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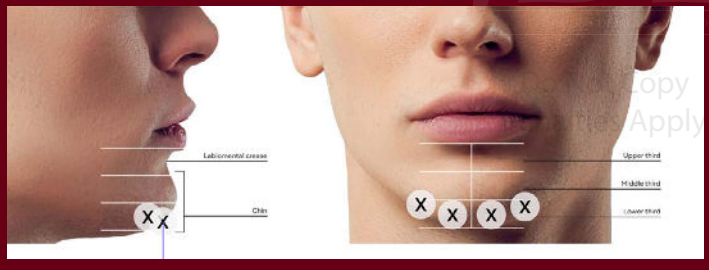

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Dermatoporosis and the March of Time: Advances in Understanding and Managing Chronic Progressive Cutaneous Fragility in Aging Skin

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Abstract

Dermatoporosis refers to a skin condition affecting the elderly, characterized by chronic progressive cutaneous insufficiency and skin fragility. Primary dermatoporosis is due to chronological skin aging, genetic factors, and environmental damage while secondary dermatoporosis is caused by chronic exposure to topical and systemic corticosteroids. Dermatoporosis may initially be seen as a cosmetic problem, but serious complications such as skin tears and deep dissecting hematomas can occur as skin fragility increases. The pathophysiologic mechanisms of dermatoporosis suggest several interventions with the potential to slow progression and reduce the risk of skin tearing. Therefore, recognizing early signs and promptly initiating treatment may help to manage the condition and reduce the risk of complications. Treatment and prevention may include sun protection, emollients, and long-term use of topical retinoids as they promote improved skin quality. Other available treatments include the application of matrikines and α-hydroxy acids, such as mandelic acid. Proper skin care can also preserve skin quality and integrity and enhance skin elasticity and smoothness by using products formulated with ingredients that target skin atrophy, dryness, and elasticity. A commercial product has applied a novel proprietary technology to create a moisturizing lotion containing Centella asiatica and mandelic acid to create a clinically effective product for dermatoporosis-prone skin (Cetaphil® Skin Care; Galderma Laboratories, LP). This product is formulated with a pH range of 4-5 to help reduce elevated pH of aged skin, improving physiological skin function, and promoting overall skin health. Maintaining the normally acidic skin pH supports normal microbial colonization and prevents the growth of pathogenic bacteria.

Introduction

Dermatoporosis is a term applied to a prevalent skin condition affecting the elderly[1] and is used to describe the many features of chronic cutaneous fragility syndrome. This name was chosen to convey a concept analogous to the age-related condition osteoporosis.[1] Primary dermatoporosis is due to endogenous or chronological skin aging, genetic factors, and exogenous factors, such as smoking and long-term exposure to solar radiation.[2] Secondary dermatoporosis is caused by some medications, such as corticosteroids and anticoagulants.[3] In primary dermatoporosis, direct damage to cells and extracellular matrix (ECM) leads to senescence and progressively thinning skin. In secondary dermatoporosis, drug interference with cell function and replication leads to an insufficient ECM environment, which leads to senescence and progressively thinning skin. Other factors that may contribute to dermatoporosis include menopause,[4] diabetes, renal failure,[5] and a sedentary lifestyle.[6] Untreated dermatoporosis can lead to severe skin damage.[3,7]

Dermatoporosis is not an uncommon condition. In 2 European studies, the prevalence of dermatoporosis was 30.7% and 32% to 37% among individuals >60 through 65 years old.[5,8] In the United States, the prevalence is likely to grow due to the aging "baby boomer" population.[9] An observational study assessed patients with a mean (SD) age of 72.6 (7.8) years (range, 60-95 years) for the prevalence and comorbidities associated with dermatoporosis (N=370).[10] The median age of patients with dermatoporosis was significantly older (77 vs 71 years, *P*<0.0001). There was a greater prevalence among men (24% vs 9%) with most being Stage 1 (8%) (Table 1).[10]

Table 1. Stages of Dermatoporosis

Stage I	Skin atrophy, senile purpura, and pseudo-cicatrices
Stage IIa	Localized and small superficial lacerations (<3 cm) due to skin fragility
Stage IIb	Larger lacerations (>3 cm)
Stage IIIa	Superficial hematomas
Stage IIIb	Deep dissecting hematomas without skin necrosis
Stage IV	Large areas of skin necrosis with potentially lethal complications

From Saurat et al, 2017.[73]

Pathogenesis

The dermis is mainly comprised of the extracellular matrix. It principally consists of hyaluronic acid, a glycosaminoglycan produced by fibroblasts, proteins, and glycoproteins. The ECM provides physical support, maintains skin hydration, and elasticity, acts as a protective barrier, and supports cell structure and vasculature.[11,12]

The amount of hyaluronic acid in the dermis decreases with age, causing the skin to atrophy and become susceptible to trauma.[12] Hyaluronic acid is also responsible for the proliferation of keratinocytes via interactions with the CD44 cell surface receptor.[7] Diminished CD44 expression is correlated with skin atrophy and may result from the decreased presence of hyaluronic acid and exposure to aggravating conditions, such as corticosteroids and ultraviolet light. As described below, CD44 may be a target for some dermatoporosis treatments.

A strong skin barrier requires a robust ECM maintained by fibroblasts and keratinocytes. Keratinocytes are an essential part of barrier protection against environmental insults. They maintain a basal population, undergo cornification, excrete intracellular components, and continuously turn over, ensuring constant regeneration of the skin barrier.[13] Fibroblasts are crucial for maintaining skin integrity and responding to skin damage and inflammation. Fibroblasts are also found in the dermis layer, producing materials for the ECM, such as collagen, elastin, and glycosaminoglycan, which also contributes to skin bulk, strength, and resilience.[14,15] They support ECM production, regulate the intracellular environment and help maintain stem cell populations.[16,17]

A newly described organelle called the hyaluronosome produces hyaluronic acid and contains CD44 and heparin-binding epidermal growth factor.[18] This organelle may be functionally deficient in patients with dermatoporosis.

Finally, up-regulation of matrix metalloproteinases (MMPs), particularly collagenase-1 (MMP-1), stromelysin-1 (MMP-3), and gelatinase A (MMP-2) occurs in aging skin, causing the breakdown of collagen and elastin during chronological skin aging.[19] Conversely, the expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) decreases with fibroblast senescence. It is via MMP activation that ultraviolet light causes photodamage to the skin.[20]

Diagnosis

Dermatoporosis is similar to other skin disorders that also result in aging skin frailty and damage caused by excessive exposure to ultraviolet A and B radiation.[21,22] The differential diagnosis includes actinic purpura, also known as solar purpura or senile purpura, characterized by dark purple macules and extensive ecchymosis,[21] and dermatoheliosis, or photoaging characterized by irregular pigmentation, lentigines, and hyperpigmentation.[22] It is most common among individuals with Fitzpatrick skin phototypes I through III. In contrast to skin disorders directly driven by ultraviolet damage, dermatoporosis is primarily due to senescence[23] and characterized by skin atrophy, purpura, pseudo scars, and skin lacerations.[3,7]

Complications

Deep dissecting hematomas are a major late-stage complication of dermatoporosis.[24] Dissecting hematomas are rapidly expanding collections of blood that split the hypodermis from the muscle fascia.[25] These may occur following minor skin trauma[25] and most commonly among older women with a mean age of 82 years in one report.[26] In one series, patients initially developed erythema and edema, progressing to skin necrosis. Hospital treatment consisted of deep incision and debridement, wound closure, and skin grafting or other standard wound care. The mean length of hospitalization was 3.5 weeks.[26]

Skin tears are another potential complication of dermatoporosis. Among subjects evaluated in one study (*N*=128), 6 (4.6%) had skin tears.[24] The frequency of prior skin tears was 19.5%.[27] Delayed wound healing is another complication in this patient population,[28] especially on the lower extremities below the knee.[7] This effect on wound healing is likely due to diminished keratinocytes and fibroblasts and overexpression of matrix metalloproteinases.

In one observational study, complications (32%) included skin lacerations (Stage 2a, 30%) and 1 patient with superficial hematomas (Stage 3a). Multivariate analysis revealed a significant association with high-potency topical corticosteroids (P=0.002), oral corticosteroids (P=0.022), anticoagulant therapy, chronic renal failure (P=0.013), and age (P=0.016).[5]

Treatments for Dermatoporosis

Understanding the early signs of dermatoporosis and promptly initiating treatment may halt disease progression and reduce the risk of complications.[28]

Retinoids

A common treatment for thinning skin conditions, including dermatoporosis, is the application of topical retinoids as they promote keratinocyte proliferation and collagen synthesis to improve the epidermal barrier, inhibit collagen degradation, and reduce transdermal water loss and metalloproteinase activity.[2,29] Retinoids can also increase hyaluronic acid synthesis and CD44 expression.[30,31] In this way, retinoids reduce the clinical signs of photoaged skin.[32-34] Retinoids include retinol (vitamin A) and related compounds such as retinoic acid, retinaldehyde, retinyl palmitate, tretinoin, and others.[29] Tretinoin improves facial wrinkling, hyperpigmentation, and skin texture[29] and is considered the gold standard for skin rejuvenation.[35] The ability of once-daily application of tretinoin 0.025% to 0.01% cream to improve the appearance of photodamaged skin has been demonstrated in large double-blind studies.[36,3738]

Matrikines

Peptides, known as matrikines, have been identified and are involved in numerous skin conditions, including skin aging.[39] Matrikines are formed by the proteolysis of ECM macromolecules, which have the ability to regulate cell activities, including cell proliferation, migration, protease production, and apoptosis.[40,41] Peptides with beneficial matrikine-like effects on aging skin include glycine-histidine-lysine tripeptide, glycine-glutamate-lysine-glycine tetrapeptide (GEKG), lysine-threonine-threonine-lysine-serine pentapeptide, and carnosine[35,40,42] Several in vitro and in vivo studies have demonstrated the topical application of the matrikine GEKG stimulates ECM protein expression of collagen, hyaluronan, and fibronectin, which was associated with significant improvement in the physiological and clinical appearance of aging skin.[43]

One clinical trial assessed the efficacy of a peptide-containing formulation on facial wrinkles and skin laxity.[44] Adult photoaged women treated for 6 months achieved significant improvement in undereye wrinkles starting at 1 month of treatment. After 6 months, 82% of treated participants showed improvement. Similarly, lateral canthal lines showed improvement beginning after 2 months of treatment, and by 6 months, 71% of participants showed improvement. A significant improvement in skin firmness was achieved after 1 month, and at 6 months, 97% of participants showed improvement.

α-Hydroxy Acids

These compounds are widely found in cosmetic products used to address aging skin.[45] It has been suggested that α-hydroxy acids owe their beneficial effects to their ability to chelate calcium ions in the epidermis, causing desquamation and promoting new skin growth.[46] When applied to the forearm, glycolic, lactic, or citric acid-containing lotions produced ~25% increase in skin thickness associated with increased mucopolysaccharides, improved elastic fiber quality, and increased collagen density.[47] Similarly, the application of citric acid lotion for several months also increased epidermal thickness and dermal glycosaminoglycans in treated skin.[48] Topical mandelic acid can also exfoliate the skin to reduce hyperpigmentation and promote collagen production.[49]

Other Therapies

Numerous other therapies have been reported to have beneficial effects on aging skin and dermatoporosis. One 6-week study demonstrated the daily application of human epidermal growth factor to skin affected with senile purpura lesions decreased the number of purpuric lesions and increased mean skin thickness, thereby reducing psychological distress and preventing the advancement of dermatoporosis.[50] The effect of the steroid hormone dehydroepiandrosterone (DHEA) on aging skin has also been assessed.[51] When topically applied to the face and hands for 4 months, DHEA improved skin brightness and improved the appearance of atrophic skin.

Vitamins can also play an important role in the cause and treatment of dermatoporosis. It has been speculated that symptoms of dermatoporosis may arise from vitamin C deficiency[52], and a 12-week randomized, double-blind study assessed the efficacy of twice-daily application of topical 5% vitamin C for treating Bateman purpura.[53] The result was clinical improvement of purpura as well as beneficial effects on skin elasticity and thickness. Similarly, vitamin D and vitamin A have preventative and therapeutic effects for aging skin.[54-56]

Prevention

The obvious first steps in preventing the occurrence of dermatoporosis are avoiding known causes of the condition, such as ultraviolet radiation exposure and smoking, and limiting the use of some medications, such as corticosteroids, whenever possible.[7] Practicing proper skin care is also important to protect the skin and maintain normal skin hydration, as well as to support a healthy skin barrier. Proper skin care can preserve skin quality and integrity and enhance elasticity and smoothness.[57,58] It is also important to become aware of the early signs of dermatoporosis so that early treatment can be initiated to halt disease progression (staging) and maintain a patient's quality of life.[59,60] Current evidence indicates proper skin hygiene and the use of emollients have preventative benefit for aging patients in the hospital and residential care settings.[61]

Achieving proper skin care requires the use of products formulated with ingredients that target skin atrophy, dryness, and elasticity. Skin atrophy can be reduced with ingredients that increase collagen production,[62-64] promote cell turnover,[63] and stimulate cellular proliferation.[64] Skin dryness can be minimized with ingredients that improve skin moisture by increasing skin surface hydration and decreasing transepidermal water loss,[62,63] which improves skin barrier function,[62] and exfoliation, which allows better penetration of beneficial ingredients into skin.[49,63] Skin elasticity can be improved with ingredients that increase elastic fibers[65] and collagen production.[62-64]

The accumulation of senescent cells in the epidermis increases with age and has a negative effect on tissue. Senescent cells are associated with fibroblast dysfunction, inflammatory cytokine production, breakdown of the ECM, and weakening of the dermo-epidermal junction.[66] Senescent cells in the epidermis are preferentially removed through JAG1-NOTCH1 signaling in the epidermis[67]; however, this mechanism declines with advancing age. It has been shown that the addition of combined microdoses of *Centella asiatica* (0.005%) and mandelic acid (0.05%) to cultured human keratinocytes and fibroblasts resulted in a significant decrease in senescent cells with associated cell toxicity.[66]

The importance of skin pH for maintaining normal skin barrier function has long been recognized.[68] The skin normally has an acid pH ranging from 4 to 6. Advancing age is associated with increasing skin pH and diminished barrier function.[69] Consequently, it is also important to regularly apply a product

with a pH range of 4-5 to help reduce elevated pH levels in aged skin, improving physiological skin function and promoting overall skin health.[70] Aged skin often has an increased surface pH of ~6, needing appropriate skin care to counterbalance this increase and improve barrier function.[70,71] Maintaining the normally acidic skin pH supports normal microbial colonization, providing optimal growth conditions for commensal microorganisms.[72] Pathogenic bacteria, such as *Staphylococcus aureus*, thrive in neutral pH conditions (eg, pH 7.5), but growth is reduced under acidic conditions.[72] Thus, increased skin pH disrupts the microbiome balance, promoting pathogenic colonization and increasing susceptibility to infections.[72] The distribution of skin lipids is also dependent on pH-regulated mechanisms, as increased skin pH can lead to defective lipid processing and delayed maturation.[72] The enzymes responsible for generating ceramides exhibit reduced activity at higher pH levels, impairing the protective skin barrier.[69,72]

Conclusion

Dermatoporosis is a common condition among the elderly with potentially far-ranging consequences. While there are several treatments available to treat dermatoporosis, greater emphasis should be placed on routine preventative measures. This includes the regular use of topical products formulated to promote collagen synthesis, stimulate dormant fibroblasts, decrease hyaluronic acid degradation, enhance keratinocyte proliferation, and maintain normal skin pH to support normal microbial colonization.

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For additional education on this topic, please see "Novel Strategy for Strengthening Dermatoporotic Skin by Managing Cellular Senescence" at https://jddonline.com/articles/novel-strategy-strengthening-dermatoporotic-skin-managing-cellular-senescence-S1545961624P8388X.

Disclosures

GA serves has served as a research investigator for Galderma.

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