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Understanding of Mechanisms of Skin Aging

Dermatoporosis, a prevalent skin condition affecting the elderly: current situation and potential treatments

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Abstract The term "dermatoporosis" was introduced a decade ago to highlight the need to pay attention to the problems posed by premature skin aging beyond esthetic considerations. People with this condition have a thinner skin that becomes fragile, tends to tear, and may lead to deep dissecting hematomas—as a final stage—corresponding to a medical emergency. Various studies have demonstrated a high prevalence of dermatoporosis in the elderly, with women being more exposed than men. We have developed a scoring system for dermatoporosis, providing different strategies to treat and prevent this skin condition, as well as a followup of patients treated at the University Hospital of Geneva.

Introduction

Until recently, skin aging was considered only as a cosmetic issue; however, people live longer and are exposed to an increasing number of environmental stressors. As a consequence, a new dimension of skin aging that extends beyond cosmetics and appearance affects a growing proportion of elderly people. We proposed in 2007 the term "dermatoporosis" to cover different characteristics of a chronic cutaneous insufficiency syndrome, to understand its molecular mechanisms, and to develop preventive or therapeutic strategies for what turned out to be a prevalent skin condition.[1–3]

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Prevalence and clinical features of dermatoporosis

The first clinical manifestations of dermatoporosis start at around 40 to 60 years of age with wrinkles, superficial excoriations, and appearance changes; however, fully developed disease is seen between 70 and 90 years. A recent study performed in a representative sample of the French population showed an overall prevalence of dermatoporosis of 37.5% in subjects older than 65 years with a woman-to-man ratio of 3:2.[4]

Early markers of dermatoporosis are skin atrophy, senile purpura, pseudoscars, and superficial excoriations.[1,5,6] These markers may be first observed at around 70 years of age, but they may also appear earlier.

The predominant sites of dermatoporosis are sun-exposed areas, such as the posterior aspects of the forearms, the dorsal surfaces of the hands, the presternal area, the scalp, and the

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pretibial zones, indicating involvement of solar radiation in its development.[7]

We distinguish between primary dermatoporosis, which is the most common type of the disease and results from both chronologic aging and long-term unprotected sun exposure, and secondary dermatoporosis, which is due to the long-term use of topical or systemic corticosteroids.

Clinical staging of dermatoporosis

Four stages of dermatoporosis have been proposed[4,7]:

- Stage I: The first markers of dermatoporosis are skin atrophy, senile purpura, pseudoscars, and superficial excoriations. This is the most common stage of dermatoporosis.
- Stage IIa: Localized and small superficial lacerations (up to 3 cm) due to skin fragility.
- Stage IIb: Larger lacerations (larger than 3 cm).
- Stage IIIa: Superficial hematomas.
- Stage IIIb: Deep dissecting hematomas without skin necrosis.
- Stage IV: Large areas of skin necrosis with potential lethal complications usually leading to amputation of an arm or leg.

Scoring system of dermatoporosis

To help clinicians assess the stage of dermatoporosis, we defined the criteria listed in Table 1 based on clinical signs and ultrasonographic measures of the skin thickness. Table 1 indicates the score for each criterium.

Table 1 Dermatoporosis scoring system

Clinical features	Absent	Present
Skin atrophy	0	1
Senile purpura	0	1
Pseudoscars	0	1
Superficial excoriations	0	1
Small lacerations	0	2
Large lacerations	0	3
Superficial hematomas	0	4
Deep dissecting hematomas	0	5
Skin necrosis	0	6
Skin thickness (ultrasonography)	**Score**	
≤0.5 mm	3	
0.51-0.75 mm	2	
0.76-0.99 mm	1	
≥1 mm	0	
Score of dermatoporosis *	**Significance**	
0	No dermatoporosis	
1-7	Early stage	
8-9	Early intermediate stage	
10-12	Late intermediate stage	
13-16	Early advanced stage	
>16	Advanced stage	

* The global score of dermatoporosis is obtained by calculating the sum of all individual scores.

Complications of dermatoporosis

Complications of dermatoporosis represent an emerging problem with an aging population. Skin lacerations with irregular superficial tear-like wounds, resulting from extreme skin fragility, are quite common in the elderly, and healing of these lesions is delayed in patients with dermatoporosis. The most advanced complication of dermatoporosis is deep dissecting hematomas. These are believed to result from trauma-induced, massive bleeding between the subcutaneous fat and muscle fascia and from fragile and aged vessels localized very close to the surface of the skin, as a result of extreme skin atrophy.[8,9]

Mechanisms of skin fragility in dermatoporosis

Decrease in skin hyaluronate and its receptor CD44

Selective suppression of keratinocyte CD44, a transmembrane receptor of hyaluronate (HA), results in skin atrophy in mice.[10] This observation paved the way for the research in dermatoporosis. HA is the major component of the extracellular matrix and is found in high amounts in the skin. HA helps to maintain the normal hydration and viscoelasticity of the skin.[11] CD44 and HA levels are lower in the dermatoporotic skin than in the skin of young individuals.[12] Ultraviolet A and B irradiation decrease the content of HA and the expression of its receptor, CD44, in mice.[13]

Hyalurosome dysfunction

The term hyalurosome designs a multimeric macromolecule complex composed of molecules involved in HA metabolism and cell signaling in keratinocytes, such as CD44; heparin-binding epidermal growth factor; and its receptor erbB1, which is functionally defective in dermatoporosis.[14] Hyalurosome mainly functions as an HA factory. Hyaluronate synthase 3 is colocalized with the keratinocyte-specific CD44 variant—CD44v3—and HA in human epidermis, suggesting that hyalurosome takes place on the keratinocyte membrane.[15] In keratinocyte cultures, CD44v3, HA, and actin are localized with filopodia, which are thin actin-rich plasma-membrane protrusions that function as antennae for cells to probe their environment.[16,17] The expression of hyalurosome molecules has been shown to be diminished in patients with dermatoporosis.[18]

Epidermal progenitor cells

The Lrig1$^+$ progenitor cells, which are inhibitors of epidermal growth factor receptor, are located in the follicular and interfollicular zones of human skin and are preserved in the epidermis of dermatoporotic skin.[19,20] In CD44 knockout mice, Lrig1$^+$ progenitor cells feed the epidermis and show a skin phenotype very similar to dermatoporosis.[20]

Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway that is involved in epidermal renewal is positively regulated by CD44 and is decreased in the epidermis of dermatoporotic skin.[20]

Calcium signaling

The expression of the calcium channel Orai-1, located in the basal layer of the epidermis and involved in keratinocyte proliferation, is decreased in the epidermis of patients with dermatoporosis.[21]

p16INK4a pathway

The cells bearing the cellular senescence-related protein p16INK4a are increased in the epidermis of dermatoporotic skin.[20]

Treatment and prevention

Hyaluronic acid

Based on observations indicating the potential role of hyalurosome deficiency in dermatoporosis, activating the hyalurosome platform to reverse skin atrophy is a target for intervention. For this purpose, HA fragments of intermediate size (80-150 kDa; HAF_i) were identified and used as CD44 ligands to activate the CD44-mediated molecular pathways that lead to skin hyperplasia. Topical application of these HAF_i on mouse skin resulted in epidermal hyperplasia and an increase in epidermal and dermal HA content, by stimulating the molecules participating to the hyalurosome.[12] Topical HAF_i prevented the skin atrophy induced by topical corticosteroids in mice without interfering with their antiinflammatory effect.[18] In a clinical trial, topical treatment with HAF_i 1% of atrophic forearm skin of patients with dermatoporosis for 1 month resulted in a significant clinical improvement, with a decrease in Bateman purpuric lesions and atrophic aspects of the skin.[12] Topical HAF_i induced the expression of hyalurosome components in dermatoporotic skin.[18]

Hyaluronic in combination with retinaldehyde

The combination of HAF_i with retinaldehyde (RAL), which is a topical retinoid that upregulates the CD44 and HA synthesizing enzymes in mouse skin,[22] increased the levels of CD44 and HA in the skin of dermatoporosis patients and corrected the skin atrophy by showing a synergistic effect at both molecular and clinical levels.[18,23] RAL and HAF_i also increase the HA and collagen content and significantly decrease the number of Bateman senile purpura in dermatoporotic skin.[18]

Epidermal growth factor

In parallel with these findings, it was shown that topical heparin-binding epidermal growth factor diminished the appearance of senile purpura by thickening the skin, suggesting that it might be helpful in preventing the development of late-stage dermatoporosis.[24]

Vitamin C supplementation

Localized scurvy has been treated with a topical formulation containing 5% ascorbic acid. After 12 weeks, the treated forearm showed fewer signs of purpura, suggesting that the purpura of dermatoporosis is due, at least in part, to vitamin C deficiency.[25] One study[26] showed that an 85-year-old woman with extensive blistering purpura and spontaneous hematomas of the legs in relation to dermatoporosis was successfully treated with oral vitamin C. These case reports indicate that it would be interesting to assess the vitamin C status of patients with dermatoporosis. Whether the reported successful treatments with vitamin C are only due to the correction of a vitamin C deficiency or would also be due to a pharmacologic effect on new therapeutic targets is an interesting question. A combination of topical and oral vitamin C could be added to current treatments for the prevention and reversion of dermatoporosis.

New therapeutic targets

Identification of new molecular targets may lead to the development of efficient therapeutic or preventive strategies in dermatoporosis. As discussed previously, Lrig1, β-catenin, Orai-1, and p16INK4a are interesting potential targets; however, new studies are needed to show the true potential of these targets for the treatment of dermatoporosis.

Followup of patients treated for dermatoporosis

The followup of the patients treated for dermatoporosis was made by clinical examination and cutaneous thickness measurements. The examination and measurements helped to establish the dermatoporosis score (Table 1). During the clinical examination, features of dermatoporosis, such as skin atrophy, purpuric lesions, pseudoscars, and excoriations,

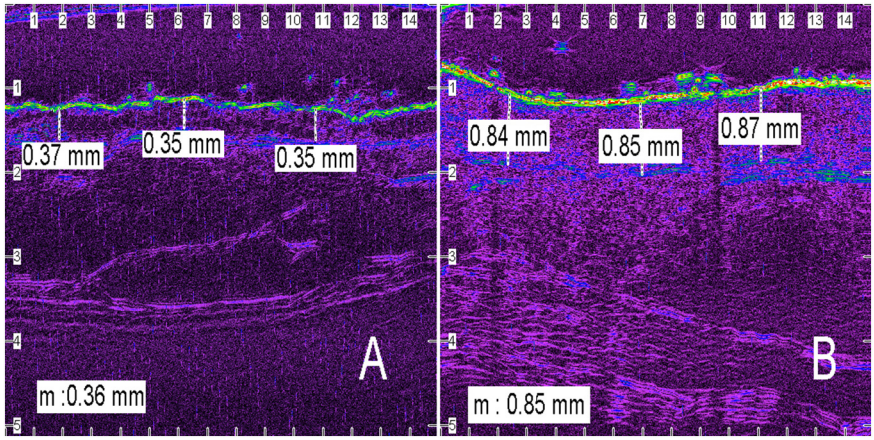

Fig. 1 Effect of a treatment for dermatoporosis. **(A)** Patient with advanced dermatoporosis (skin thickness: 0.36 mm). **(B)** Same patient 1 month after a topical treatment with retinaldehyde (RAL) and hyaluronate fragments of intermediated size (HAF_i) (skin thickness: 0.85 mm).

were assessed. Skin thickness measurements were performed using a skin ultrasound system (Episcan, Longport Inc, Glen Mills, Pennsylvania), usually either only on the forearms or on five different locations: the dorsal side of both forearms, the dorsal side of both legs, and the chest.

The presence or absence of skin lesions and the pretreatment values of skin thickness in the first consultation were noted on the dermatoporosis scoring sheet. The second consultation was usually scheduled 1 month after the beginning of topical treatment, and the dermatoporosis score was compared with the values of the first consultation. Depending on the response of the patient, the next consultations were organized for 3, 6, or 12 months later.

The typical skin thickness of the forearm is $\geq$1 mm. Most of the dermatoporosis patients had values between 0.5 to 1 mm; however, we also had patients with advanced dermatoporosis whose skin thickness was under 0.5 mm.

Topical treatment with RAL and HAF_i twice a day resulted in a rapid improvement of the skin thickness, which was already detectable after 1 month (Figure 1). In our experience, a plateau in skin thickness increase, with an approximate value of 1 mm, is attained after a period of 3 or 6 months of treatment,[18] after which we recommend maintenance therapy with topical RAL and HAF_i once a day for 1 year. We have also observed that the number of purpuric lesions on the affected skin sites of patients with dermatoporosis is dramatically and rapidly decreased after topical treatment,[18] suggesting that purpuric lesions can be used as a clinical indicator of response to treatment.

Conclusions

Dermatoporosis has a high prevalence in the elderly and poses a real problem to this population. Dermatologists and other health professionals, including geriatricians and family physicians, should transmit this information to their patients to help delay the onset of excessive skin aging and to be aware of the best strategies for treating patients affected by this condition.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

1. Kaya G, Saurat JH. Dermatoporosis: a chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology* 2007;215:284-294.
2. Kaya G, Saurat JH. Dermatoporosis: a new concept in skin aging. *Eur Geriatr Med* 2010;1:216-219.
3. Kaya G, Kaya A, Sorg O, et al. Dermatoporosis: a further step to recognition. *J Eur Acad Dermatol Venereol* 2018;32:189-191.
4. Saurat JH, Mengeaud V, Georgescu V, et al. A simple self-diagnosis tool to assess the prevalence of dermatoporosis in France. *J Eur Acad Dermatol Venereol* 2017;31:1380-1386.
5. Karadag AS, Parish LC, Lambert WC. Senile purpura as a stage of dermatoporosis. *Skinmed* 2017;15:91-92.
6. Menzinger S, Saurat JH, Kaya G. Morphological analysis of dermatoporosis by in vivo reflectance-mode confocal microscopy and ultrasonography. *Dermatol Helv* 2013;25:24-26.
7. Kaya G. New therapeutic targets in dermatoporosis. *J Nutr Health Aging* 2012;16:285-288.
8. Kaya G, Jacobs F, Prins C, et al. Deep dissecting hematoma: an emerging severe complication of dermatoporosis. *Arch Dermatol* 2008;144:1303-1308.
9. Toutous-Trellu L, Weiss L, Tarteaut MH, et al. Deep dissecting hematoma: a plaidoyer for an early and specialized management. *Eur Geriatr Med* 2010;1:228-230.
10. Kaya G, Rodriguez I, Jorcano JL, et al. Selective suppression of CD44 in keratinocytes of mice bearing an antisense CD44 transgene driven by a tissue-specific promoter disrupts hyaluronate metabolism in the skin and impairs keratinocyte proliferation. *Genes Dev* 1997;11:996-1007.
11. Laurent TC, Fraser JR. Hyaluronan. *FASEB J* 1992;6:2397-2404.

12. Kaya G, Tran C, Sorg O, et al. Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. *PLoS Med* 2006;3:e493.
13. Calikoglu E, Sorg O, Tran C, et al. UVA and UVB decrease the expression of CD44 and hyaluronate in mouse epidermis which is counteracted by topical retinoids. *Photochem Photobiol* 2006;82:1342-1347.
14. Barnes L, Tran C, Sorg O, et al. Synergistic effect of hyaluronate fragments in retinaldehyde-induced skin hyperplasia which is a CD44-dependent phenomenon. *PLoS One* 2010;5, e14372.
15. Barnes L, Carraux P, Saurat JH, et al. Increased expression of CD44 and hyaluronate synthase 3 is associated with accumulation of hyaluronate in spongiotic epidermis. *J Invest Dermatol* 2012;132:736-738.
16. Barnes L, Ino F, Jaunin F, et al. Inhibition of putative hyalurosome platform in keratinocytes as a mechanism for corticosteroid-induced epidermal atrophy. *J Invest Dermatol* 2013;133:1017-1026.
17. Mattila PK, Lappalainen P. Filopodia: molecular architecture and cellular functions. *Nat Rev Mol Cell Biol* 2008;9:446-454.
18. Nikolic DS, Ziori C, Kostaki M, et al. Hyalurosome gene regulation and dose-dependent restoration of skin atrophy by retinaldehyde and defined-size hyaluronate fragments in dermatoporosis. *Dermatology* 2014;229:110-115.
19. Barnes L, Puenchera J, Saurat JH, et al. Lrig1 and CD44 v3 expression in the human folliculosebaceous unit. *Dermatology* 2015;231:116-118.
20. Barnes L, Saurat JH, Kaya G. Senescent atrophic epidermis retains Lrig1+ stem cells and loses wnt signaling, a phenotype shared with CD44 KO mice. *PLoS One* 2017;12, e0169452.
21. Darbellay B, Barnes L, Boehncke WH, et al. Reversal of murine epidermal atrophy by topical modulation of calcium signaling. *J Invest Dermatol* 2014;134:1599-1608.
22. Kaya G, Grand D, Hotz R, et al. Upregulation of CD44 and hyaluronate synthase by topical retinoids in mouse skin. *J Invest Dermatol* 2005;124:284-287.
23. Cordero A, Leon-Dorantes G, Pons-Guiraud A, et al. Retinaldehyde/hyaluronic acid fragments: a synergistic association for the management of skin aging. *J Cosmet Dermatol* 2011;10:110-117.
24. McKnight B, Seidel R, Moy R. Topical human epidermal growth factor in the treatment of senile purpura and the prevention of dermatoporosis. *J Drugs Dermatol* 2015;14:1147-1150.
25. Humbert P, Fanian F, Lihoreau T, et al. Bateman purpura (dermatoporosis): a localized scurvy treated by topical vitamin C-double-blind randomized placebo-controlled clinical trial. *J Eur Acad Dermatol Venereol* 2018;32:323-328.
26. Kluger N. Dermatoporosis and vitamin C deficiency. *J Eur Acad Dermatol Venereol* 2018;32:e383.