Oral Retinoid-induced Cheilitis

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INTRODUCTION

Retinoids are a class of molecules, structurally related to Vitamin A and have an important role in the modulation of cell proliferation and differentiation. The utility of retinoids in dermatology can be highlighted by the fact that retinoids are being regularly used in various disorders of keratinization (psoriasis, lichen planus, Darier’s disease, and acne vulgaris), cutaneous T-cell lymphomas, and chemoprevention. Acitretin and isotretinoin are available in oral forms and are being extensively used by dermatologists across the globe. Mucocutaneous toxicity forms an important group of side effects of oral retinoid therapy and limits the further dose escalation.[1] Cheilitis (lip chapping) is the most common and bothersome mucocutaneous adverse effect of oral retinoid therapy. Effective management of retinoid-induced cheilitis requires understanding of basic etio-pathogenic pathway for rational and realistic treatment.

MICROANATOMY OF LIPS

The lips are a central defining feature of the lower face and distinct from the surrounding skin. The appearance of the lips has a major effect on the esthetic perception of the face.

The purpose of this review is to point out some of the similarities and differences between epithelia of skin and oral mucosa, with special emphasis on the effect of different class of retinoids on barrier function and sebaceous secretion. The lip is a specialized region that represents the transition from the skin to the oral mucosa. The lips comprise three anatomic subdivisions; two of them are external and one is internal. The external or “dry” subdivisions include the skin of the lips, with dermal appendages, and the highly vascular vermilion (“red”) borders of the lips which, in contrast, lack dermal appendages such as sweat gland and hair, but does contain sebaceous glands (Fordyce spots). Fordyce spots are sebaceous glands containing neutral lipids similar to those found in skin sebaceous glands, but are not associated with hair follicles, most often located under the epithelium of the cheek and free lip border. The internal “wet” portion of the lip, the labial mucosa, demonstrates prominent vascular markings. The entire mucosal surface is lined by stratified (layered) squamous (scale-like) epithelium, highly organized, an avascular, and semipermeable ectodermal tissue that varies in thickness and surface keratinization according to its location in the mouth and the functional demands of that location. Lamina propria is the oral counterpart of the corium; the deeper subcutaneous tissue is the submucosa, rich in minor salivary glands. Because they are constantly being stimulated in the course of function, oral epithelial cells have a relatively rapid turnover time (14–21 days).[2] Lip epithelium thickness would increase from the external part to the most internal mucosal part. Normal skin epidermis would gradually change from ortho-keratinized epithelium of the vermilion border to para-keratinized thick intermediate tissue (premucosal area) and then to non-or para-keratinized mucosa.[3] As one progresses from the external vermilion zone of the lip into the oral cavity, there is a transition from keratinized to nonkeratinized epithelium. In all regions, the outer portions of the epithelium provide a protective permeability barrier, which varies regionally. The non-keratinized epithelial regions do not produce a stratum corneum. Lamellar granules (Odland bodies, membrane-coating granules) are not produced in non-keratinizing epithelia. Lipids in the outer portion of the oral epithelium determine the permeability barrier function. Ceramides, fatty acids, and
cholesterol are the primary lipids which attribute to the permeability barrier of the epidermal and oral stratum corneum. Transepidermal water loss is a parameter for the barrier function of the stratum corneum.\(^4\) Barrier function is less effective in nonkeratinizing epithelia than in keratinizing epithelia. The superficial layers of nonkeratinizing epithelium of labial mucosa contain abundant phospholipids, but it does not contribute to barrier function. The incomplete formation of the corneal layer of the surface of the lips may be responsible for the decreased barrier function and water-holding capacity.

**PATHOPHYSIOLOGY OF RETINOID-INDUCED CHEILITIS**

Frequently observed mucocutaneous toxicity with systemic retinoids reflects a decreased sebum production, reduced stratum corneum thickness, and altered skin barrier function. Dry lips or cheilitis is the earliest and the most frequent sign that appears after starting therapy and is often used to monitor compliance.\(^5\) As a result of poor barrier function and low water-retaining capacity, the lips are highly susceptible to environmental effects and certain medications. The mucocutaneous side effect profile of systemic retinoids depends on the nature of retinoids used and is dose dependent. Isotretinoin (13-cis retinoid acid) has a profound inhibitory effect on sebaceous gland secretion as compared to etretinate.\(^6\) Isotretinoin does not bind to retinoic acid receptor (RAR) and its anti-seborrhic action is RAR-independent. The metabolic fate of isotretinoin in the pilosebaceous apparatus is not known, but the fact that the drug was not detected in surface sebum collection during oral therapy indicates that extensive metabolism or degradation takes place in the sebocytes or in the follicular epithelium. The sebosuppressive effect is slowly reversed on discontinuation of therapy. The decrease in sebaceous gland secretion and decrease in the size of sebaceous glands attribute to alteration in skin surface lipids and thus, barrier function. Cheilitis is the most common encountered mucocutaneous side effect of systemic retinoids (isotretinoin and acitretin). Acitretin does not have sebostatic effect, except at higher doses. Retinoids have the general effect of altering differentiation and promote shedding. There is alteration in the epidermis, particularly stratum corneum. Decrease in the thickness of stratum corneum attributes to poor barrier function and photosensitivity.

The combination of these factors leads to cheilitis, xerosis, and dryness of the mucous membranes, dryness of palmoplantar skin and skin fragility in dose-dependent manner, and type of retinoid used. Incomplete formation of corneocytes of the surface of the lips in contrast to surrounding skin may be responsible for poor barrier function and retinoid-induced cheilitis.

**CLINICAL FEATURES OF CHEILITIS**

Patients receiving retinoids, commonly isotretinoin, develop lip chapping within days to few weeks of starting treatment. In routine clinical practice, cheilitis starts within the first 7 days of treatment and marks the onset of sebosuppressive action. Clinically, one can appreciate dryness, exfoliation, and fissuring at places [Figure 1]. Severe cheilitis may interfere with food intake and normal communication and speech. Retinoid-induced cheilitis may worsen in winter seasons, especially in colder parts of India, especially Northern states (Delhi, Haryana, Punjab, and Uttar Pradesh). Ornelas et al. have developed an isotretinoin cheilitis Grading Scale incorporating the following four characteristics: Erythema, scale/crust, fissures, and inflammation of the commissures.\(^7\) Fissures may show punctate hemorrhagic spots. On cessation of isotretinoin therapy, lips usually return to their normal physiology within a few days.

**PREVENTION OF RETINOID-INDUCED CHEILITIS**

Currently, there is no effective prophylactic treatment for retinoid-induced cheilitis. A study by Kus et al. did not show any benefit of 800 IU/day of oral Vitamin E supplementation on retinoid-induced mucocutaneous side effects (facial erythema, facial dryness, and cheilitis).\(^8\) However, in contrast to the above study, topical application of Vitamin E acetate (VEA® lipogel) showed good therapeutic benefit in retinoid-induced cheilitis in a multi-center study.\(^9\)

**INVESTIGATIONS IN A CASE OF RETINOID-INDUCED CHEILITIS**

The diagnosis of retinoid-induced cheilitis is essentially based on history of retinoid intake and clinical grounds. No further investigations are needed.
### Table 1: Various lip moisturizers

| Brand name                               | Contents                                                                                                                                 |
|------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Sunkroma Lip Balm™                        | Octylmethoxy cinnamate, octocrylene, liquorice extract, dimethicone, cetyl alcohol, cetyl palmitate, canauba wax, ceresin wax, microcrystalline wax, bees wax, lanolin, light liquid paraffin, isopropyl myristate, methyl paraben, propyl paraben, dub ININ, peppermint flavor, menthol, super white petroleum jelly, butylated hydroxyl toluene |
| Chaptex™                                 | Octylmethoxy cinnamate, octocrylene, lanolin alcohol, avobenzone, almond oil, avocado oil, tocopheryl acetate, D-panthenol, white soft paraffin, cyclomethicone, phenyl trimethicone, white bees wax, butylated hydroxyl toluene, C30-C45 olefin |
| Lip talk lip balm™                       | Seilift DPHP, octinoxate, shea butter, vinyl pyrrolidone/eicosene copolymer, heavy liquid paraffin, hydrogenated polyisobutene, cyclomethylsiloxane and dimethiconol blend, microcrystalline wax, cetostearyl alcohol, cetomacrogol 1000, methyl glycolate-20 (Gliceme E20) EG20, dipolyhydroxyesterate, diethylene glycol monooctyl ether, flavor |
| Sebamed Lip Defense SPF30™               | Caprylyl/capric/succinic triglyceride, cera alba, isoamyl-methoxy cinnamate, R. communis seed oil, caprylc/capric triglyceride, ethylvhyl salicylate, tocopherol acetate, C12-C15 alkyl benzoate, oryza sativa bran wax, S. chinensis seed oil, glyceryl ricinoleate, butyl methoxydibenzoylmethane, bisabolol, parfum |
| Vaseline Lip care™                       | Mineral oil wax, microcrystalline wax, octylmethoxy cinnamate, cyclomethicone, tridecyl salicylate, butylmethoxy dibenzoyletane, butylated hydroxytoluene, cyclomethicone and dimethiconol, perfume |
| NMFe lip care™                           | Aloe vera, Vitamin E                                                                                                                                                                     |
| Neutrogena Lip balm™                     | PABA free Sunblock SPF 15, ethylhexyl methoxy cinnamate, benzophenone-3                                                                                                               |
| LIPZ Lip moisturizer™                    | Squalene, mineral oil, kokum butter, shea butter, sun filters, silicon oil                                                                                                               |
| Lipolent UV™                             | Octyl methoxy cinnamate 7.50%, mineral oil 5.00%, avobenzone 2.00%, Vitamin E 0.10%, along with silicon oil, shea butter, squalene, kokum butter, roomled and tea tree oil in white petroleum jelly base |
| Kelyane HD Lip balm™                     | Aqua, glycerin, petrolatum, glyceryl stearate, PEG-12, stearic acid, butyrospernum parkii (shea butter) fruit, cyclomethicone, mineral oil (paraffinum liquidiun), propylene glycol, 10-hydroxydecanoic acid, chlorophenisin, disodium EDTA, O-cymen-5-0I phenoxyethanol, triethanolamine |
| Blistex Lip Balm™                        | Camphor, menthol, ocitoxoate, oxybenzone, petrolatum                                                                                                                                 |
| Nivea Hydrocare Lip balm™                | Octyldecanol, microcrystalline Wax/Cire microcrystalline, Caprylic/capric triglyceride, R. communis (Castor) seed oil, cetyl palmitate, ethylhexyl methoxy cinnamate, myristyl myristate, polyglyceryl-3 diisostearate, Water/Eau, glycerin, butyl methoxydibenzoylmethane, cetaryl alcohol, octocynelc, Copernica cerifera (carnauba) Wax/Cire de carnauba, butyrospernum parkii (shea butter), aloe barbadensis leaf juice, glyceryl glucoside, C20-C40 Alkyl Stearate, Beeswax/Cire d’abeille, BHT, benzyl alcohol, parfum/fragrance |
| Nivea Essential care™                    | Cera microcrystalline, oxyldodecanol, hydrogenated polydecene, cetyl palmitate, R. communis seed oil, Myristyl Myristate, VP/eicosene copolymer, cetaryl alcohol, polyglyceryl-3 diisostearate, butyrospernum parkii butter, Caprylic/capric triglyceride, pentaylthryl tetraisostearate, VP/hexadecene copolymer, C20-C40 alkyl stearate, Copernica cerifera cera, panthenol, glycercyld glucoside, glycerin, Aqua, cera alba, limonene, linalool, benzyl alcohol, benzyl benzoate, citral, parfum |
| Vaseline Petroleum Jelly Jar™            | 100% pure white petroleum jelly                                                                                                                                                         |
| Lotus Herbals Cherry Lip Balm™           | Shea butter, kokum butter, and cherry extract                                                                                                                                              |
| Lotus Herbals Raspberry Lip balm™        | Raspberry extract, honey, jojoba oil, almond oil, wheat germ oil                                                                                                                         |
| Nivea Fruity Shine Cherry™               | R. communis seed oil, polyisobutene, oxyldodecanol, pentaylthryl tetraisostearate, hydrogenated polydecene, candelilla cera, butyropernum parkii butter, cera microcrystallina, isopropyl palmitate, synthetic wax, polyglyceryl-3 diisostearate, glycerin, glyceryl glucoside, aqua, P. cerasus juice, mica, silica, propylene glycol, BHT, limonene, euugen, aroma, CI 15850, CI 77891, CI 77492, CI 77499 |

**R. communis**: Ricinus communis, **S. chinensis**: Simmondsia chinensis, **P. cerasus**: Prunus cerasus, **PEG-12**: Polyethylene glycol-12, **EDTA**: Ethylenediaminetetraacetic acid

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**MANAGEMENT OF RETINOID-INDUCED CHEILITIS**

Retinoid-induced cheilitis is a dose-dependent side effect and marks the anti-seborrheic activity of retinoid therapy. To ensure compliance, the dermatologist must counsel the patients regarding muco-cutaneous adverse effects and prescribe lip moisturizers with added sunscreens to counteract lip chapping. Table 1 gives a list of lip moisturizers which can be prescribed and asked to be applied as many times as possible. Best results are obtained when lip moisturizers are applied on prehydrated lips.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Kaur S. Retinoids as chemopreventive agents. Indian J Dermatol Venereol Leprol 2016;82:59-64.
2. Kobayashi H, Tagami H. Functional properties of the surface of the vermilion border of the lips are distinct from those of the facial skin. Br J Dermatol 2004;150:563-7.
3. Dawson DV, Drake DR, Hill JR, Brogden KA, Fischer CL, Wertz PW. Organization, barrier function and antimicrobial lipids of the oral mucosa. Int J Cosmet Sci 2013;35:220-3.
4. Ya-Xian Z, Suetake T, Tagami H. Number of cell layers of the stratum corneum in normal skin – Relationship to the anatomical location on the body, age, sex and physical parameters. Arch Dermatol Res 1999;291:555-9.
5. Shalita AR. Mucocutaneous and systemic toxicity of retinoids: Monitoring and management. Dermatologica 1987;175 Suppl 1:151-7.
6. Hommel L, Geiger JM, Harms M, Saurat JH. Sebum excretion rate in subjects treated with oral all-trans-retinoic acid. Dermatology 1996;193:127-30.
7. Ornelas J, Rosamilia L, Larsen L, Foolad N, Wang Q, Li CS, et al. Objective assessment of isotretinoin-associated cheilitis: Isotretinoin Cheilitis Grading Scale. J Dermatolog Treat 2016;27:153-5.
8. Kus S, Gün D, Demirçay Z, Sur H. Vitamin E does not reduce the side-effects of isotretinoin in the treatment of acne vulgaris. Int J Dermatol 2005;44:248-51.
9. Cassano N, De Benedittis M, Petruzzi M, Carbonara M, Agnusdei C, Alessandrini G, et al. Topical Vitamin E acetate for the treatment of cheilitis: A multicentre experience. Eur J Inflamm 2003;1:125-8.