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An overview of zinc and its importance in dermatology-Part II: The association of zinc with some dermatologic disorders

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Abstract

Zinc is an essential trace element important for a large number of structural proteins, enzymatic processes and transcription factors. It plays main roles in the cell-mediated immunity, bone formation, tissue growth, brain function, growth of the fetus and child. It also has roles in pathogenesis of some dermatological disorders.

Zinc can be used as effective agent for treatment of some skin and hair disorders, but generally, it seems that with the exception of states relating to zinc deficiency, there is very little evidence to support the efficacy of zinc as a first-line treatment for most of dermatological conditions.

Herein, we collected and summarized the appropriate manuscripts and papers regarding the importance of zinc in some of the most important dermatological disorders.

Introduction

In human beings, zinc (Zn) constitutes less than 0.005% of total body weight, and is present in all types of cells [1]. It is an essential trace element important for a large number of structural proteins, enzymatic processes and transcription factors [2]. Zn is important for the cell growth, development, and differentiation [3]. In the world, the prevalence of Zn deficiency is estimated at more than 20% [2].

In this article, we collected and summarized the appropriate manuscripts and papers regarding the importance of Zn in some of the most important dermatological disorders. Hence, we searched the computerized bibliographic database PubMed entering the keywords "zinc" and "dermatology". After finding the related abstracts, we selected the manuscripts suitable for our paper. Our article gives an overview of Zn importance in dermatology.

The association of the zinc with some dermatological disorders

The followings are some dermatological disorders in which Zn plays a role in the pathogenesis or treatment (Table 1).

Acrodermatitis entropathica

AE is rare congenital form of Zn deficiency [3]. The clinical manifestations of this disease usually start following weaning from breast feeding, when the protective effect of the Zn binding ligand from the mother's milk is no longer present [4]. They include growth retardation, diarrhea, alopecia, and characteristic cutaneous lesions involving acral, periorificial, and anogenital areas [3-5]. It appears that the cutaneous lesions in this disorder are caused by apoptosis of keratinocytes, which are easily controlled by Zn supplementations [5].

In a study on humans and mice with Zn deficiency, Kawamura *et al.* revealed that allergic contact dermatitis was diminished, whereas irritant contact dermatitis was more severe and prolonged than that in controls. They also proved that epidermal Langerhans cells, which play a protective role against the ATP-mediated inflammatory signals, were decreased in number in humans and mice with the AE under the Zn-deficient diet [3].

Seborrheic dermatitis

Seborrheic dermatitis (SD) is a chronic dermatosis affecting sebum-rich areas [6]. Its manifestations include flaking and pruritus with underlying inflammation and hyperproliferation [7].

In an in vitro study, Guillard *et al.* showed that a Zn compound named Zn L-cysteat had a significant anti-seborrheic effect [8]. In addition, Zn in the form of Zn pyrithione shampoo is effective in treatment of this disease [6]. Zn pyrithione can decrease the cell turnover rate in hyperproliferative dermatoses. It also has fungistatic and antimicrobial activities [9]. In a comparative study, Shin *et al.* showed that although the response to betamethasone lotion and tacrolimus ointment was more rapid than zinc pyrithione shampoo, patients treated by Zn pyrithione improved continuously even after cessation of the treatment [6]. In a randomized, prospective, parallel-group, investigator-blinded trial conducted by Quadri *et al.*, the efficacy of thermophobic foam

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Table 1. The association of the zinc with some dermatological disorders.

Dermatologic condition	Definition	Role of zinc in pathogenesis	Role of zinc in treatment
Acrodermatitis entropathica	Rare congenital form of Zn deficiency, characterized by growth retardation, diarrhea, alopecia, and characteristic cutaneous lesions involving acral, periorificial, and anogenital areas [3-5]	Zn deficiency is the main cause of this disease [3].	Clinical manifestations are easily controlled by oral Zn supplementations [5]
Seborrheic dermatitis	Chronic dermatosis affecting sebum-rich areas, characterized by flaking and pruritus with underlying inflammation and hyperproliferation [6,7]	unknown	Topical zinc preparations are effective in its treatment [6,7,9-11].
Pityriasis [tinea] versicolor	Chronic superficial fungal infection involving the upper trunk, neck, and upper arm [11]	Unknown	Topical zinc preparations are effective in its treatment [11].
Eczema and contact dermatitis	Chronic, relapsing, and itchy inflammatory skin condition [12]	Unknown	Arguable role of oral and topical Zn supplementations in treatment of these conditions [13,14,17-19]
Telogen effluvium	increase in number of the hairs entering the telogen [resting] phase of the hair cycle from the anagen [growing] phase [21]	Arguable	Oral Zn supplementation improves hair growth [22,25].
Alopecia areata	Recurrent, non-scarring hair loss [27]	Arguable	Zn supplementation can be prescribed as adjuvant therapy in combination with other therapeutic methods [22]
Acne vulgaris	Prevalent skin disorder, characterized by a spectrum cutaneous lesions range from non-inflammatory comedones [30]	Unknown	Oral and topical Zn supplementation can reduce the severity of mild and moderate inflammatory [30,33,34,36-40]
Rosacea	Chronic cutaneous disorder, characterized by intermittent episodes of exacerbation and remission of facial erythema, telangiectasia, inflammatory papules and pustules [52]	Unknown	Arguable [53,54]
Hidradenitis suppurativa	Chronic suppurative dermatosis involving the apocrine gland-bearing areas [55]	Unknown	The efficacy of oral zinc has been shown in treating this disease [55].
Folliculitis decalvans	Neutrophilic inflammatory disease of the scalp, characterized by painful, recurrent purulent follicular exudation resulting in cicatricial alopecia [56]	Unknown	The efficacy of oral zinc has been shown in treating this disease [57].
Perifolliculitis capitis abscedens et sufodiens	Characterized by the formation of pimples, nodules, and abscesses on the scalp, communicating between each other resulting in atrophic, hypertrophic, and keloidal scars [58]	Unknown	Oral Zn is effective in treatment of this disease [23,58].
Molluscum contagiosum	Self-limiting disorder caused by the molluscum contagiosum virus [59]	Unknown	The efficacy of topical zinc has been shown in treating this disease [59].
Viral warts	skin and mucosal epithelial proliferations caused by different types of human papillomavirus [23]	Unknown	The role of oral, topical and intralesional Zn suplimmentations have been shown in treating this disorder [62,23,61,63-65].
Recurrent herpes simplex	Painful erythema and blisters in the skin and mucous membrane around the lip and mouth, caused by Herpes simplex viruses [67]	Arguable [66, 71]	Zn is effective in treating this disease [68-70].
Cutaneous leishmaniasis	Zoonotic disease in humans and animals, mainly caused by the two species of leishmania tropica and major [72]	Unknown	The efficacy of Zn supplementations have been described in this disorder [1,23,, 67,73,74]
Leprosy	Chronic infectious disease, caused by the Mycobacterium leprae [75]	A correlation between the serum Zn and the severity and the type of leprosy has been shown [75-79].	Oral Zn supplementation is useful in the treatment of this disease [80].
Necrolytic acral erythema	Introduced as early cutaneous marker of hepatitis C virus and closely associated to a group of necrolytic erythemas and metabolic syndromes [84,85]	Low serum Zn levels have been reported as one of the most consistent findings [85].	Arguable
Necrolytic migratory erythema	Rare condition associated with the high plasma levels of circulating glucagon and glucagonoma [88]	Low serum Zn levels have been reported [88,89].	Oral Zn supplementation is useful in the treatment of this disease [88,89].
Uremic pruritus	One of the most common symptoms in hemodialysis patients [90]	Decreased serum Zn has been shown [90].	Oral Zn supplementations are effective in the treatment of this disorder [23,90].
Melasma	Disorder of the skin pigmentation, characterized by symmetric hyperpigmented patches with irregular border in sun-exposed parts [68]	Unknown	The efficacy of topical Zn preparations have been shown in treating this condition [68,91,92].
Cutaneous ageing	seen on exposed areas of the skin secondary to significant alterations in the structure and function of the extracellular matrix of the connective tissues [93]	Unknown	The efficacy of topical Zn preparation has been shown in treating this condition [93].
Skin cancers	Includes melanoma, basal carcinoma, and squamous cell carcinoma, mostly affecting sun-exposed areas [94]	Arguable [95-99]	The efficacy of topical and intralesional preparations of Zn have been shown in preventing and treating these disorders [94,95,101-103]
Cutaneous wounds and ulcers	Including wound and ulcer caused by different intrinsic and extrinsic factors	Role of Zn has been shown in wound healing; in addition, an association between Zn deficiency and poor postoperative wound healing has been shown [71,72,74].	The efficacy of oral Zn supplementations have been shown in treating these conditions [71,72,74]; about the topical Zn preparations, the results are arguable [76-79].

Vitiligo	Acquired, idiopathic, progressive, well-defined depigmentation of the skin, hair and mucosal surfaces [1,118-121]	Arguable [119]	Arguable [118,120,121]
Lichen planus	Chronic inflammatory disease, involving the skin and mucous membranes [124]	Arguable [23,126-129]	Arguable [124,130]
Psoriasis	Chronic inflammatory disorder of the skin [131]	Arguable [9,23,132, 133,138]	Arguable [9,131,135,136]
Systemic lupus erythematosus and Sjögren's syndrome	Classified as connective tissue diseases. With complex array of autoimmune responses [139]	Arguable [140]	Unknown
Behcet's disease	Multisystemic disease with periods of activation and remission [141]	Arguable [142]	The efficacy of oral Zn supplementation has been revealed [142].
Recurrent aphthous stomatitis	The most common oral mucosal disease [143]	Arguable [143]	The efficacy of oral Zn supplementation has been revealed [143].
Oral pre-malignant and malignant lesions	The most common neoplasms in developing countries [135]	Serum and salivary Zn levels are reliable parameters as a diagnostic and prognostic index in case of the craniofacial tumors [128,144].	Unknown
Bullous pemphigoid	Characterized by large, tense, subepidermal bullae, involving the groin, axillae, trunk, thighs, and forearms [139]	The decreased serum level of Zn has been reported [147]	Unknown
Epidermolysis bullosa	A group of rare genetic disorders, common in the formation of blisters in response to minor physical injury [139]	Arguable [148,149]	Arguable [149]
Acrokeratosis paraneoplastica [Bazex syndrome]	A paraneoplastic syndrome, particularly associated with squamous cell carcinoma of the upper aerodigestive tract and adenopathy above the diaphragm [150]	Arguable [151]	Unknown
Sweet's syndrome	Characterized by nodular and diffuse dermal infiltrate of neutrophils along with karyorrhexis and papillary dermal edema [139]	Unknown [152]	Topical Zn preparation may be effective in treating this disease [152].
Nail disorders	Including any nail disorders	Unknown	Arguable [151]

containing 1% ketoconazole, 0.5% Zn pyrithione, and 2% salicylic acid was compared with the 2% keteconazole fluid in the treatment of scalp dandruff. Their study showed that the thermophobic foam was more active than ketoconazole fluid in the treatment of severe dandruff [10].

In a study conducted by Schwartz *et al*., the probability of tachyphylaxis in SD was evaluated. In this study a survey questionnaire was sent to 722 dermatologists in five countries. Their study showed that there was no evidence for tachyphylaxis in the treatment of SD with Zn pyrithione shampoo [7].

Pityriasis (tinea) versicolor

Pityriasis (tinea) versicolor (PV) is a chronic superficial fungal infection involving the upper trunk, neck, and upper arm. Its etiology is the changes of the lipophilic yeast Malassezia from the blastospore form to the mycial form under the influence of predisposing factors [11].

In the treatment of this disease, the Zn pyrithione shampoo is appropriate. Other therapeutic options include propylene glycol, ketoconazole shampoo, cyclopiroxamine, selenium sulfide and topical antifungals [11].

Eczema and contact dermatitis

As defined by the World Allergy Organization (WAO) revised nomenclature in 2003, eczema, also known as atopic dermatitis, is a chronic, relapsing, and itchy inflammatory skin condition [12].

It remains unknown whether Zn supplementations and elemental diets are effective in treatment and controlling eczema. Schmitt *et al*., in a systematic review, assessed the efficacy of Zn supplementation in reducing the severity of eczema. They were responding to a randomized clinical trial that had compared the efficacy of oral Zn sulphate with placebo in decreasing the disease severity score [13]. This study conducted by Ewing *et al*., had revealed that there was no significant difference in combined disease severity score between the Zn sulphate and placebo [13, 14]. On the other hand, in an in vivo study on HR-1 hairless mice performed by Makiura *et al*., the effect of diet low in the magnesium (Mg) and Zn in comparison with the normal diet was assessed on the skin manifestations. Their study showed that mice on low Zn-Mg diet had skin dryness, wrinkle like changes, scratching behavior, decreased skin water content, increased trans-epidermal water loss and raised blood immunoglobulin E levels [15]. In addition, in other similar study on mice conducted by Akamatsu *et al*., the effectiveness of low diet in Mg and Zn was compared with the normal diet. Their study revealed that mice on low diet in the Mg and Zn had significantly greater scratching frequency, and the plasma histamine and eotoxin concentrations in comparison with the mice on the normal diet [16].

Zn, in the form of topical Zn oxide, has been used for centuries to sooth, lubricate and cool the subacute eczema. Tar in mixture with Zn paste has been administered for the localized forms of eczema. In addition, the compositions of Zn, menthol and camphor can relieve itching secondary to this disease [17]. In a study, Arad *et al*. compared topical eosin, Zn oxide paste, and corticosteroid cream in the treatment of diaper dermatitis. This study showed that the rate of complete healing with eosin was significantly higher in comparison with the two other agents. They also observed that the fastest improvement was achieved by corticosteroid cream [18]. In a prospective, block randomized, investigator-blinded clinical trial, Wananukul *et al*. showed that Zn oxide ointment was as effective as dexpanthenol ointment in the treatment of irritant diaper dermatitis. This study revealed that both of the agents significantly decreased the trans-epidermal water loss in comparison with the ointment base [19].

In one study by Wallengren, it was shown that Zn oxide is as effective as moderate potency topical corticosteroid in suppressing the manifestations of contact dermatitis. This study also showed that tea tree oil was even more effective than Zn oxide in suppressing

contact dermatitis. In addition, Wallengren reported that Zn oxide reduced significantly the flare reaction secondary to histamine, but not as effectively as topical clobetasone butyrate [17]. Conversely, in a study by Gäfvert and Färm the efficacy of Zn oxide in inhibiting rosin-induced allergic contact reactions was assessed. They concluded that the addition of Zn to the rosin in adhesives could not be regarded as an appropriate approach for suppressing these reactions [20].

Telogen effluvium

Telogen effluvium (TE) is defined as an increase in number of the hairs entering the telogen (resting) phase of the hair cycle from the anagen (growing) phase [21]. Checking the serum level of Zn is necessary to evaluate the hair loss of an unknown cause [22].

Oral Zn supplementation has been used for many decades for the treatment of TE [22,23,24]. Studies have shown that oral Zn supplementation improves hair growth [22,25]. It appears that Zn is effective in the treatment of TE via the following mechanisms, all of which are required for normal control of the hair growth cycle:

1. Recovering activities of the appropriate metalloenzymes
2. Playing a role in hedgehog signaling
3. Its efficacy in immunomodulation (26)

Alopecia areata

Alopecia areata (AA) is a recurrent, non-scarring hair loss that can affect any hair bearing area. It appears that an imbalance of the trace elements may trigger the process of this disease [27].

It has been reported that some patients with AA have significantly decreased serum levels of Zn [7,21], but its pathogenesis in these patients is unknown [22]. In a case-control study on 50 patients with AA, Bhat *et al.* demonstrated that serum Zn levels were significantly decreased in patients whose disease was extensive, prolonged, and resistant to treatment, whereas serum Cu and Mg levels showed insignificant rises compared to the controls [27]. In another study, Naginiene *et al.* showed a lower Zn level in the blood and urine of children with AA, whereas the Cu and chromium concentrations showed a rise in their hair [28].

The role of Zn in the treatment of AA has not universally been clarified. For the first time in Korea, Park *et al.* showed that oral Zn had a positive effect in the treatment of AA, but this effect was not statistically significant. This clinical trial study enrolled 15 AA patients with low serum Zn levels, revealed that serum Zn levels of the positive response group increased more than those of the negative response group [22]. On the other hand, Ead's clinical trial study showed that the oral administration of Zn had no effect on treatment of AA [29].

Generally, Zn supplementation can be prescribed as adjuvant therapy in combination with other therapeutic methods in the treatment of AA, especially in patients with low serum Zn levels [22].

Acne vulgaris

Acne vulgaris (AV) is characterized by a spectrum cutaneous lesions range from non-inflammatory comedones [30].

The efficacy of oral Zn supplementation has been reported in the treatment of AV [1,23,30-32]. Studies have shown that oral Zn supplementation can reduce the severity of mild and moderate inflammatory AV when either administered alone or in combination with other acne treatments [30,33,34]. In addition, Zn can be considered as an alternative treatment for the AV when cyclines are contraindicated [35].

In a multicenter randomized double-blinded, controlled clinical trial conducted by Dreno *et al.*, the effectiveness of oral Zn gluconate was compared with minocycline. This study introduced Zn gluconate as alternative treatment for AV [36]. In another study, Dreno *et al.* showed that 30 mg/day of Zn gluconate significantly decreased acne lesions, especially inflammatory ones, during 2 months [37]. Feucht *et al.* conducted a double-blinded study and assessed the efficacy of topical erythromycin combined with oral Zn in the treatment of AV. Their study showed that this regimen applied twice daily reduced the acne severity grade and papule count in comparison with placebo and was just as effective as oral tetracycline twice a day [38].

Topical preparations of Zn are also used as alternative acne treatment. Habbema *et al.*, compared the efficacy of 4% erythromycin-Zn combination with 2% erythromycin lotion in the treatment of acne. Their study showed the superiority of erythromycin-Zn lotion in the acne treatment [39]. Schachner *et al.*, in another study showed the superiority of 4%erythromycin-1.2% Zn acetate formulation in comparison with 1% clindamycin solution in the treatment of acne. The authors concluded that this superiority could be due to higher concentration of erythromycin, and also enhancement of the product activity by the Zn acetate [40]. In a randomized clinical trial, Chu *et al.* compared the efficacy of benzoyl peroxide 5%/erythromycin 3% gel with erythromycin 4% Zn 1.2% solution in 72 AV patients. Their study showed that the efficacy of benzoyl peroxide 5%/erythromycin 3% solution was significantly more than the other one in the treatment of inflammatory and non-inflammatory acne lesions [41]. In one study, Fluhr *et al.* revealed that Zn acetate as well as the combination of Zn acetate and erythromycin was effective in reducing both the P.acnes strains and micrococcaceae in the sebaceous gland infundibula of acne patients [42]. In a randomized, single-blinded clinical trial, Langner *et al.* compared the efficacy of topical clindamycin+benzoyl peroxide (Duac) and topical erythromycin+Zn acetate (Zineryt) in the treatment of mild to moderate facial AV. They observed that clindamycin+benzoyl peroxide had an earlier onset of action with a faster significant reduction in the total lesion counts than erythromycin+Zn acetate [43]. In another study, Heffernan *et al.* assessed the efficacy of picolinic acid gel, a Zn finger therapy, in the treatment of acne. The results of this study suggested that 10% picolinic acid gel applied twice daily was safe and effective in the treatment of mild to moderate acne [44]. Cunliffe *et al.* in a multicentric, randomized, observer-blinded clinical trial compared the efficacy of topical clindamycin/Zn gel and topical clindamycine lotion in the treatment of AV. Their study demonstrated that the efficacy and safety of clindamycin/Zn gel either once or twice daily and clindamycin lotion twice daily was equivalent. They suggested that the treatment regimen of clindamycin/Zn gel administered once daily could significantly enhance compliance and thus treatment success in the patients with acne [45]. Dreno also noted that topical clindamycin and erythromycin are effective against inflammatory acne in concentrations of 1-4% with or without the addition of Zn [46]. In a double-blinded, controlled, randomized study, Papageorgiou and Chu compared the efficacy of chloroxylenol and Zn oxide containing cream and benzoyl peroxide cream in the treatment of acne. Their study showed that the efficacy of both creams was the same in the treatment of inflammatory and non-inflammatory acne lesions, but side effects such as peeling and dryness secondary to the treatment were significantly less in the group taking cream containing chloroxylenol and Zn oxide [47].

According to the mentioned studies, it seems that Zn salts are

helpful in reducing the severity of inflammatory acne via a variety of mechanisms [30] including:

1. Preventing and attenuating the inflammatory process [30,35] via inhibiting the migration of neutrophils to site of inflammation [30,37], induced by a decreased granulocyte Zn level [32,48]

2. Hindering the growth of P. acnes [30,49]

3. Inhibiting the immune response via reducing Toll-like receptor (TLR) 2 on the surface of keratinocytes [30,50]

4. Decreasing the release of both TNF-α [53,59] and IL-6, which are involved in inflammatory processes [30]

5. Inhibiting 5α- reductase [37]

6. Stimulating the anti-radical enzyme system, mainly superoxide dismutase [37]

7. Modulating the expression of integrins [37]

8. Suppressing the cytokine-induced nitric oxide [51]

Rosacea

Rosacea is a chronic cutaneous disorder, characterized by intermittent episodes of exacerbation and remission of facial erythema, telangiectasia, inflammatory papules and pustules [52].

In a randomized, controlled, crossed-over, double-blinded study, Sharquie *et al*. assessed the efficacy of oral Zn sulphate in the treatment of rosacea. In this study, 25 patients were enrolled. A disease severity score was calculated for each patient. They observed that the mean disease severity score in patients undergoing oral Zn therapy started to decrease directly after the first month of therapy to significantly lower levels. Their study showed that oral Zn could be a good therapeutic option for rosacea [53]. Conversely, in a randomized, double-blinded study, Bamford *et al*. revealed that oral Zn sulfate was not associated with greater improvement in the rosacea severity compared with placebo [54].

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic suppurative dermatosis involving the apocrine gland-bearing areas [55].

In a pilot study on 22 patients with HS, Brocard *et al*. showed that Zn salts could provide a new therapeutic approach for the treatment of this disorder. In this study, Zn gluconate at a dose of 90 mg/day was prescribed. They reported a clinical response in all patients, with complete remission in 8 cases and partial remission in 14 patients [55].

Folliculitis decalvans

Folliculitis decalvans (FD) is a rare neutrophilic inflammatory disease of the scalp. It is characterized by painful, recurrent purulent follicular exudation resulting in cicatricial alopecia [56].

Abeck *et al*. reported 3 cases of FD successfully treated by a combination therapy consisting of oral and topical fusidic acid and oral Zn sulphate [57].

Perifolliculitis capitis abscedens et sufodiens

Perifolliculitis capitis abscedens et sufodiens is characterized by the formation of pimples, nodules, and abscesses on the scalp, communicating between each other resulting in atrophic, hypertrophic, and keloidal scars [58].

Oral Zn is effective in treatment of Perifolliculitis capitis abscedens et sufodiens [23,58].

Molluscum contagiosum

Molluscum contagiosum (MC) is is caused by the molluscum contagiosum virus**,** a DNA virus of the poxvirus family that replicates only in the human epidermal keratinocytes [59].

Safa and Darrieux showed that Zn oxide cream containing colloidal oatmeal extracts was effective in the treatment of this viral infection [59]. It has been demonstrated that oat extract has inhibitory effects on eicosanoid formation, expression of cytosolic phospholipase A2, and arachidonic acid mobilization in human keratinocytes [59,60]. On the other hand, phospholipase A2 plays a critical role in infectivity of some viruses such as parvoviruses [59]. Although Safa and Darrieux attributed the efficacy of their agent to colloidal oatmeal, it appears that Zn in the structure of zinc oxide cream is also effective in treating the molluscum contagiosum via up-regulating the local immune system.

Viral warts

Warts are skin and mucosal epithelial proliferations caused by different types of human papillomavirus [23]

In an open-label study, Cassano *et al*. compared conventional standard therapy with the combination of conventional standard therapy and oral supplementation containing methionine, Echinacea, Zn, probiotics and other antioxidant and immunostimulating compounds in the treatment of warts. They showed that the addition of oral supplementation was associated with a significantly more complete remission and less development of new warts ($P<0.001$ and $P=0.004$, respectively) [61]. In a randomized double-blinded prospective study, Stefani *et al*. compared the efficacy of cimetidine and Zn sulphate in the treatment of warts. Their study, which enrolled 18 patients with warts, showed that Zn sulphate was more effective than cimetidine for the treatment of children and adults with multiple and recalcitrant warts [23]. Another study by Al-Gurari *et al*. revealed that Zn sulphate at the dose of 10/mg/kg (maximum 600 mg/day) was effective in the treatment of recalcitrant warts [62]. Yaghoobi *et al*. also confirmed the efficacy of oral Zn sulphate in the treatment of warts [63].

In one study consisting of pilot and double-blinded clinical trials, Sharquie *et al*. compared the efficacy of 5% and 10% Zn sulphate solution with placebo in the treatment of plane and common warts. Their study showed that the full response in patients with planar warts under treatment of 10% Zn sulphate preparation was the highest and statistically significant. Eventually, they introduced 10% Zn sulphate solution as a new effective and safe modality for treatment of planar warts [64].

In another study, Sharquie and Al-Nuaimy compared the efficacy of intralesional injections of 2% Zn sulphate and 7% hypertonic sodium chloride solutions in the treatment of common warts. Their study observed the total clearance rate of 98.2% in lesions treated with intralesional Zn preparation, while this rate was 8.3% in lesions when treated by hypertonic sodium chloride. This large-scale study enrolled 623 lesions and recommended that Zn sulphate prescribed intralesionally was a new and effective local therapy for the viral warts, especially for the recalcitrant common ones [65].

Recurrent herpes simplex

Herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) are large DNA viruses [60], belonging to the family herpesviridae [66]. HSV-

1 can cause herpes labialis, characterized by painful erythema and blisters in the skin and mucous membrane around the lip and mouth [67]. HSV-2 produces genital ulcerative disease [66].

Studies have shown that Zn is effective in treating recurrent herpes simplex [68]. In a study on 46 herpes labialis patients, Godfrey *et al.* showed that the time period between the appearance of herpes lesions and their recovery was shortened by the prompt treatment of lesions with Zn oxide and glycine cream [69]. In another study, Kneist *et al.* compared the efficacy of 1% Zn sulfate gel and placebo in patients with herps labialis. Their study showed that after 5 days, 50% of the patients in the treatment group were symptom-free, compared with 35% in the placebo group [70].

For the first time, a study, Wayengera showed that Zn finger nucleases with specificity to the HSV-2 genomic DNA were potential precursors for the novel host-genome expressed HSV-2 gene-therapeutics or vaccines [66]. In another study, Kamakura *et al.* observed that a host cell protein named Zn finger transcription factor insulinoma-associated 1 (INSM1) was markedly up-regulated by the HSV-1 infection. They concluded that this up-regulation played a positive role in the viral replication [71].

Cutaneous leishmaniasis

Cutaneous leishmaniasis (CL) is a zoonotic disease in humans and animals, mainly caused by the two species of leishmania tropica and major [72].

The efficacy of Zn sulphate has been described in CL [1,23,35,68,73,74]. A comparative clinical trial conducted by Sharquie *et al.* compared the intralesional treatments of acute leishmaniasis with 2% Zn sulphate, 7% sodium chloride and sodium stibogluconate. In this study, Zn sulphate gave a high cure rate (94.8%) usually with a single injection [74]. Iraji *et al.* in a prospective, double-blinded, case-control clinical study compared the efficacy of intralesional injections of 2% Zn sulphate with those of meglumine antimoniate. The cure rates were 60% and 83.8% for meglumine antimoniate and Zn sulphate, respectively. This study showed that the efficacy of treatment with Zn sulphate was significantly higher than that with meglumine antimoniate after the second and fourth weeks ($p<0.01$), but after 6 weeks, no significant difference was observed ($p>0.05$) [73].

Leprosy

Leprosy is a chronic infectious disease, caused by the Mycobacterium leprae. It affects the skin and peripheral nerves [75].

Sethi *et al.* evaluated the serum Zn level in 80 untreated patients with TT, BT, BL, and LL types of leprosy. Their study revealed that there was a correlation between the serum Zn and the severity and the type of leprosy. With therapy, there was a shift of the serum Zn toward the normal values [76]. Other studies have also confirmed that the serum Zn levels are decreased in leprosy [75,77-79],

Oral Zn supplementation is useful in the treatment of leprosy [80]. Studies have shown that non- oral Zn therapy along with multidrug therapy in leprosy patients can reduce the frequency, duration and severity of erythema nodosum leprosum reactions (type II) in leprosy patients [75,81,82]. On the other hand, the use of topical Zn oxide in treatment of plantar ulcers in leprosy patients did not have satisfying results [83].

In one study, Gupta *et al.* observed that the peripheral blood mononuclear cells of leprosy patients showed spontaneous apoptosis after 24 h of culture in the absence of mitogens compared with the cells from normal individuals [75]. In this study, the addition of Zn to the culture could inhibit this apoptosis.

1. It seems that Zn is effective in the treatment of leprosy via the following mechanisms:

2. Suppressing the production of TNF-α and TNF-α- induced apoptosis of the peripheral blood mononuclear cells

3. Blocking Ca^{2+}-dependent apoptosis of the peripheral blood mononuclear cells by blocking Ca/Mg^{2+}-dependent endonuclease activity and an inhibitor of the caspase 8

4. Inducing IL-2 production in the peripheral blood mononuclear cells, which may help to overcome bacterial infections and increase the survival of cells by up-regulating levels of bcl-2

5. Inducing the proliferation of anergic cells by promoting IL-2 production

6. Playing the role of a cofactor for calcineurin (an important component of the TCR pathway) and many transcription factors, some of which activate the IL-2 promoter [75].

Necrolytic acral erythema

Necrolytic acral erythema is a newly recognized entity, which has been introduced as an early cutaneous marker of hepatitis C virus [84-86] and closely associated to a group of necrolytic erythemas and metabolic syndromes [85]. However, in a few cases, this association has not been reported [84,85].

The characteristic clinical manifestations of necrolytic acral erythema include a pruritic, symmetric, well-defined hyperkeratotic, erythematous-to-violaceous, lichenified plaque-type eruption with a rim of marked dusky erythema on the dorsal aspects of the feet and extending to the toes, over the Achilles tendons, malleoli, legs, and knees. Necrolytic migratory erythema, acrodermatitis entropathica, biotin deficiency, niacin deficiency and essential fatty acid deficiencies are listed as differential diagnoses of necrolytic acral erythema [85].

In this disorder, low serum Zn levels have been reported as one of the most consistent findings [85]. Oral Zn supplementations have been tried with variable successes [86]. Some studies have reported that the response to oral Zn supplementation is dramatic even in patients with normal serum Zn levels [84,85], and clinical improvement has been noted with from mild to complete resolution [85]. Studies have been shown that the most consistent improvement is achieved by oral Zn at the dose of 440 mg/day [85,87].

Necrolytic migratory erythema

Necrolytic migratory erythema is a rare condition associated with the high plasma levels of circulating glucagon and glucagonoma [88].

Sinclair and Reynolds reported a case of this disease with cirrhosis, without evidence of glucagonoma. Their patient showed a decreased serum Zn level, in whom rapid and complete resolution of the eruption resulted from the Zn supplementation [88]. In another study, Topham and Child reported a patient with a desquamation, predominantly flexural erythema and glossitis secondary to combination of alcoholism, Zn and amino acid deficiencies. Their patient's manifestations were similar to necrolytic migratory erythema, which can be seen with Zn deficiency or protein malnutrition, often in patients with alcoholic liver disease in the absence of glucagonoma. The patient showed a striking

recovery following the Zn replacement [89].

Uremic pruritus

Pruritus is one of the most common symptoms in hemodialysis patients. There have been a number of reports suggesting that uremic patients are Zn deficient. In one study, Sanada *et al.* showed that in uremic patients, there were decreased serum Zn and increased serum histamine levels [90].

Oral Zn supplementations are effective in the treatment of uremic pruritus [23,90]. In a study, Sanada *et al.* showed that oral Zn sulphate at the dose of 440 mg/day could relieve pruritus subjectively in 53% of the patients [90].

It seems that Zn, via an inhibitory effect on the histamine-releasing mast cells, can suppress pruritus in the uremic patients [90].

Melasma

Melasma is a disorder of the skin pigmentation. It presents as symmetric hyperpigmented patches with irregular border, commonly affecting sun-exposed parts of the skin [68].

Topical Zn sulphate has been introduced as an alternative therapy for melasma [68,91,92]. It seems that Zn is effective in the treatment of melasma via its roles as anti-inflammatory, anti-oxidant, peeling, sun-screening and a healing agent [68,91].

In a study on 14 patients with melasma, Sharquie *et al.* revealed the efficacy of 10% Zn sulphate solution in the treatment of melasma. They reported that its effect was statistically significant (P<.0005), and most of the patients maintained this improvement 3 months after cessation of therapy. The only reported side effect was mild stinging in few cases [91].

On the other hand, in an investigator-blinded, randomized, control trial study on 72 patients with melasma, Iraji *et al.* compared the efficacy of 10% Zn sulphate solution with 4% hydroquinone cream in the improvement of melasma. Their study showed that topical Zn sulphate is not as effective as hydroquinone in the treatment of melasma [68].

Cutaneous ageing

Cutaneous ageing, as seen on exposed areas of the skin, reflects significant alterations in the structure and function of the extracellular matrix of the connective tissues particularly the collagen and elastic fibers. The aging process consists of two clinically and biologically distinct components including innate skin aging, inflicts the skin in a similar age-associated progressive manner, and extrinsic ageing, secondary to exposure to environment, especially ultraviolet (UV) irradiation [93].

In a clinical trial, Mahoney *et al.* assessed the efficacy of 0.1% Cur-Zn malonate-containing cream in reversing the skin ageing. Their study showed that this bi-metal containing topical preparation is effective in improving aging via provoking elastin biosynthesis and regeneration, including those extending perpendicularly towards the dermo-epidermal junction within the papillary dermis. It seems that the chelating function between the Cu and Zn constituents and the surrounding proteins and amino acids is responsible for effacing the skin wrinkles [93].

Skin cancers

Sun exposure is the main cause of the development of skin cancers. Studies have shown that chronic continuous UV radiation induces malignant melanoma, whereas intermittent high-dose UV exposure induces basal carcinoma, and actinic keratosis as the precursor lesion for the development of squamous cell carcinoma. In this respect, the administration of sunscreens seems to be important [94].

Zn in the form of the Zn oxide has been used as sunscreen for many decades [94]. On the other hand, the topical use of Zn as antioxidant can favorably supplement sunscreen protection and provide additional anti-carcinogenic protection [95].

In addition, UV radiation can induce apoptosis of keratinocytes by generating reactive oxygen intermediates [96,97]. Superoxide dismutase is one of the most active scavengers of these reactive oxygen intermediates, providing defense against cellular oxidative stress. Zn in the form of the Cu, Zn-superoxide dismutase, one of the isoenzymes of superoxide dismutase, can increase the level of antioxidant enzymes, suppressing the UVB-induced apoptosis of keratinocytes [96-98].

Zn oxide and other inorganic sunscreens such as titanium oxide have a wide spectral range of activity in comparison with most of the organic sunscreens. Photo-contact allergy is uncommon with the inorganic sunscreens, but their cosmetic acceptability is still lower than the one given by the organic sunscreens. In addition, there are many controversial reports regarding the probability of systemic toxicity secondary to the use of organic sunscreens [94].

Pinnell *et al.* compared the efficacy of microfine Zn oxide and microfine titanium dioxide. Their study showed that microfine Zn oxide was superior to microfine titanium dioxide in protecting against the long-wave UVA and was cosmetically more acceptable at a given concentration [99]. Recently, by using modern galenic techniques such as micronization and encapsulation, inorganic sunscreens with high quality have been produced [94].

Greenberg *et al*., for the first time, reported a case with a pigmented macule as a result of Zn deposition. They described this lesion in a snow-skier after topical application of Zn-containing sunscreen. Studies have shown that heavy metal deposition occurs in the following situations: prolonged topical application to intact skin, topical application to eroded or ulcerated skin, following parenteral administration, and following traumatic exposure [100].

Zn chloride is used as an escharotic or caustic agent for treating the skin cancers [101]. It is also used as part of Mohs chemosurgery fixed-tissue technique [101,102]. A study on mice melanoma by Kalish *et al.* showed that Zn chloride fixative paste acted as an immune adjuvant. Their study should that Zn chloride fixation of the more immunogenic K1735p melanoma increased resistance to subsequent tumor challenge [102]. In another study, Sharquie *et al.* introduced intralesional 2% Zn sulphate solution for the treatment of basal cell carcinoma [103]. Calap *et al.* commented on the interest of X Ray microanalysis in dermatology, especially the Cu/Zn index in determination of skin tumors and their prognosis [104].

Cutaneous wounds and ulcers

In the early 1900s, with advances in biochemistry, the role of Zn, vitamin C and other nutritional components in wound healing was discovered [105].

It is estimated that approximately 50% of patients admitted to hospitals are malnourished and require dietary supplementation [105]. Studies have shown that there is an association between Zn deficiency and poor postoperative wound healing [106,107]. In addition, malnutrition is a risk factor for the development of pressure ulcers [108].

In a study of 17 patients with a chronic leg ulcer, Rojas and Philips showed that serum Zn, vitamins A, E and carotene levels were significantly low in patients [109]. In another study of 50 patients with non-healing leg ulcers conducted by Balaji and Mosley, Zn deficiency was reported in 18% of patients with arterial and venous disorders and 75% of patients without arterial and venous disorders [107].

Studies have shown that in patients with eating disorders, there is high probability of slow wound healing and pressure ulcer secondary to Zn deficiency [110].

The existence of nutritional deficiency increases the risk of pressure ulcers in patients with femoral neck fracture [107,111]. On the other hand, in a randomized, double-blinded study, Houwing *et al*. assessed the effect of nutritional supplementation on pressure ulcer development in patients with hip fracture. In this study, the patients were divided into two groups; one group took supplement enriched with protein, arginine, Zn and antioxidants, and another group took placebo. Their study revealed that the incidence of pressure ulcer was not significantly different between two groups, but incidence of stage II of pressure ulcer was significantly higher in the placebo group. In addition, they showed that the onset of pressure ulcers in the placebo groups was earlier than the other group [108].

Topical Zn compositions have been used for treating the wounds with differing degrees of success. In a comparison between occlusive dressings containing Zn oxide and hydrocolloid in the treatment of leg ulcers, Brandrup *et al*. showed that the efficacy of the two occlusive dressings showed no major differences [112]. Falanga and Iriondo applied Zn chloride paste for debridement of chronic leg ulcers. Their study showed that this paste fixed the tissue, leading to eschar formation that fell off within a few days, leaving a granulating bed suitable for grafting [113]. On the other hand, in a study on domestic pigs, Agren *et al*. showed that apart from inhibiting bacterial growth, no additional benefit was seen by dressing of wounds with Zn oxide [114]. A randomized controlled clinical trial by Cameron *et al*. compared the efficacy of Cavilon No Sting Barrier Film (NSBF) and Zn paste compound in protecting and managing maceration and irritation in the peri-wound area of venous leg ulcers. Their study showed that the both agents were equally effective barrier preparations, but the average time required to remove and re-apply the protectant was significantly more in the cases using Zn paste. In addition, reduction of pain was higher in the NSBF group [115].

Zn-hyaluronate is an organotherapeutic compound, marketed under the trade name of Curiosin. It is favorable for acceleration of the acute and chronic wound healing [116].

Tenaud *et al*. investigated the probable mechanism of Zn gluconate in keratinocyte wound healing. Their study showed that Zn gluconate was effective in wound healing by inducing the alph2, alpha3, alpha V, and alpha6 integrins. It seems that these integrins are effective in the cellular mobility in the proliferation phase of wound healing [117].

Vitiligo

Vitiligo is characterized by acquired, idiopathic, progressive, well-defined depigmentation of the skin, hair and mucosal surfaces [1,118-121].

For the first time, Bagherani hypothesized that a lack of protein named Zn-α2- glycoprotein might be associated with vitiligo [119].

Arora *et al*. did not find any significant alteration in serum Zn levels in vitiligo patients [122]. On the other hand, in another study Helmy *et al*. reported that serum Zn and Cu levels were significantly higher in active vitiligo patients secondary to their release from the peripheral blood mononuclear cells due to apoptosis [123].

For the first time, Bagherani *et al*. suggested oral Zn sulphate as a new therapeutic option for vitiligo [118,120,121]. They compared the efficacy of topical corticosteroid with and without oral Zn sulphate in treatment of this disorder. Their study showed that the combination of topical corticosteroid and oral Zn was more effective than the topical steroid alone, but this difference was not statistically significant [118,120].

It seems that Zn can be effective in preventing and treating vitiligo through the following mechanisms:

1. Preventing apoptosis of melanocytes
2. Inhibiting oxidative stress
3. Its role in the melanogenesis
4. Its immunomodulatory role
5. Its antibacterial effect
6. Release of α- melanocyte stimulating hormone
7. Precipitating Zn-α2- glycoprotein in the site of lesions [1,120].

Lichen planus

Lichen planus (LP) is a chronic inflammatory disease, involving the skin and mucous membranes [124]. The association between Zn and LP is controversial.

In dental restoration, Zn has been used for many years [125]. Zn in this form can cause oral LP [125,126], a maculopapular rash, and systemic contact dermatitis [125]. It appears that the complications due to Zn in the dental metal are low. For example in a study by Rapp *et al*. on 206 patients with dental metal, oral LP could be attributed to amalgam mixed metals including in the Cu, tin, Zn and silicon in only 1 patient [127].

Ayinampudi and Narsimhan observed significant an increase in the salivary Zn levels in the patients with oral LP when compared to the normal control group [128].

For the first time, Ito *et al*. reported disseminated LP due to Zn chloride present in the metallic dental crown in a 62-year-old- woman. Before this report, all of the previous studies had shown that there was no association between Zn in the dental restoration and LP lesions localized in the oral cavity. Ito *et al*. showed that the Th1-predominant immunological status secondary to the Zn allergy was strongly involved in the appearance of LP in their patient [129].

Studies have shown that the prescription of Zn compounds along with steroids decreases the symptoms of LP [130].

In a randomized clinical trial on patients with erosive oral LP, Mehdipour *et al*. compared the efficacy of fluocinolone ointment with and without Zn mouthwash. Their study showed that the decrease in irritation and pain severity was identical in both groups (P=0.11), but decrease in surface area was significantly more in the group that had used Zn mouthwash (P=0.037) [124].

It appears that Zn is effective in the treatment of oral LP via below mechanisms:

1. Regeneration of epithelium and repair of the endothelium of vessels

2. Its role in strengthening the local defense system, which reduces inflammation and bacterial growth

3. Its role as a cofactor in numerous transcription factors and enzyme systems, including the Zn-dependent matrix metalloproteinases that augment the auto-debridement and keratinocyte migration during the wound repair [124].

Psoriasis

(Psoriasis) Ps is a chronic inflammatory disorder of the skin [131] characterized by scaly erythrodermic patches and plaques.

In a case-control study, Ala *et al.* compared serum Zn and Cu in patients with Ps and in a normal control group. They observed that the mean serum Cu level was significantly higher in patients with Ps ($p=0.003$), but no significant difference was observed in the Zn concentration between the two groups ($p=0.57$). This work was the first study that compared serum Zn and Cu levels in Iranian psoriatic patients [132].

Leibovici *et al.* assessed neutrophil chemotaxis in patients with Ps and psoriatic arthritis before and after Zn supplementation therapy. Their study revealed that although Zn sulphate could modulate neutrophil chemotaxis, it had no effect on the inflammatory process of the underlying disease [133]. In another clinical trial that enrolled 25 patients with chronic plaque type Ps, Burrows *et al.* showed similar results [134]. Both of these studies confirm that neutrophils play a secondary role in the pathogenesis of Ps.

On the other hand, Verma and Thakur reported a case with the subacute form of generalized pustular Ps, treated successfully with oral Zn [135]. It seems that oral Zn is effective in the treatment of psoriasis via the below mechanisms:

1. Modifying neutrophil migration and chemotaxis

2. Modulate TLR 2 surface expression in the keratinocytes, which shows increase in number during the exacerbation of Ps

3. Its role in the immunomodulatory action, controlling bioavailability of neuropeptide mediators like substance P, and neurokinin A by the Zn-dependent enzymes, the Zn metalloproteases [135].

Studies have shown that Zn pyrithione can decrease the cell turnover rate in hyperproliferative dermatosis [9,131]. It can be successfully used for the treatment of scalp Ps (9), but its effectiveness in the treatment of Ps lesions involving sites other than the scalp is controversial. In a randomized, double-blinded, right/left study on patients with mild to moderate plaque-type Ps conducted by Housman *et al.*, it was shown that the efficacy of clobetasol propionate foam with and without Zn pyrithione spray in treatment of this disease was not significantly different [136]. In another randomized, double-blinded study, Sadeghian *et al.* showed that topical formulation of Znpyrithione was effective in the treatment of localized Ps [131].

Controversially, there are reports that have shown that dental Zn restoration can cause palmoplantar pustulosis [125,137]. Nielsen and Menné reported an eruption of pustular Ps in a patient with stable Ps secondary to allergic contact dermatitis following the use of Zn pyrithione shampoo [138]. In another study, Jo *et al.* reported aggravation of Ps lesions on the scalp and appearance of pustular Ps on the both forearms in a patient with stable Ps for 25 years after using Zn pyrithione shampoo. They discovered that allergic contact dermatitis following the use of shampoo provoked Ps as the consequence of the Koebner phenomenon [9].

Systemic lupus erythematosus and Sjögren's syndrome

Systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) are classified as connective tissue diseases. In both of these, a complex array of autoimmune responses target and affect collagen or ground substances [139].

Carbonic anhydrase is a basic Zn metalloenzyme, important for the regulation of acid-base status. In a study, Inagaki *et al.* showed that in 31.6 % of the patients with SLE and 20.8% of patients with SS, the autoantibodies reactive to carbonic anhydrase were found in the sera [140].

Behcet's disease

Behcet's disease is a multisystemic disease with periods of activation and remission [141].

In a randomized, controlled, cross-over, double-blinded trial conducted by Sharquie *et al.*, patients with Behcet's disease were recruited between November 2001 and February 2003. For assessing disease severity, clinical manifestation index (CMI) was considered. This study showed that mean serum Zn level was statistically significantly lower in patients with Behcet's disease than it in healthy control group. Their study also revealed that the mean CMI started to decline directly after the first month of therapy with Zn sulphate to significantly lower levels. They suggested that Zn sulphate could be a good option in the treatment of Behcet's syndrome especially its oral lesions [142].

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease [143] with recurrent attacks of painful lesions in the oral mucosae.

In a clinical trial, Sharquie *et al.* compared the efficacy of dapsone and oral Zn in the treatment of RAS. This study showed that both dapsone and Zn sulphate were effective agents for prophylaxis and treatment of this disease. They also reported that Zn sulphate was slightly better than dapsone, especially at week 6 of therapy, and was much safer, because Zn is a trace nutrient element and can be prescribed during the pregnancy [143].

The probable mechanisms of action of Zn in the treatment of RAS are thorough its immunomedulatory, antibacterial, and antioxidant actions or through its efficacy on wound healing [143].

Oral pre-malignant and malignant lesions

Cancers of the oral cavity are the most common neoplasms in developing countries. In addition, the incidence of pre-malignant lesions of the oral cavity such as leukoplakia and submucous fibrosis is also very high in these countries [128].

Studies have shown that serum and salivary Zn levels are reliable parameters as a diagnostic and prognostic index in case of the craniofacial tumors [128,144]. Ayinampudi and Narsimhan in a study on patients with pre-malignant and malignant lesions of the oral cavity observed that there was significant difference of the mean salivary Cu and Zn levels in these patients when compared to normal controls.

Additionally, they showed that the Cu/ Zn ratio decreased in this group when compared to the normal one [128]. Previous studies on serum and saliva of patients with pre-malignant and malignant oral lesions had also generated similar results [145,146].

It seems that Zn can provoke the oral lesions via its roles in the regulation of cell cycle, cell division and activation of DNA polymerase [128].

Bullous pemphigoid

Bullous pemphigoid (BP) is characterized by large, tense, subepidermal bullae, involving the groin, axillae, trunk, thighs, and forearms [139].

A study by Tasaki *et al.* showed that the serum level of Zn was significantly decreased in cases of BP [147].

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a group of rare genetic disorders, common in the formation of blisters in response to minor physical injury [139].

Fine *et al.* assessed the plasma and erythrocyte Zn levels along with nine other nutrients in 73 patients with various forms of inherited EB. This study showed that there was a notable abnormality in Zn in the junctional and recessive dystrophic types of EB [148]. In another study, Ingen-Housz-Oro *et al.* assessed 14 patients with recessive dystrophic EB. They found deficiency in the Zn, iron, vitamins D, C, B6, PP, and selenium in 36-70% of the patients, without clinical expression, except in one case. It seems that involvement of the oral mucosa and oesophagus stenosis are responsible for severe nutritional deficiencies. The dietary supplementations in these patients are necessary to obtain healing of the chronic wounds [149].

Acrokeratosis paraneoplastica (Bazex syndrome)

Bazex syndrome is a rare paraneoplastic syndrome, particularly associated with squamous cell carcinoma of the upper aerodigestive tract and adenopathy above the diaphragm [150].

Taher *et al.* reported a 68-year-old woman with Bazex syndrome secondary to lobular breast carcinoma. Their report was unique because they demonstrate laboratory findings consistent with relative Zn deficiency and porphyria cutanea tarda. They commented that Zn played a possible etiologic role in appearance of this syndrome [151].

Sweet's syndrome

Sweet's syndrome is characterized by nodular and diffuse dermal infiltrate of neutrophils along with karyorrhexis and papillary dermal edema [139].

Anavekar *et al.* reported a 36-year-old man who presented with facial Sweet's syndrome mimicking rosacea fulminance. They were able to get rapid clinical improvement by high dose oral prednisolone, topical hydrocortisone cream and ichthamol in Zn ointment [152]. This study showed thattopical Zn may be effective in treating the manifestations of Sweet's syndrome via regulation of neutrophils.

Nail disorders

Scheinfeld *et al.* reported that there was no evidence which supports the use of supplementations with Zn for improving the nail health in well-nourished patients or improving the appearance of nails affected by pathologic disease [151].

Miscellaneous

Wahie and Lawrence reported three cases with episodes of an inflammatory dermatosis associated with alcohol abuse. Their patients didn't respond to zinc replacement therapy. Their dermatosis improved promptly following treatment with emollients and topical steroids [153]. Their report showed that Zn is not always effective in treatment of alcohol-related dermatoses.

In eating disorders, there are a mixture of the following dermatological manifestations: xerosis, lanugo-like body hair, TE, carotenoderma, acne, hyperpigmentation, SD, acral coldness, acrocyanosis, perniosis, livedo reticularis, petechiae, prurigo pigmentosa, edema, linear erythema craquele, pellagra, scurvy, AE, self-induced trauma due to psychiatric morbidity, and Russell's sign (knuckle calluses). One study by Strumia in Italy showed that in these patients, combination of anti-bacterials such as erythromycin with Zn can be prescribed for treatment of acne because of the possibility of the Zn deficiency in them [110].

Conclusion

Zn is an essential metal for normal cellular functions [22]. It can be used as an effective agent for the treatment of some skin and hair disorders, but generally, it seems that with the exception of the states relating to Zn deficiency, there is very little evidence to support the efficacy of Zn as a first-line treatment for many dermatological conditions [31].

As a hypothesis, it has been suggested that the efficacy of Zn in improving some dermatological conditions is via its action as the anti-inflammatory, anti-oxidant, cytotoxic, and healing agent [68].

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