of a **diagnosis** of diabetes may lead to increased **stress** in patients and psychosocial stress affects the immune response, barrier function, wound healing and resistance to infection of healthy skin. Psychosocial stress **r**esults in a delay

in barrier recovery and impairs the expression and the production of antimicrobial peptides, predisposing to cutaneous infection [29, 30].

Chronic psychosocial stress skews the immune response from a predominantly Th1 to a Th2 phenotype and disrupts barrier function via glucocorticoid induced inhibition of epidermal lipid synthesis, which consequently impairs LB formation and decreases the size and density of corneodesmosomes.

Cutaneous Barrier in Diabetics: Dermocosmetic Management

The aim of the dermocosmetic management of the CB in diabetic patients is to prevent and improve early stage of loss of integrity of the skin and reestablish normal hydration in order to mitigate the action of internal and external factors which influence the antimicrobial, antioxidant and ultraviolet radiation UVR protective functions. The therapeutic intervention involves a multidisciplinary approach: clinical, aesthetic and oncological dermatology.

It is essential to know the physiology of CB and skin ageing in diabetes mellitus in order to advise and provide proper treatments that will improve patient's quality of life.

Permeability Alteration

One of the most common skin manifestations of diabetes mellitus is xerosis (dry skin) which varies in severity and clinical symptomatology.

Skin barrier function, adequate cutaneous microcirculatory and autonomic nervous activity are mutually associated in healthy adults [31]. Several studies have shown that a deterioration of skin properties, an impaired cutaneous microcirculation function and an imbalance of autonomic nervous activity are observed in smokers and in patients with diabetes mellitus or Raynaud's phenomenon.

In diabetic patients with diabetic microangiopathy, there is an abnormal cutaneous perfusion caused by loss of cutaneous capillaries. Reduced skin blood flow (SkBF) recovery after cold stress and impaired responsiveness to local warming are thought to have a possible role in dry skin [32]. Diabetes and dry skin are a well documented associations and the presence of microvascular complications is related to its development in insulin dependent patients [33].

The term "dry skin" is used to refer to clinically dehydrated, rough and scaly skin. It happens when there is an alteration in the cornification process resulting in hyperkeratosis, scaling and abnormalities in the SC function. It may be seen in the entire cutaneous surface although it is mostly present in feet, pretibial areas and cheeks. Clinical manifestations include light roughness to major scaling with large plaques.

Xerosis is not only related to alterations of diabetes itself, but it is also linked to skin ageing process and others associated pathologies as well [34, 35]. Therefore,

Table 5.3 Differential diagnosis of xerosis

Malignancy	Linfoproliferative diseases
Autoinmune/infalmatory disease	Systemic lupus erythematosus Dermatomyositis Sarcoidosis Eosinophilic fascitis
Nutritional disease	Malnutrition Malabsorption (celiac disease/pancreatic insufficiency)
Metabolic disease	Diabetes Chronic renal failure Chronic hepatic dysfunction Hypothyroidism Hyperparathyroidism Hypopituitarism
Infectious disease	AIDS HTLV-I HTLV-II Leprosy
Neurologic	Sympathectomy
Medications	Statins Calcium channel blockers Cimetidine Nicotinic acid

people with diabetes have dry skin due to multifactorial origin [36]. Some of the most common causes of xerodermia are listed in Table 5.3.

It is important to point out the external factors that influence the degree of affectation such as use of medicines, environmental pollution, exposure to sun, diet, and smoking [37, 38].

Moisturizing and keratolytic agents are useful to treat dry skin. Diabetic patients with dry skin are specially predisposed to skin infections. That is why it is sometimes necessary to prescribe topical antibiotics [39].

Creams containing lipids and substances as urea are most commonly used [40, 41].

Lipids are divided according to their way of action in physiological and non-physiological [2].

Topical Treatment

Non Physiological Lipids

They are not usually found in LBs. They fill up extracellular spaces of SC. They are hydrophobic and block water movement and electrolytes.

These non-physiological lipids may quickly restore normal permeability of CB but only partially and without correcting the abnormality that originated it. Petrolatum (Vaseline), lanolin, bees wax, etc., are some examples of these.

Physiological Lipids

They are lipids or precursors that are usually found in LBs (cholesterol, free fatty acids and ceramides). These lipids are carried through SC to granular stratum cells where they mix with the pool of endogenous lipids and join the LBs (Fig. 5.2).

Ceramides make up 50% of intercellular lipids in the epidermis and are molecules often added to moisturizing creams [7].

Topical treatments with exogenous physiological lipids help reestablish both normal permeability of CB and antimicrobial function [42].

Antimicrobial peptides are packed into LBs to be released later into SC extracellular space. The availability of exogenous lipids leads to increase of production and release of these peptides.

A particularly interesting physiological lipid present in some creams for treatment of xerosis is *N*-palmitoylethanolamine. It acts at a cutaneous level as Cannabinoid Receptor agonist. These receptors play a role in the modulation of nociceptive symptoms. Its topical use has shown to be of great use in clinical studies to relieve chronic pruritus of various origins and in the treatment of postherpetic neuralgia [43, 44].

It may be useful to apply a mixture of physiological and non-physiological lipids as the response of physiological lipids is slow while non-physiological ones, such as petrolatum, result in partial improvement in permeability of CB almost at once.

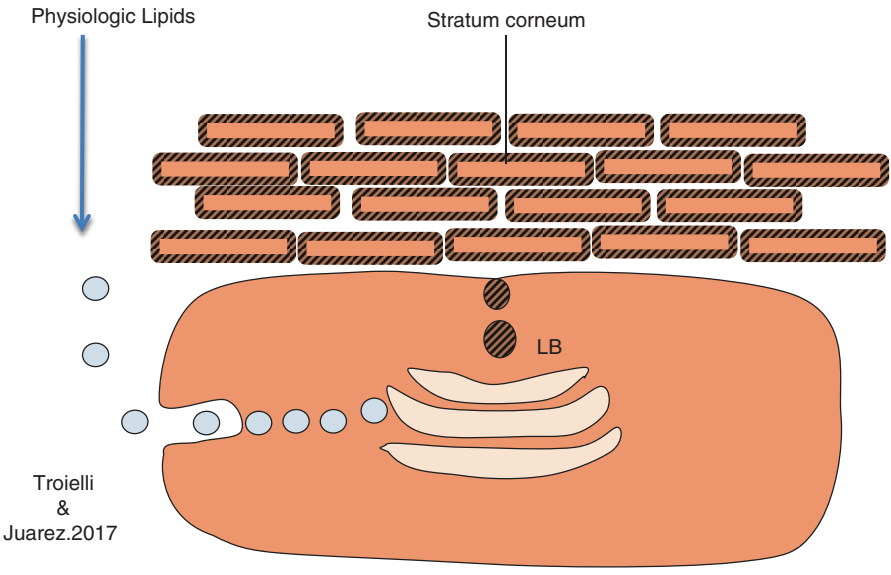

Fig. 5.2 Physiologic lipids traverse the stratum corneum, enter the nucleated cell layers, targeting the lamellar body (LB) secretory system (reproduced from Cutaneous Manifestations of Diabetes. Cohen Sabban E.N. 2017)

Topical Urea

Urea is an organic compound whose chemical structure is made up of a carbonyl group joined to two amino residues. Urea plays a very important physiological role in metabolism and excretion of nitrogenized products.

Topical urea is an effective therapeutic option in dry skin patients [45, 46].

Urea mechanism of action in the skin is still not fully understood. The studies suggest that the keratolytic and moisturizing effects of urea are due to the rupture of hydrogen bonds in the SC that leads to the rupture of the keratin molecules and increases the number of sites available for the unity of the water molecules. This aids restoration of altered CB and contributes to the scaling of normal skin [47].

There is evidence that urea also has antimicrobial properties, Grether et al. have shown that topical applications of urea at 20% improves the CB function and increases the expression of antimicrobial peptides in normal skin [45].

The urea uptake is followed by regulatory events such as expression of urea transporting elements and critical genes for the function of CB. These genes impact on the differentiation of keratinocytes, synthesis of lipids and production of antimicrobial peptides.

Urea is particularly interesting for use in diabetic patients as moisturizer and restorer. The ideal concentration is 20% (creams and ointments) and may be prescribed at 40% considering its keratolytic effect in patients with hyperkeratosis, e.g., plantar. In severe hyperkeratosis, the use under occlusion is recommended [48].

Urea shows excellent efficacy and safety profile although some patients may experience burning or stinging sensation during the first days of treatment [49].

Antioxidants and Sunscreens

Oxidative stress and action of AGEs are two processes that contribute to the impairment of CB function [20].

Besides, they are directly and indirectly related to the mechanisms that lead to photoageing and photocarcinogenesis which impact on the physical and mental health of patients.

Photoprotection diminishes ROS generated by UV radiation, partially prevents direct damage of cellular DNA, inflammation, immunosuppression and remodeling of extracellular matrix.

There is scientific evidence showing that combining sunscreens and topical antioxidants produce greater effect than the use of one of them on its own.

Antioxidants should be applied before sunscreen. Examples of most commonly used antioxidants are detailed in Table 5.4.

Sunscreens should have a broad spectrum protection, which means against UVB and UVA rays and Solar Protection Factor 30 or higher. Dry skin can be benefited with moisturizing sunscreens, as they contain lanolin, oils and dimethicone in their cream, lotion or ointment formulation. Otherwise, recommend patients to apply moisturizing cream.

Table 5.4 Commonly used antioxidants

Molecule	Role
Vitamin C	Suppresses UV production of free radicals Attenuates UV damage in the skin Promotes cutaneous wound healing Increase epidermal moisture content
Vitamin E	Suppresses lipid peroxidation Modulates photoaging Exhibit antiinflamatory roles
Polyphenols (phytochemical derivates) • Flavoniods: tea, soy, grapeseed • Non-flavonoids: grape, tea, polypodium leucotomos, nuts, peanuts	Antioxidants, anti-inflammatory and immunomodulatory action

Most broad spectrum formulas contain antioxidant ingredients.

Patients can be motivated to use daily sunscreen and antioxidants due to antiaging and cancer prevention benefits, so, explaining these advantages increases adherence to the treatment and improves the health care setting.

Pruritus

Pruritus is defined as an unpleasant sensation which results in scratching and may have an impact on a person's quality of life. It is a common symptom in diabetic patients caused by alteration of CB present in diabetes coupled to conditions associated to xerosis, like age, nephropathy, use of medicines (see Table 5.2). These conditions cause itching due to inflammation, dry skin, or xerosis.

Diabetic polyneuropathy is a very common cause of neuropathic pruritus. This type of pruritus flares when a nerve dysfunction occurs due to impairment or inflammation. Diabetic patients with neuropathy usually experience pain and/or itching in symmetrical distribution. Initially, it affects lower limbs and then extends to proximities. These symptoms have also been shown as chronic trunk pruritus and localized in scalp.

The management of this symptom is of the outmost importance, preventing the itch-scratch cycle. Scratching worsens the alteration already present in CB leading to chronic inflammation and infections.

Psychosocial Stress

Mental health in diabetic patients may be affected by psychological processes such as anger, denial, depression, stress, diabetic distress (stress generated by having the disease). These conditions alter the quality of life and impact patient's physical and mental health [50].

The skin responds to stress in two main ways: central and peripheral. The central way corresponds to hypothalamic pituitary adrenal (HPA) axis, the locus coeruleus-norepinephrine sympathetic adrenomedullary system. The peripheral equivalent refers

to intracutaneous HPA axis and release of mediators from peripheral sensory and autonomic nerves. Activation of these two ways affects the cutaneous immune system, the CB function, healing and susceptibility to infections [29].

Studies carried out on animals and humans show that psychological stress alters the epidermal lipids synthesis. Recovery of CB function from any disturbance of the skin is delayed during periods of stress compared to periods of low stress. Moreover, it has been proven that psychosocial stress decreases the expression and release of epidermal AMP increasing the risk of infection.

Diet

A healthy diet contributes to adequate metabolic control of glycaemia and several associated risk factors and may also benefit the activity and physiology of CB.

A diet rich in natural antioxidants, low in AGEs and with adequate intake of water will maximize the effects of dermatology treatments.

Other estrategies

Diabetic patients must avoid cold air, low environmental humidity, and excessive contact with water (e.g., long baths) that impairs xerosis, particularly in winter time.

Frequent use of soap or products for body drying such as powders or gels contribute to the onset of xerosis and associated pruritus, therefore, the use of soaps with moisturizers or soap substitutes (syndet) are highly recommended.

Baths should not be longer than 10 min and taken only with warm water. It is convenient to apply moisturizing cream immediately after the bath and several times during the day to ensure proper moisturizing.

Low winter temperatures, dry weather and heating worsen xerosis, so the use of humidifiers may be useful.

Adequate therapy for the correct function of CB must include, besides moisturizing creams, the use of sunscreens and topical antioxidants in areas exposed to sunlight.

Conclusions

Alteration of CB in diabetes is due to diabetes per se and multiple factors such as ageing, physical and mental associated diseases, use of some drugs, and environmental insults.

It is crucial to preserve the integrity of CB of all diabetic patients not only of those with visible xerosis.

Patients must be taught to care for their skin and practice healthy habits to avoid xerosis and diminish damage from external factors.

This will reduce water loss and minimize the exposure to irritating and allergenic factors.

Symptoms such as pruritus and xerosis may alter quality of life and generate complications in the form of infections.

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