

Possible relationship between poor skin disorders prognosis and serum zinc level: A narrative review

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Abstract

Zinc is a trace nutrient essential for the normal growth and development of human body. The main aim was to evaluate the significant association between measured zinc status in relation to different skin disorders and their severity. PubMed®, Google® Scholar™ and Cochrane© Reviews databases were searched for studies from January 2017 to June 2021, using the terms; zinc serum levels, zinc plasma levels and different dermatosis in the review, only human studies in English language were reviewed and the studies designs were controlled, cross sectional, observational and analytic types. A total of forty-eight research studies were included in this review. All studies have evaluated serum zinc in skin diseases including psoriasis, atopic dermatitis, pityriasis alba, androgenetic alopecia areata, telogen effluvium, vitiligo, melasma, acne, seborrheic dermatitis and hidradenitis suppurativa. It was found that 33 studies had validated statistically significant differences in serum zinc levels between patients and controls. There is a predominance of low serum zinc levels in all the dermatoses reviewed. The clinical significance of this finding highlights the possible value, and need to investigate, the use of Zinc supplementation as an adjuvant therapy in the management of chronic inflammatory and autoimmune skin diseases proven to manifest altered zinc levels.

Introduction

For humans, zinc is an essential trace nutrient, involved in structural tissues and catalytic and regulatory systems for metabolic processes. The overall amount

present is regulated at around 2.6g.¹ The skin ranks third in zinc-containing tissue in the body at around 4.2%, with a greater proportion in the epidermis than in the dermis.²

Serum zinc concentration is preserved by homeostatic mechanisms in healthy individuals within a narrow range, although there is a growing list of conditions where zinc homeostasis is known to be affected.³ WHO/UNICEF/IAEA/IZiNCG recommend zinc status of populations is assessed through and the measurement of serum or plasma zinc concentration.^{4,5}

The reference range for plasma zinc levels is 11-15µmol/L (70-150 µg/dL) with a lower cut-off for morning-non fasting plasma zinc are 10.5µmol/L (66 µg/dL) in females and 11µmol/L (70 µg/dL) in males.⁶

Zinc plays an essential role in both structure and function of a range of proteins, transcription factors, enzymes, hormone receptor sites, and surface membranes in the body. It is also involved in gene expression, signal transduction and can potentiate apoptosis.⁷ Zinc is essential to the normal functioning of immunity, particularly neutrophils, natural killer cells, and lymphocytes, as well as for the skin barrier.⁸

In the absence of clinical signs or reliable sensitive and specific laboratory investigations, evaluation of deficiency is challenging.

Zinc may result from inadequate dietary intake, or increased losses.⁹ However, a concomitant intake of a potent inhibitor of zinc absorption are likely the most common causative factor such as unrefined cereals, nuts and legumes which contain phytic acid.¹⁰

Materials and Methods

This paper reviews reported serum zinc levels in a range of skin disorders. A review of literature for the previous five years was undertaken through searches using the PubMed® site, Google® Scholar™, and Cochrane search engines. The subject was human skin disorders associated with documented zinc deficiency. Studies reviewed were in English language, the search words were serum/plasma zinc level and the dermatoses mentioned in this review. In addition to skin pathologies which are known to be caused by mutations of zinc transporters, many inflammatory, autoimmune and pigmentary dermatological conditions have been suggested to be associated low serum zinc. The study designs included controlled, cross sectional, analytic and observational, that mainly address serum zinc concentration as an index of zinc status. Studies that evaluated other trace elements and

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micronutrients also included, however, only the outcome of zinc level result in relation to dermatoses was interpreted in this review. The outcome of zinc level in the hair or tissue were not interpreted. The results of the study are reported below.

Psoriasis

Psoriasis is characterized externally by plaques and scaly papules. The aetiology is complex, multifactorial, and poorly understood. In addition to skin and joints, psoriasis is associated with metabolic syndrome, cardiovascular disease, obesity, and mental

diseases.¹¹⁻¹³ Five studies were included in this review, that investigated the correlation between serum zinc level and psoriasis with different levels of severity. Three studies reported a significant decrease in the mean serum level of zinc in patients exhibiting mild, moderate and severe disease compared to controls.¹⁴⁻¹⁶ Two studies examined the copper/zinc ratio and both showed a higher copper/zinc ratio in patients with psoriasis compared to controls.^{17,18}

Atopic dermatitis

Atopic dermatitis is a chronic, relapsing inflammatory disorder of the skin presenting as eczematous skin plaques with lichenification, xerosis and severe pruritus.^{19,20} Again, the aetiology of the condition is poorly understood, but both genetic and environmental factors are recognized.²¹ Studies have linked the defective skin barrier and altered immune responses with a filaggrin gene mutation.²² The role of zinc as a trace element in Atopic Dermatitis has been the subject of a limited number of studies. Three studies, one controlled and two observational, tested serum zinc level in children with varying severity of atopic dermatitis and concluded a strong correlation between zinc levels and the severity of atopic dermatitis which was statistically significant.²³⁻²⁶ However, Esenboga *et al.* in their controlled study, concluded that serum zinc levels did not change with the severity of the disease, nor did the presence of atopy influence serum zinc levels among other trace element tested.²⁷

Pityriasis alba

Pityriasis alba is asymptomatic, scaly ill-defined hypopigmented skin patches, mainly affecting children aged >15 years. The pathogenesis of PA is not yet understood; it often is found with atopic dermatitis and is perceived as a milder form. It occurs more commonly in individuals with darker skin complexion. Other potential risk factors are xerosis, and mineral deficiencies.^{28,29}

Two recent controlled studies evaluated the zinc level in children with pityriasis alba, and demonstrated serum Zinc was lower in patients with PA than controls. Further it correlated significantly with both the number and size of lesions.³⁰ Zinc deficiency was found to increase the risk of pityriasis alba by more than 15 folds.³¹

Androgenic alopecia

Androgenic alopecia (male pattern baldness), is the most common cause of progressive hair loss. Around 30% of Caucasian men will experience it around age 30 years, 50% by age 50 and 80% by the age of 70 years.³² There are variable pathogenetic pathways leading to hair loss, including genetic and non-genetic factors.³³ Five studies were found. All tested serum zinc levels in relation to androgenetic alopecia. One study involved females with androgenetic alopecia serum zinc levels in the patient group were significantly lower than that in the control.³⁴ Another study showed that females with the Ludwig clinical pattern had lower plasma zinc levels.³⁵

Kondrakhina *et al.*³⁶ in his case-controlled study that enrolled males with androgenetic alopecia, studied many nutrient parameters, however, differences were shown in zinc content only. El Esway *et al.* similarly tested males and demonstrated a similar outcome. However, a non-significant relationship was found between the grade of alopecia and zinc level.³⁷ Gowda involved other non-scarring hair loss problem like telogen effluvium and alopecia areata and detect for other micronutrients, nevertheless, zinc deficiency was seen in 11.76% of participants with MPHL, and no significant difference in other micronutrients was observed between micronutrient levels and androgenetic alopecia.³⁸

Telogen effluvium

Telogen effluvium is diffuse non-scarring hair loss, caused by any disruption of hair cycle occurring as a reaction pattern to various physical or mental stressors and resulting in increased, synchronized telogen hair shedding.^{39,40}

Data from studies are conflicting. Four studies in females with telogen effluvium were located, three of which showed no statistical difference between patients and controls.⁴¹⁻⁴³ However, in one study from Bangladesh, the authors concluded that zinc level was significantly lower in telogen effluvium patients.⁴⁴

Alopecia areata

Alopecia areata is a non-scarring, autoimmune, inflammatory hair loss occurring most commonly on the scalp and/or the body. Etiology and pathogenesis are not understood but a complex interplay

between environmental and genetic factors is currently thought to lead to the development of alopecia areata. Research has focussed on whether serum levels of micronutrients are different in these patients.⁴⁵ Histopathology reveals an increase in catagen and telogen follicles, with inflammatory lymphocytic infiltration in the peribulbar region considered characteristic.⁴⁶

Four studies were identified for this review; three were controlled studies that evaluated serum zinc in alopecia areata patients.^{47,48} Zinc level was significantly lower in patients than controls with a significant correlation both between occurrence and duration of alopecia and serum Zinc.⁴⁹ Conversely, in a cross-sectional study for alopecia areata where zinc level was documented in 22 patients, only one patient was reported to be zinc deficient.⁵⁰

Vitiligo

Vitiligo is a common depigmenting disorder affecting the skin and hair with 0.1-2% incidence rate.^{51,52} The cause appears to be a loss of functional melanocytes. It is generally agreed that there is an absence of functional melanocytes as result of autoimmune destruction. The etiology is multifactorial and has polygenic inheritance.^{53,54}

The seven studies included in this review documented that patients with vitiligo had serum zinc levels significantly lower than in healthy controls.⁵⁵⁻⁵⁹ There was also a negative correlation between vitiligo extent and severity and serum zinc levels.⁶⁰

Mirnezami and Rahimi⁶¹ observed significantly different zinc levels in patients with generalized vitiligo and the controls, and correlated lower serum zinc levels with disease duration. They further demonstrated a negative relationship between serum zinc level and the age of the patient with vitiligo.

Acne vulgaris

Acne vulgaris is a common skin disorder characterized by inflammation of the sebaceous glands with follicular unit keratin obstruction which leads to the formation of acne lesions primarily on the face, chest and back.⁶²⁻⁶⁴ Four involved mechanisms include follicular proliferation with ruptures, sebum production, inflammation, and the presence of *Cutibacterium acnes* which induces inflammation.^{51,65}

In the last five years eight studies were identified that measured serum zinc level in patients with acne. Data are conflicting as

five of these studies concluded significant differences in serum zinc levels between acne and control groups.⁶⁶⁻⁶⁹ Otami⁷⁰ stated that serum zinc levels significantly varied between mild and the moderate–severe acne group, as the deficiency was more evident in higher grade acne. Conversely, a controlled study with 200 patients tested, found no correlation between zinc level and presentation or severity of acne, except that in females, acne severity was affected by zinc level.⁷¹ Two other studies have also failed to identify a relationship between serum zinc level and acne.^{72,73}

Hidradenitis suppurativa

Hidradenitis suppurativa, is an inflammatory disorder affecting around 1% of the population.⁷⁴ It is characterized by inflamed nodules and abscesses, complicated with scarring and sinuses particularly in intertriginous areas. The severity varies between patients and is categorized into 3 stages based on the presence of sinus tracts and scarring in a classification proposed by Hurly in 1989.⁷⁵ Due to the associated pain, mobility restriction, purulence and systemic involvement, the disease can profoundly affect the quality of life.^{76,77} In a large controlled study that tested serum zinc level in 122 patients with different stages of Hs and 122 controls, Low serum zinc levels were found in patients graded Hurley stage III.⁷⁵

Seborrheic dermatitis

Seborrheic dermatitis is a common inflammatory skin disease with unknown etiology and a chronic relapsing course. Colonisation with *Malassezia furfur*, active sebaceous gland, hormones, dysregulation of the immune system and external factors contribute to the pathogenesis of seborrheic dermatitis.^{78,79} It was postulated that zinc is known to be involved in many biological processes that appear to contribute to the development of seborrheic dermatitis, so zinc level was investigated in controlled studies of patients. Three studies were found, two of which found no significant difference between patients and controls,⁸⁰ despite the lower concentrations measured in the patients group.⁸¹ However, Karabay and Cerman⁸² in their controlled study concluded that significantly lower serum zinc levels were found in patients than in controls, although no correlation with severity was detected.

Melasma

Melasma is an acquired hyperpigmentation skin disorder that is caused by dysfunction of melanogenesis. Zinc has a role in anti-oxidative and anti-inflammatory processes including melanogenesis. Four studies were included, two studies validated a significant correlation between melasma and zinc deficiency and high negative correlation between serum zinc level and both modified Melasma Area Severity Index (mMASI) and duration of melasma was also proven,^{83,84} while other controlled study found the difference was not statistically significant between patients and controls.⁸⁵ An observational analytic study by Rambe⁸⁶ also stated that there was no significant relationship between serum zinc levels and the severity of disease in 30 melasma patients.

Discussion

Psoriasis

The studies in this review were consistent with the data from a 2019 metanalysis that analyzed studies from 1989 to 2015, and confirmed that serum zinc levels were generally decreased in patients with psoriasis.⁸⁷

However, the results in this review contradict with an earlier study that showed that serum zinc levels were increased in patients with psoriasis.⁸⁸ Other earlier studies proved no significant difference of zinc level between patients and controls.⁸⁹⁻⁹²

Psoriasis is characterised by hyperproliferation of keratinocytes with failure of differentiation. Zinc is an essential component of processes in protein synthesis, DNA and RNA synthesis and repair, and regulation of enzymatic processes including scavenging of free radicals.⁹³ In human keratinocyte culture, zinc and its transporter ZIP2 are found in the epidermis and closely associated with the differentiation of keratinocytes and cell turnover of epidermal layers.⁹⁴ Zinc can impact psoriasis by means of regulating keratinization in the epithelium, enzymatic and immunological functioning.⁹⁵

Atopic dermatitis

The limited number of studies in this review, demonstrated a strong correlation between low zinc levels and atopic dermatitis severity. Low serum zinc levels increase the risk of severe atopic dermatitis. This was in line with recent review of earlier

studies that also concluded that low serum, hair and erythrocyte zinc levels are associated with atopic dermatitis.⁹⁶

A recent *in vitro* study has tested the effect of zinc supplementation on the Th1-driven reaction in mixed lymphocyte cultures. In physiological dose, zinc supplementation was associated with a significant reduction in cell proliferation and pro-inflammatory cytokine production following reactivation, compared to untreated controls.⁹⁷

This is consistent with many studies, some in murine samples, that proved zinc deficiency can cause inhibition of the anti-inflammatory processes, and how can that affect Th2 cytokines, which has significant role in the pathogenesis of AD, and thus suggests a correlation.^{98,99}

Low zinc levels can also disrupt the integrity of the membrane barrier, which can further affect atopic dermatitis progression.⁹⁷⁻¹⁰⁰

Hair loss

The relationship between zinc and hair loss has been researched extensively in literature, with results broadly consistent with current findings. A meta-analysis that searched published data up to 30 April 2016 looking at trace elements and alopecia areata, suggested that low serum levels of zinc were risk factors for alopecia areata.¹⁰¹ A review article on zinc in patients with alopecia areata showed in 4/6 4 out of 6 case–control studies, that zinc levels were lower in patients than controls.¹⁰² In another study of four types of hair loss, all groups with hair loss had statistically lower zinc concentration.¹⁰³ However, a study in males with androgenic alopecia did not find a difference in zinc levels between patients and controls.¹⁰⁴ Zinc is an element of finger motifs for variant transcription factors that use hedgehog signaling to control hair growth. Its inhibitory role on apoptosis-related endonucleases also inhibits catagen.^{105,106} Paus *et al.*¹⁰⁷ described zinc to be is a potent immunomodulator of hair follicles and also, an inhibitor of hair follicle regression, accelerating follicle recovery. This suggests zinc is essential to the hair growth cycle rather than as a component of the hair *per se*.

Vitiligo

The role of zinc deficiency in vitiligo has been validated in many studies. All are consistent and support two earlier studies, the first which was a review published in 2014 in Chinese literature that included data from 16 studies including 891 patients with vitiligo and 1682 healthy controls.¹⁰⁸ Another metanalysis involved 11 studies

including 570 vitiligo cases and 580 controls also confirmed that lower zinc level can increase the risk of vitiligo.¹⁰⁹

The proposed mechanism through which zinc deficiency develops is that inflammatory cytokines promote the expression of zinc transporters, which mobilises zinc into cells resulting in hypozincemia and augmentation of the inflammatory process. The cytokines IL-6 and IL-17 promote the expression of the zinc transporters ZIP14 and ZIP8.^{110,111}

This correlation between interleukins and zinc metabolism was further supported in another recent study in vitiligo patients.⁵⁸ Zinc, among other micronutrients, has a key role in the process of melanogenesis and specifically the final stage of eumelanin formation. It is involved in catalysis of 5, 6-dihydroxy indole-2-carboxylic acid production and increased polymerisation to eumelanin.^{112,113}

Pilosebaceous disorders

Zinc levels in the sera of patients with acne are significantly lower, and this was validated in the majority of studies identified from the last five years,⁶⁹⁻⁷³ this also was confirmed by a recent review in 2020 that concluded the correlation of low serum zinc level and suggested that zinc is effective in the treatment of acne as an adjuvant or as monotherapy.¹¹⁴ Three studies did not find this association,⁷⁴⁻⁷⁶ nor did an earlier study.¹¹⁵

The relation between zinc and acne can be explained through its inhibitory role on tumor necrosis factor- (TNF-) α and IL-

6.^{116,117} Furthermore, in keratinocyte cell culture studies zinc gluconate decreased IL-8 secretion through inhibition of TLR2 and TLR4 expression, which have all proven to have a significant role in acne pathogenesis.¹¹⁸ Zinc also has a regulatory role in vitamin A metabolism through protein synthesis and zinc dependent retinol dehydrogenase enzyme.¹¹⁹

Low serum zinc levels may increase androgen production,¹²⁰ which in turn affects sebaceous gland activity. Thus, zinc was considered a contributory factor in the pathogenesis of several inflammatory skin diseases associated with dysregulation of innate immunity, such as inflammatory acne and hidradenitis suppurativa.

In this update, the correlation between low zinc level and hidradenitis suppurativa was evident in patients at Hurly stage III, primarily in one study in 2018,⁸⁰ which was consistent with the data from a recent systematic review that revealed the association between low serum zinc levels and increased lesion count in hidradenitis suppurativa.¹²¹

In regards to seborrheic dermatitis, 2 studies concluded no significant relationship to zinc level,^{83,84} whilst one correlated disease activity to serum zinc level.⁸⁵

Zinc deficiency

Zinc deficiency may be either inherited or acquired, with similar clinical cutaneous manifestation. Acrodermatitis enteropathica (Figure 1), the inherited form, classically presents during infancy and characterized by diarrhea, dermatitis and alopecia.¹²² The acquired form is caused by reduced zinc intake or absorption due to other causes, like restricted or deficient diets and malabsorption states.¹²³ Bel-Serrat *et al.*, is a useful detailed summary of factors affecting zinc absorption and quantification of all routes of zinc loss.³ When depletion is sufficient the rash develops over a few days and is mainly acral and periorificial in location. It presents as eczematous scaly plaques that progress into vesicles, bullae, or pustules, with underlying scald like erythema or fissuring, often with symmetrical distribution around the mid-line.¹²⁴ Similarly as proven in this review, many inflammatory and autoimmune skin diseases can drastically affect the skin and produce changes in zinc losses and absorption. The treatment of acrodermatitis enteropathica is supplementation of oral zinc, the recommended dose is between 1 and 3 mg/kg/day of elemental zinc.¹²⁵⁻¹²⁷

Conclusions

It will be valuable to apply knowledge about zinc levels in skin disorders, and the known roles of zinc in cell biology and body functions toward future treatment strategies in skin disorders.

Zinc status is frequently overlooked and not routinely tested; thus, it is recommended to identify skin disorders that are associated with zinc deficiency, and test serum zinc to define zinc status while initiating the treatment plan. Zinc therapy as an adjuvant is an attractive choice due to its availability, cost-effectiveness and low side effect profile.

Researchers need to integrate existing data into further large-scale interventional studies further investigating the role of zinc in diverse cutaneous disorders, in order to consolidate the role of zinc supplement as a future, hopefully evidence-based therapeutic intervention.

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Figure 1. Well-defined, crusted erosions on the neck and around the ear, with alopecia on the scalp, used with permission.¹²⁶

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