Review paper

Zinc: an undervalued microelement in research and treatment

Zofia Hawrysz, Anna Woźniacka

Department of Dermatology and Venereology, Medical University of Lodz, Lodz, Poland

Adv Dermatol Allergol 2023; XL (2): 208–214
DOI: https://doi.org/10.5114/ada.2023.127639

Abstract

Recent years have seen a growing interest in a healthy lifestyle, particularly nutrition. An important component of a balanced diet is the microelement content. Zinc is the second most abundant trace element, after iron. It has antioxidant and immunomodulatory functions, and plays important roles in the pathogenesis of various diseases, including dermatoses. Individuals with a zinc deficiency may present with nonspecific erythematous, pustular, erosive, and bullous lesions as well as alopecia, nail dystrophy, and a variety of systemic symptoms. Any individual assessment of zinc levels should consider risk factors for deficiency, clinical symptoms, type of diet, and results of laboratory analyses. Recent research has shed light on the systemic and topical effects of zinc, indicating the value of its supplementation for many conditions.

Key words: acrodermatitis enteropathica, alopecia, deficiency, wound healing, zinc.

Introduction

In recent years, following a healthy lifestyle has become extremely popular. An important part of such a lifestyle is a balanced diet, which is essential for protecting the body from diseases and maintaining well-being. The important role played by microelements in the proper functioning of the human body has been emphasized in many studies.

The second most abundant trace element, after iron, is zinc. It plays an important role in the body by participating in various processes, both at the cellular and systemic level, contributing to cell proliferation, differentiation and apoptosis, DNA and RNA synthesis and repair, and cell membrane stabilization [1–6]. Zinc also regulates immunological processes, affecting hematopoiesis, lymphocyte maturation and differentiation and antibody production [4, 7–10]. It is a cofactor of over 300 enzymes involved in wound healing, a component of proteins including collagen and a regulator of genetic expression [7, 8, 10]. It is also involved in neurotransmission [11], affecting learning and memory processes [10]. In addition, it participates in maintaining normal glucose levels by sensitizing cells to insulin. Zinc also plays an important role in the synthesis of nitric oxide, which influences the relaxation of blood vessel muscles and contributes to their expansion.

Epidemiological studies have found low dietary zinc to be associated with an elevated cancer risk [5], being involved in the pathogenesis of neoplastic diseases such as lung cancer, pancreatic cancer, breast cancer and hepatocellular carcinoma [2, 9, 10, 12]. Zinc deficiency is also associated with malaria, tuberculosis, viral infections including HIV and HCV [2, 8, 9, 13], and the development of atherosclerosis, schizophrenia, depression, Alzheimer's disease, multiple sclerosis, diabetes or Ehlers-Danlos syndrome [2, 9, 10, 14, 15].

For this reason, many people took zinc supplements during the SARS-CoV-2 pandemic; however, it has not been confirmed that the course of COVID-19 disease is milder in zinc-supplemented individuals [16, 17]. Nevertheless, it has been proven to be effective in treating childhood diarrhoea, Wilson's disease, age-related macular degeneration [7, 9], and hepatic encephalopathy [12].

Metabolism

As the human body is unable to synthesize zinc, it is necessary to provide the mineral in the diet or as pharmacological supplementation. It is estimated that the total zinc content in the human body is about 1.5–3 g [9, 10, 18, 19]. The highest tissue Zn concentrations are found in the skeletal muscle (about 60%), bone (about 30%), skin

Address for correspondence: Zofia Hawrysz MD, Department of Dermatology and Venereology, Medical University of Lodz, Plac Hallera 1, building No. 6, 90-647 Lodz, Poland, phone: +48 42 639 30 93, e-mail: zofia.hawrysz@gmail.com
Received: 9.08.2022, **accepted:** 18.08.2022.

(about 5%, mostly in the epidermis) and liver (about 5%) [2, 4, 19]. There is also a relatively small amount of Zn in blood serum (about 0.1% of the total zinc stores) [13, 20, 21]. However, the human body does not have a specific store for the element [2, 3, 6, 18, 22]. Transcriptional mechanisms and transmembrane transport modulate zinc homeostasis, and these protect the body from the effects of excess dietary zinc, or its deficiency, to some extent [4, 8]. It is necessary to take in optimal doses of zinc, adequate for daily requirements, to maintain its homeostasis [6, 10]. Zinc is absorbed in the duodenum and proximal jejunum, while it is excreted mostly in the faeces, and to a lesser extent through renal filtration and surface losses [3, 7, 13, 18]. The rate of absorption is concentration dependent, and rises with increasing dietary zinc content [13]. The total pool of the element in the body also affects intestinal absorption, which is enhanced in zinc-deficient individuals [13].

Assessment of zinc stores in the body

Blood serum analysis

In clinical practice, the most commonly used Zn assay is serum Zn concentration. Normal values are assumed to be within the range of 80–100 µg/dl (12–15 µmol/l) [23]. Although serum testing is technically easy, the interpretation of the results has some limitations [7, 13, 21, 24–26]. Intracellular zinc ion content may be low despite normal serum values. This is due to the possibility of Zn release from cells in states of severe deficiency [24, 27]. On the other hand, low blood zinc content does not necessarily indicate a general deficiency, but only reflects a physiological response to the inflammatory processes taking place in the organism [13, 20, 28]. For example, during the acute phase of the immune response, zinc is transported from the serum to the liver, leading to hypozincemia [9, 13, 15, 27]. The resolution of inflammation leads to the release of Zn from tissues into the blood [9].

In serum, zinc binds to albumin, α_2-macroglobulin and transferrin [8, 9]. It is estimated that free Zn^{2+} ions in serum account for only about 0.0001% of the total body Zn stores [8, 10]; albumins bind approximately 70–80% of the pool of zinc circulating in the blood [13, 29, 30].

Serum zinc levels are reduced during hypoalbuminemia [13, 20, 22], through *inter alia* increased urinary excretion [12, 29]. A similar effect occurs during hormonal treatments, including glucocorticosteroids, when Zn is transported into cells [13, 27].

Zinc concentrations increase as a result of intravascular and extravascular haemolysis following its release from erythrocytes [20, 27, 31]. Serum Zn levels also demonstrate as much as 20% diurnal variability [13, 23]. In addition, zincemia rapidly increases after a meal, before decreasing after 2–4 h [25]; following this, serum Zn concentration gradually increases until the next meal [13]. Furthermore, the highest blood serum Zn values are found in the morning, after several hours of fasting [13, 23].

Urine analysis

To determine the zinc content in urine, it is necessary to perform a 24-hour urine collection. It is assumed that the daily amount of zinc excreted in urine should be within the range of 300–600 µg, i.e. 4.6–9.2 µmol/24 h. Urine zinc levels may vary over the day and these depend on both diuresis and the amount of Zn in the diet. Hyperzincuria may occur due to high dietary zinc supply or poor absorption in the small intestine, which in turn may be due to alcoholism, cirrhosis, acute porphyria, type II diabetes mellitus, lead poisoning, proteinuria, and treatment with chelating compounds [31]. Starvation, intense exercise and trauma can also increase urinary zinc elimination [32]. In contrast, in most zinc-deficient individuals, urinary excretion is reduced in order to limit excessive loss [27, 33]. However, it should be noted that in conditions such as liver cirrhosis, chronic kidney disease or sickle cell anaemia, it is paradoxically hyperzincuria that presents as a sign of zinc deficiency [31]. Hence, determination of urinary Zn levels can sometimes be inconclusive and difficult to interpret [22, 33].

Hair analysis

Hair is another substrate that can potentially be used to assess zinc content in the human body. Sample collection is pain free and non-invasive [28, 34]. Hair Zn concentration accurately reflects tissue zinc stores, and can present a long-term picture of zinc content for up to several months prior to sample collection [28, 33, 34]. Therefore, it is not suitable for a comprehensive assessment of a patient's current zinc status. In addition, hair zinc content is also influenced by factors such as age, gender, hair growth rate and season [28, 32]. Furthermore, in conditions of retarded hair growth, e.g. in malnutrition or severe zinc deficiency, Zn hair concentration may paradoxically be normal or even high [11]. Therefore, despite its advantages, no standardized procedures have been developed for hair collection, preparation and analysis [32], and its clinical usefulness and reference values remain unclear [20, 26, 32, 35, 36].

Zinc deficiency

It is estimated that zinc deficiency may affect up to 17% of people worldwide [8, 10], most of whom being from Africa or Asia [8]. Zn deficiency is rarely diagnosed in developed countries, and is mainly observed in elderly people with multiple comorbidities, especially autoimmune or inflammatory diseases [8, 9, 37]. The condition can be caused by increased demand, decreased supply, impaired absorption, or excessive loss [3, 10, 27]. The highest demand for Zn occurs in pregnant and lactating

women, in children and in the elderly [3, 13]. Zn deficiency may also result from a deficient diet, with limited or no animal protein, in malnourished individuals, and in those with inflammatory bowel diseases or cirrhosis [7, 8, 10]. Chronic diarrhoea, parenteral nutrition or alcohol abuse may also contribute to the development of zinc deficiency [7, 8].

Mild zinc deficiency

The possible symptoms of zinc deficiency are presented in Table 1. Mild and moderate zinc deficiency is characterized by non-specific symptoms: roughened skin, alopecia, nail dystrophy, loss of appetite, impaired wound healing, taste and smell disorders or photophobia [3, 7, 20, 27, 38, 39]. Zinc-deficient individuals demonstrate increased susceptibility to infections associated with lymphopenia, abnormal lymphocyte function, thymic atrophy and oxidative stress [3, 6, 8, 9]. In children, Zn deficiency is associated with growth retardation and delayed puberty [3, 20, 38].

Table 1. Symptoms of zinc deficiency

• Dryness and roughness of skin
• Skin lesions: erythema, scaling, bullae, pustules, erosions, ulcerations
• Telogen effluvium
• Nail dystrophy
• Loss of appetite
• Impaired wound healing
• Recurring infections
• Smell and taste impairment
• Photophobia
• Diarrhoea
• Loss of body weight
• Growth retardation and delayed puberty
• Hypogonadism and defective spermatogenesis in males
• Neurological and behavioural disorders

Acrodermatitis enteropathica

Acrodermatitis enteropathica (AE) is a disease associated with a severe zinc deficiency caused by a genetic defect in the cellular transporter ZIP4 (Zrt/Irt-like protein 4), which is responsible for intestinal absorption [2, 4, 9]. If undiagnosed and untreated, AE can lead to death [3, 4, 6, 9]. The condition is inherited in an autosomal recessive pattern. Its incidence is estimated at about 1 in 500,000 children [19]. AE manifests soon after the cessation of breastfeeding, or earlier if the child is fed with formula milk [33, 39]: breast milk generally provides a sufficient source of zinc for the first 6 months of life [33].

The most common symptoms in children are diarrhoea, weight loss and recurrent infections [13, 26]. Skin lesions often appear later in the course of the disease [13]. In most cases, the lesions are erythematous, pustular or bullous [3, 20, 33, 38], and because of scaling, they might resemble psoriatic plaques [20, 33, 39] (Figure 1). Erosions or non-healing ulcers may also be present [13, 38] (Figures 2, 3). The skin lesions are sharply demarcated from the surrounding skin [33]. Signs of bacterial and/or yeast infection are also frequently observed. Typically, the skin lesions are centred around natural body orifices (anogenital, perioral region) and on acral areas [18, 19, 20, 26, 33, 38, 39] suggesting that their development may be influenced by irritants such as saliva, urine, faeces or external factors [19, 38]. It has been found that zinc-deficient individuals demonstrate lower numbers of Langerhans cells in the skin, due to a decrease in tumor growth factor-β1 expression [10, 19]; this causes an abnormal release of adenosine triphosphate

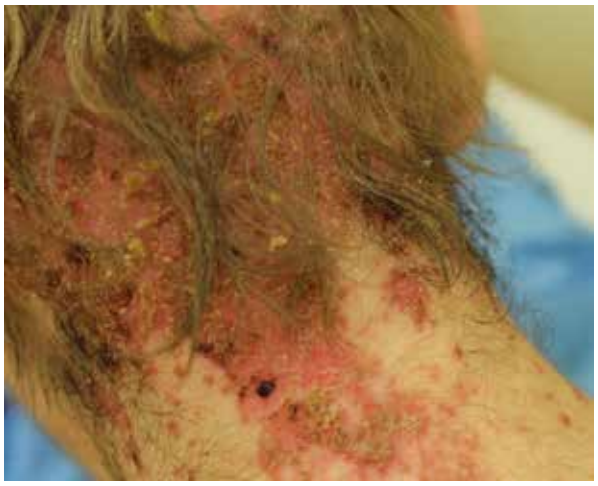

Figure 1. Erythematous, scaly patches, crusts and alopecia

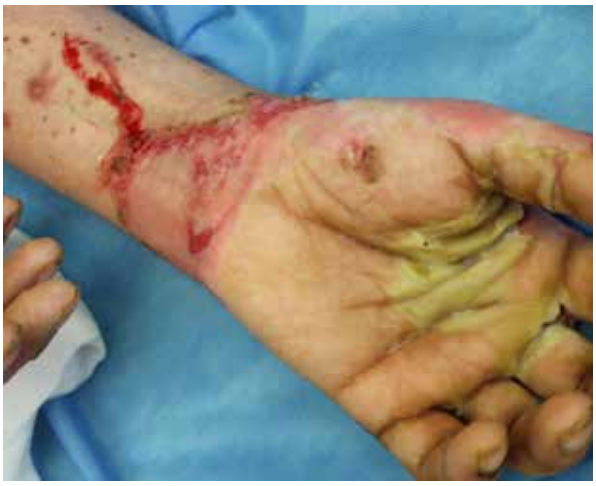

Figure 2. Erosions, vesicles and bullae with signs of bacterial infection

from keratinocytes in response to external irritants, resulting in the development of irritant contact dermatitis [19].

Diffuse telogen effluvium and nail dystrophy are also common in AE [3, 7, 19]. It has been shown that patients with telogen effluvium not suffering from AE also have lower serum zinc concentrations compared to healthy individuals, and zinc supplementation enables hair to regrow [19]. Presumably, as a result of Zn deficiency, the process of keratinization in hair is disturbed and the telogen phase occurs prematurely [19]. However, the exact mechanisms of this phenomenon have not been established [19].

The histopathological examination of the skin lesions reveals non-specific features which are also characteristic of necrotic migratory erythema or vitamin B_3 deficiency [19, 33], with common findings being ballooning degeneration of keratinocytes, parakeratosis, thick chromatin aggregates, acanthosis, focal acantholysis, decreased stratum granulosum and increased mitosis [19, 33, 40, 41]. Dilated capillaries and lymphohistiocytic infiltration in the papillary dermis may also be present [33, 41].

Zinc is a key element for the proper synthesis, storage and secretion of male sex hormones [10]. In men, Zn deficiency can lead to symptoms of hypogonadism and impaired spermatogenesis [3, 7, 10, 20]. In addition, cognitive decline, memory and behavioural disorders are sometimes observed in patients of both sexes [10, 13].

The basic treatment of acquired zinc deficiency is Zn supplementation in the dosage of 0.5–1 mg/kg b.w./day [9, 20]. In most patients, a few months' therapy is sufficient to achieve optimal Zn levels. However, in *acrodermatitis enteropathica,* patients require higher doses of zinc (3 mg/kg b.w./day) and the supplementation must be maintained throughout life [20, 33, 39].

Zinc and chronic leg ulcers

Ulceration is, by definition, the loss of the full thickness of skin [42]. It is estimated that chronic venous insufficiency may account for 50–80% of all leg ulcers, occurring in 0.3–1% of the population in Western countries, and even more often in the elderly [25, 42–44]. Leg ulcerations also commonly arise in association with arterial diseases, diabetes and pressure [44, 45]. Healing time is approximately 6 to 12 months, and the majority of patients (50–70%) have recurrent lesions [43, 44, 46, 47]. The accompanying pain and reduced mobility leads to a significantly reduced quality of life.

Many zinc-dependent proteins, such as metallothioneins, metalloproteinases, integrins, alkaline phosphatase and transcription factors, are involved in wound healing [4, 19, 45]. Wound healing is a multistep process consisting of inflammation, proliferation, angiogenesis, epithelialization, wound contraction and remodelling [4, 45]. Zinc regulates inflammation, accelerates epidermis restoration and collagen synthesis in the ulcer, and stimulates fibroblast and keratinocyte proliferation [1, 10, 48].

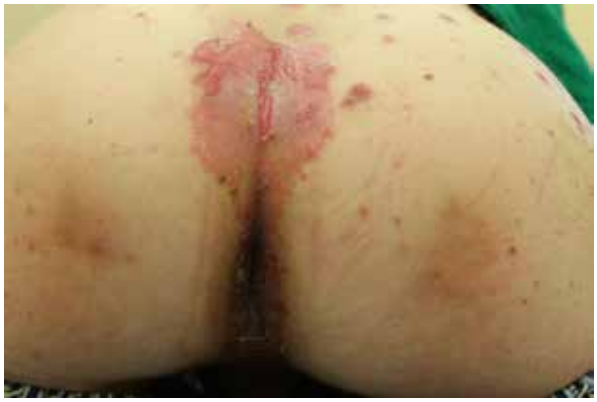

Figure 3. Erythema, erosions and scaly papules

Many studies report reduced serum zinc levels in patients with chronic ulcers [49–51]. In the 1970s, Henzel *et al*. observed that patients with significantly slower healing of postoperative wounds showed lower levels of zinc in serum, wound margins and granulation tissue [52].

However, there is still insufficient evidence to suggest that oral Zn supplementation or topical preparations improve healing of ulcerations, especially in patients with normal Zn levels [4, 7, 33, 53]. A 2014 meta-analysis of six studies reached no clear conclusions regarding the usefulness of zinc supplementation in ulcer healing; still, it should be emphasized that the authors only analysed a small number of studies, conducted many years ago on relatively small groups [25].

Zinc in the pathogenesis of other dermatoses

It is likely that zinc deficiency also plays a role in the pathogenesis of other skin diseases by increasing oxidative stress and influencing the immune system [54]. Significantly lower serum and hair Zn concentrations have been noted in patients with atopic dermatitis (AD) compared to healthy populations [28, 55–59]. However, there is no consensus whether zinc supplementation reduces the severity of clinical symptoms of AD, or the need for oral and topical medications [28, 55, 58–61]. Similarly, lower serum Zn levels have been found in patients with seborrheic dermatitis [54], Behcet's disease [62], acne vulgaris [63], melasma [64], alopecia areata [65], and oral lichen planus [66]. Interestingly, patients with erosive oral lichen planus demonstrated lower mean serum Zn levels than those with the non-erosive type [66]. Zinc deficiency has also been observed in bullous pemphigoid [65], epidermolysis bullosa [67] and pemphigus vulgaris [68].

Excess zinc

Due to the low toxicity of zinc, especially when administered orally, overdose is relatively rare [14, 27]. Excess Zn may cause nausea, vomiting, headache, dizziness

and fatigue, and it may result in anaemia, neutropenia or decreased levels of high-density lipoproteins if the recommended dose is significantly exceeded [3, 7, 20, 27, 28]. Paradoxically, impaired immune function may be a consequence of both Zn deficiency and excess [5, 9]. Chronic high zinc intake may also result in a copper deficiency as it impairs copper absorption in the gastrointestinal tract [8, 18, 28]. In individuals with optimal body Zn concentrations, 40 mg/day is considered the upper limit of zinc intake tolerated by adults [10, 35].

Supplementation and diet

The recommended daily intake of zinc by healthy individuals is not clearly determined. However, the World Health Organization (WHO) recommends values of 3–14 mg/day in adults based on age, sex and dietary phytate content [2]. The US Institute of Medicine recommends a zinc intake of 8 mg/day for women and 11 mg/day for men [10, 35, 39].

The most abundant sources of dietary zinc include fish and seafood (especially oysters), red meat, poultry, legumes, pumpkin and sunflower seeds, eggs, dairy products, and nuts [2, 7, 9, 10, 39]. The form of zinc intake and the dietary composition play a very important role as a meal has much lower zinc bioavailability than water-based solution [8, 11, 13]. On the other hand, the amount of protein in a meal is positively correlated with zinc absorption, with the exception of the milk protein casein [13, 69]. In addition, as Zn from animal products is absorbed more efficiently, vegetarians and vegans are more likely to be zinc deficient [2, 13, 20, 39].

Phytates are phytic acid salts and an important storage of phosphates and minerals [13, 70]. As chelators of zinc ions, they limit its absorption from the gastrointestinal tract, forming complexes that are difficult to dissolve [8, 9, 13, 69, 70]. Legume seeds and cereals are products rich in phytates [8, 13]. Whole grain products are particularly rich in phytates, which is found in the aleurone layer and the germ [70]. However, milling, thermal processing, leavening of bread, germination, and fermentation reduce the adverse effects of phytates, thus improving zinc bioavailability [13, 69].

High doses of iron (Fe), especially in water-based solution, can interfere with zinc absorption if administered simultaneously and with a high Fe/Zn ratio [69]. No such effect is observed for the iron contained in foods [13]. Thus, it seems that even long-term use of iron supplements does not affect zinc absorption, given appropriate doses and intervals in their intake [69].

Calcium supplements and calcium-fortified foods may also have a negative impact on zinc absorption [70]. However, the mechanism is complex and probably not associated with calcium itself, rather than the potential augmentation of the inhibitory impact of phytates [13].

Zinc in topical formulations

Topical formulations containing Zn, mainly in the form of 1–15% zinc oxide or sulfate, are commonly used to support the treatment of ulcers, acne vulgaris, rosacea or diaper rash [7, 39]. It is also used as an ingredient in sunscreens as zinc oxide provides broad-spectrum protection against UV radiation [39]. In high concentrations (20–25%), zinc sulfate has cytotoxic effects, inducing cell apoptosis and necrosis, which is valuable in treatment of precancerous conditions (solar keratosis, xeroderma pigmentosum) and basal cell carcinoma [39].

Topically-applied zinc acts as an astringent, debriding and antiseptic agent [3, 40]. Such formulations create a barrier film, protecting the wound from exudation, maceration and irritation of the surrounding skin [71]. However, zinc formulations are not transparent, thus the wound margin is partially obscured, making the observation of the epithelialization process difficult [71]. Local hypersensitivity reactions to zinc oxide are rare, although possible [40, 71].

Commercially available zinc paste-impregnated bandages can be used in patients with chronic venous insufficiency, and those with ulcerations [40]. These form semi-rigid dressings, which can also act as a type of compression therapy (the so-called Unna boot) [71]. Nowadays, dressings made of elastic bandages are easier to use, better fitted and provide sustained pressure, and are hence in more common use [71]. However, non-elastic materials demonstrate better hemodynamic efficiency, and thus greater elimination of venous hypertension, reduction of swelling, and better healing conditions; as such, the Polish Dermatological Society recommendations indicate a preference for zinc paste dressings in the treatment of venous ulcers at the healing stage [72].

Summary

The first reports on the important role of zinc in physiological processes date back to the early 20th century, when its content in human tissues was first determined. Despite its relatively low concentrations, Zn is known to have a considerable influence on the functioning of the human body. A number of recent studies examining the optimal concentration of zinc in serum and the mechanisms of its systemic and local effects have demonstrated the usefulness of zinc supplementation in many diseases. However, a number of questions regarding the potential use of zinc in the treatment of skin diseases still remain open.

Acknowledgments

The study was conducted in the Department of Dermatology and Venereology, Medical University of Lodz, 90-647 Lodz, Plac Hallera 1 building No. 6.

Conflict of interest

The authors declare no conflict of interest.

References

1. Heyland DK, Jones N, Cvijanovich NZ, et al. Zinc supplementation in critically ill patients: a key pharmaconutrient? JPEN J Parenter Enteral Nutr 2008; 32: 509-19.
2. Gammoh N, Rink L. Zinc in Infection and Inflammation. Nutrients 2017; 9: 624.
3. Kogan S, Sood A, Garnick M. Zinc and wound healing: a review of zinc physiology and clinical applications. Wounds 2017; 29: 102-6.
4. Lin PH, Sermersheim M, Li H, et al. Zinc in wound healing modulation. Nutrients 2017; 10: 16.
5. Skrajnowska D, Bobrowska-Korczak B. Role of zinc in immune system and anti-cancer defense mechanisms. Nutrients 2019; 11: 2273.
6. Bonaventura P, Benedetti G, Albarède F, et al. Zinc and its role in immunity and inflammation. Autoimmun Rev 2015; 14: 277-85.
7. Saper RB, Rash R. Zinc: an essential micronutrient. Am Fam Physician 2009; 79: 768-72.
8. Read SA, Obeid S, Ahlenstiel C, et al. The role of zinc in antiviral immunity. Adv Nutrition 2019; 10: 696-710.
9. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. Nutrients 2017; 9: 1286.
10. Chasapis CT, Ntoupa PSA, Spiliopoulou CA, et al. Recent aspects of the effects of zinc on human health. Arch Toxicol 2020; 94: 1443-60.
11. Gibson RS. Nutritional Assessment of Zinc status deficiency intake diet stature. https://nutritionalassessment.org/zinc/.
12. Katayama K. Zinc and protein metabolism in chronic liver diseases. Nutr Res 2020; 74: 1-9.
13. Roohani N, Hurrell R, Kelishadi R, et al. Zinc and its importance for human health: an integrative review. J Res Med Sci 2013; 18: 144-57.
14. Ruz M, Carrasco F, Rojas P, et al. Nutritional effects of zinc on metabolic syndrome and type 2 diabetes: mechanisms and main findings in human studies. Biol Trace Elem Res 2019; 188: 177-88.
15. Mezzetti A, Pierdomenico SD, Costantini F, et al. Copper/zinc ratio and systemic oxidant load: effect of aging and aging-related degenerative diseases. Free Radic Biol Med 1998; 25: 676-81.
16. Mukattash TL, Alkhalidy H, Alzu'bi B, et al. Dietary supplements intake during the second wave of COVID-19 pandemic: a multinational Middle Eastern study. Eur J Integr Med 2022; 49: 102102.
17. Li J, Cao D, Huang Y, et al. Zinc intakes and health outcomes: an umbrella review. Front Nutr 2022; 9: 798078.
18. European Food Safety Authority (EFSA), Parma, Italy. Scientific Opinion on Dietary Reference Values for zinc. EFSA J 2014; 12: 3844.
19. Ogawa Y, Kawamura T, Shimada S. Zinc and skin biology. Arch Biochem Biophys 2016; 611: 113-9.
20. Maverakis E, Fung MA, Lynch PJ, et al. Acrodermatitis enteropathica and an overview of zinc metabolism. J Am Acad Dermatol 2007; 56: 116-24.
21. Grüngreiff K, Gottstein T, Reinhold D, et al. Albumin substitution in decompensated liver cirrhosis: don't forget zinc. Nutrients 2021; 13: 4011.
22. Heintschel M, Heuberger R. The potential role of zinc supplementation on pressure injury healing in older adults: a review of the literature. Wounds 2017; 29: 56-61.
23. Hess SY, Peerson JM, King JC, et al. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull 2007; 28 (3 Suppl): S403-29.
24. Mocchegiani E, Romeo J, Malavolta M, et al. Zinc: dietary intake and impact of supplementation on immune function in elderly. Age 2013; 35: 839-60.
25. Wilkinson EA. Oral zinc for arterial and venous leg ulcers. Cochrane Database Syst Rev 2014; 2014: CD001273.
26. Hambidge M. Human zinc deficiency. J Nutr 2000; 130 (5S Suppl): 1344S-9S.
27. Livingstone C. Zinc: physiology, deficiency, and parenteral nutrition. Nutr Clin Pract 2015; 30: 371-82.
28. Kim JE, Yoo SR, Jeong MG, et al. Hair zinc levels and the efficacy of oral zinc supplementation in patients with atopic dermatitis. Acta Derm Venereol 2014; 94: 558-62.
29. Tokuyama A, Kanda E, Itano S, et al. Effect of zinc deficiency on chronic kidney disease progression and effect modification by hypoalbuminemia. PLoS One 2021; 16: e0251554.
30. Duncan A, Yacoubian C, Watson N, et al. The risk of copper deficiency in patients prescribed zinc supplements. J Clin Pathol 2015; 68: 723-5.
31. Prasad AS. Laboratory diagnosis of zinc deficiency. J Am Coll Nutr 1985; 4: 591-8.
32. King JC, Brown KH, Gibson RS, et al. Biomarkers of nutrition for development (BOND)-zinc review. J Nutr 2015; 146: 858S-85S.
33. Glutsch V, Hamm H, Goebeler M. Zinc and skin: an update. J Dtsch Dermatol Ges 2019; 17: 589-96.
34. Fedor M, Urban B, Socha K, et al. Concentration of zinc, copper, selenium, manganese, and Cu/Zn ratio in hair of children and adolescents with myopia. J Ophthalmol 2019; 2019: 5643848.
35. Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): National Academies Press (US); 2001.
36. Mikulewicz M, Chojnacka K, Gedrange T, et al. Reference values of elements in human hair: a systematic review. Environ Toxicol Pharmacol 2013; 36: 1077-86.
37. Wessels I, Rolles B, Rink L. The potential impact of zinc supplementation on COVID-19 pathogenesis. Front Immunol 2020; 11: 1712.
38. Kawamura T, Ogawa Y, Nakamura Y, et al. Severe dermatitis with loss of epidermal Langerhans cells in human and mouse zinc deficiency. J Clin Invest 2012; 122: 722-32.
39. Gupta M, Mahajan VK, Mehta KS, et al. Zinc therapy in dermatology: a review. Dermatol Res Pract 2014; 2014: 709152.
40. Lansdown AB, Mirastschijski U, Stubbs N, et al. Zinc in wound healing: theoretical, experimental, and clinical aspects. Wound Repair Regen 2007; 15: 2-16.
41. Borroni G, Brazzelli V, Vignati G, et al. Bullous lesions in acrodermatitis enteropathica. Histopathologic findings regarding two patients. Am J Dermatopathol 1992; 14: 304-9.
42. Narbutt J, Bowszyc-Dmochowska M, Kapińska-Mrowiecka M, et al. Chronic venous insufficiency – epidemiology, classification and clinical picture. Diagnostic and therapeutic recommendations of the Polish Dermatological Society. Part I. Dermatol Rev 2018; 105: 473-85.
43. Franks PJ, Barker J, Collier M, et al. Management of patients with venous leg ulcers: challenges and current best practice. J Wound Care 2016; 25 Suppl 6: S1-67.

44. Raffetto JD, Ligi D, Maniscalco R, et al. Why venous leg ulcers have difficulty healing: overview on pathophysiology, clinical consequences, and treatment. J Clin Med 2020; 10: 29.
45. Gould L, Abadir P, Brem H, et al. Chronic wound repair and healing in older adults: current status and future research. Wound Repair Regen 2015; 23: 1-13.
46. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care 2015; 4: 560-82.
47. Gillespie DL. Venous ulcer diagnosis, treatment, and prevention of recurrences. J Vasc Surg 2010; 52 (5 Suppl): 8S-14S.
48. Tenaud I, Leroy S, Chebassier N, et al. Zinc, copper and manganese enhanced keratinocyte migration through a functional modulation of keratinocyte integrins. Exp Dermatol 2000; 9: 407-16.
49. Rojas AI, Phillips TJ. Patients with chronic leg ulcers show diminished levels of vitamins A and E, carotenes, and zinc. Dermatol Surg 1999; 25: 601-4.
50. Agren MS, Strömberg HE, Rindby A, et al. Selenium, zinc, iron and copper levels in serum of patients with arterial and venous leg ulcers. Acta Derm Venereol 1986; 66: 237-40.
51. Hallböök T, Lanner E. Serum-zinc and healing of venous leg ulcers. Lancet 1972; 2: 780-2.
52. Henzel JH, DeWeese MS, Lichti EL. Zinc concentrations within healing wounds. Significance of postoperative zincuria on availability and requirements during tissue repair. Arch Surg 1970; 100: 349-57.
53. Wilkinson EA, Hawke CI. Does oral zinc aid the healing of chronic leg ulcers? A systematic literature review. Arch Dermatol 1998; 134: 1556-60.
54. Aktaş Karabay E, Aksu Çerman A. Serum zinc levels in seborrheic dermatitis: a case-control study. Turk J Med Sci 2019; 49: 1503-8.
55. Vaughn AR, Foolad N, Maarouf M, et al. Micronutrients in atopic dermatitis: a systematic review. J Altern Complement Med 2019; 25: 567-77.
56. David TJ, Wells FE, Sharpe TC, et al. Low serum zinc in children with atopic eczema. Br J Dermatol 1984; 111: 597-601.
57. Di Toro R, Galdo Capotorti G, Gialanella G, et al. Zinc and copper status of allergic children. Acta Paediatr Scand 1987; 76: 612-7.
58. Esenboga S, Cetinkaya PG, Sahiner N, et al. Infantile atopic dermatitis: serum vitamin D, zinc and TARC levels and their relationship with disease phenotype and severity. Allergol Immunopathol 2021; 49: 162-8.
59. Gray NA, Dhana A, Stein DJ, et al. Zinc and atopic dermatitis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2019; 33: 1042-50.
60. Sugiura T, Goto K, Ito K, et al. Chronic zinc toxicity in an infant who received zinc therapy for atopic dermatitis. Acta Paediatr 2005; 94: 1333-5.
61. Ewing CI, Gibbs AC, Ashcroft C, et al. Failure of oral zinc supplementation in atopic eczema. Eur J Clin Nutr 1991; 45: 507-10.
62. Saglam K, Serce AF, Yilmaz MI, et al. Trace elements and antioxidant enzymes in Behçet's disease. Rheumatol Int 2002; 22: 93-6.
63. Yee BE, Richards P, Sui JY, et al. Serum zinc levels and efficacy of zinc treatment in acne vulgaris: a systematic review and meta-analysis. Dermatol Ther 2020; 33: e14252.
64. Rostami Mogaddam M, Safavi Ardabili N, Iranparvar Alamdari M, et al. Evaluation of the serum zinc level in adult patients with melasma: is there a relationship with serum zinc deficiency and melasma? J Cosmet Dermatol 2018; 17: 417-22.
65. Tasaki M, Hanada K, Hashimoto I. Analyses of serum copper and zinc levels and copper/zinc ratios in skin diseases. J Dermatol 1993; 20: 21-4.
66. Gholizadeh N, Mehdipour M, Najafi S, et al. Evaluation of the serum zinc level in erosive and non-erosive oral lichen planus. J Dent 2014; 15: 52-6.
67. Ingen-Housz-Oro S, Blanchet-Bardon C, Vrillat M, et al. Vitamin and trace metal levels in recessive dystrophic epidermolysis bullosa. J Eur Acad Dermatol Venereol 2004; 18: 649-53.
68. Yazdanpanah MJ, Ghayour-Mobarhan M, Taji A, et al. Serum zinc and copper status in Iranian patients with pemphigus vulgaris. Int J Dermatol 2011; 50: 1343-6.
69. Lönnerdal B. Dietary factors influencing zinc absorption. J Nutr 2000; 130 (5S Suppl): 1378S-83S.
70. Schlemmer U, Frølich W, Prieto RM, et al. Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis. Mol Nutr Food Res 2009; 53 Suppl 2: S330-75.
71. O'Connor S, Murphy S. Chronic venous leg ulcers: is topical zinc the answer? A review of the literature. Adv Skin Wound Care 2014; 27: 35-44; quiz 45-6.
72. Narbutt J, Bowszyc-Dmochowska M, Kapińska-Mrowiecka M, et al. Chronic venous insufficiency – pathogenesis, diagnosis and pharmacological treatment. Diagnostic and therapeutic recommendations of the Polish Dermatological Society. Part II. Dermatol Rev 2018; 105: 486-97.