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Review Article

The role of trace elements in dermatology: a systematic review

Kripa Ahuja, MS[1], Peter Lio, MD[2,3]

[1] Eastern Virginia Medical School, Norfolk, VA, USA, [2] Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [3] Medical Dermatology Associates of Chicago, Chicago, IL 60654, USA

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Background

Trace Elements (TEs) have a multitude of important functions in the skin, including maintaining structural integrity, mitigating oxidative damage, and accelerating wound healing. TEs have been used as primary or additional treatment in dermatologic disorders. Though TEs are vital to homeostasis, consumption over a threshold can lead to toxicity.

Objective

This review aims to discuss the role of trace elements in the treatment of dermatological conditions as well as the potential side effects and toxicities of such therapies.

Methods

This review was conducted by doing an extensive literature search of multiple sources, including PubMed, Cochrane Library, and MedLine.

Results

Thermal Spring Water and Dead Sea Mud take advantage of the positive roles of trace elements in dermatology. In wound healing and collagen synthesis, zinc and copper have vital roles. Selenium inhibits tyrosinase at the cutaneous level. Silica supports the connective tissue matrix, but excess supplementation can have detrimental side effects. Topical strontium may be used to reduce pruritus.

Conclusion

Trace minerals are imperative for healthy skin function. The lack of trace minerals may lead to premature graying, increased inflammation, and systemic evidence of oxidative damage.

INTRODUCTION

Trace elements or minerals (TEs) play a crucial component in many physiological functions of life, including but not limited to: enzyme systems, energy metabolism, and the transport of oxygen.[1] At the cellular level, TEs are integral in maintaining structural integrity in cutaneous cells as well as neutralizing oxidative damage.[2] Due to the ubiquitous nature of these compounds, some TEs are used in the treatment of dermatological conditions.[3] However, there is little data available regarding the use of trace minerals as part of a therapeutic regimen.[2,3] Despite being naturally occurring, if TEs are consumed beyond a certain dose, toxicity occurs.[1]

A deficiency or excess of TEs is difficult to diagnose because their laboratory evaluation has many faults.[4] For example, plasma and epidermal levels of minerals are not correlated,[2] measurement of elements such as iron, zinc, and manganese are prone to erroneously high values if the sample is not correctly collected and processed.[4] Finally, samples are highly susceptible to contamination even in the carefully controlled clinical laboratory due to the omnipresent existence of trace minerals even at micro-levels.[4] Nevertheless, TEs play an important biological function in the skin: genetically, TEs are involved in the transcription of growth factors and cytokines; structurally, TEs are involved in collagen synthesis; and cellularly, TEs mediate inflammatory injury.[1,2] This review aims to discuss the role of trace elements in the treatment of dermatological conditions as well as the potential side effects and toxicities of such therapies.

THERMAL WATER

Thermal Spring Water (TSW) refers to naturally-occurring water originating from hot springs.[5] There are several sources for this type of water.[5] For example, one of French origin is a low-mineral spring water used to treat many inflammatory dermatological diseases, including psoriasis, atopic dermatitis, and lichen planus.[5] Though the complete mechanism leading to the beneficial effects of TSW is incompletely understood, TSW likely exerts its therapeutic

effects by changing the fluidity of the cell membrane, stimulating keratinocyte differentiation, mediating oxidative and inflammatory damage, and altering the cutaneous microbiome.[5,6]

In particular, TSW mediates oxidative and inflammatory damage by generating immunomodulatory dendritic cells that can produce anti-inflammatory cytokines such as Interleukin 10 (IL-10).[7] One TSW has been shown to contain the microorganism *Aquaphilus dolomiae*.[7] This bacteria, even in its non-viable state referred to as a parabiotic, causes the production of more IL-10 and decreases CD-4 T cell activation, which may further contribute to lower levels of inflammation.[7]

Hydrotherapy is also becoming an increasingly well-recognized treatment modality for photoaging and supportive skin care.[5,6] In rabbit studies, thermal water improved skin regeneration by increasing keratinocyte proliferation and favorably modulating regenerated collagen and elastic fibers in the dermis.[8] A hyaluronic acid-based gel with mineralized thermal water significantly improved complexion radiance, complexion homogeneity, plumpness, and smoothness in a study of women exposed to pollution and other extrinsic risk factors for photoaging.[6] While there is great potential for TSW, more evidence is needed, especially when it comes to differentiating between the sources given the wide variation in both mineral and bacterial content.

DEAD SEA MINERAL MUD

Similar to thermal mineral waters, mineral muds and salts from the Dead Sea (DS) have promising therapeutic properties[9] and have been shown to have a host of benefits in psoriasis, atopic dermatitis, and rheumatological disorders.[10] While the exact mechanism of Dead Sea mineral treatment remains unknown,[11] Dead Sea products typically contain zinc oxide, magnesium, calcium, potassium, and strontium.[11] These hydrophilic salts cross the hydrophobic barrier of the stratum corneum to exert their effects.[11] The penetration through the stratum corneum is one possible mechanism of the efficacy of Dead Sea products in dermatological disorders where the stratum corneum is damaged, including psoriasis, atopic dermatitis, and contact dermatitis.[11] Topical application of Dead Sea salts on skin organ cultures has resulted in the down-regulation of aging biomarkers and stimulation of mitochondrial activity, a possible mechanism for the therapeutic effects of DS salts.[11] Chiefly, the high content of salts and trace elements are thought to elicit an antimicrobial, anti-inflammatory, and antioxidant effect while promoting cell-proliferation, migration, and fibroblast cellular activity.[9] Dead Sea mud contains DS salts along with established skin-care ingredients such as aloe vera extract, pro-vitamin B5, and vitamin E.[11] The combination of mud and minerals results in the DS mud product having a cream-based consistency that enhances its function as a leave-on emollient, or "mud pack."[11] Dead sea mud may accelerate wound healing by enhancing granulation, wound contraction, epithelization, angiogenesis, and collagen deposition.[9] Dead Sea mud has also been suggested to be protective against UVB-induced photoaging by increasing cell viability, increasing total antioxidant capacity and uric acid contents in the epidermis, and decreasing the level of cellular apoptosis and cytokine secretion.[11] Dead Sea mud also has an excellent safety profile as the application has not been shown to increase skin malignancy, the levels of all minerals are within a therapeutic range to not induce toxicity, and treatment with Dead Sea mud does not increase blood pressure.[10] Only extreme ingestion of Dead Sea water is toxic due to cardiac arrhythmias from electrolyte abnormalities.[10] Recommended application of Dead Sea mud has not shown microcirculatory or skin temperature changes.[12]

ZINC

Zinc has expansive functions in dermatology: structurally, genetically, and cellularly.[2] First, zinc offers a structural role in the epidermis in keratinization by binding sulfhydryl groups on keratohyalin grains.[2] Next, zinc is also a cofactor for DNA and RNA polymerase as well as for the essential enzyme collagenase in the collagen synthesis pathway.[2] A genetic mutation in a zinc transporter leads to the disorder acrodermatitis enteropathica with characteristic perioriﬁcial and acral lesions, while an acquired zinc deficiency has a less characteristic and more variable presentation.[13] Finally, all forms of zinc deficiencies lead to impairments in wound healing, as matrix metalloproteinases are a class of zinc-dependent proteins that break down collagen fragments.[14]

Zinc's large role in the interplay of many aspects of dermatology is evident with the effect of oral supplementation on various disorders. A large meta-analysis found that atopic dermatitis is associated with significantly lower serum, hair, and erythrocyte zinc levels with subsequent improvement in atopic dermatitis upon zinc supplementation.[15] However, zinc supplementation does not seem to significantly improve the severity of psoriasis with standardized treatments.[16] Zinc supplementation also offers no perceived benefit in rosacea.[17] However, zinc supplementation in patients with acne demonstrated a significant decrease in mean papule count and showed an overall clinical improvement.[17,18] Zinc supplementation in infants with diaper dermatitis showed that the infants gained more height and weight, but not significantly.[17] Nevertheless, zinc supplementation caused a significant reduction in the incidence of infants developing diaper rashes.[17]

The effect of zinc supplementation at varying doses was evaluated for hidradenitis suppurativa (HS). In one study, patients with mild to moderate HS treated with oral zinc gluconate 90 mg/day twice daily for 3 months found that there was a significant decrease in disease severity, the extent of erythema, and a number of inflammatory nodules.[17] However, there was no significant difference in the number of fistulas or the intensity of pain.[17]

Another study evaluated patients with mild to severe HS who consumed 90 mg/day of oral zinc gluconate for 4 months.[17,19] By the end of the study, 36% of patients experienced complete remission, and 64% experienced par-

tial remission.[17,19] In patients with complete remission, reducing the dosage to 30-60 mg/day resulted in a relapse of the disease.[17,19] Increasing the dose prevented relapse.[17,19] The authors concluded that 90 mg of zinc is anti-inflammatory, while 30-60 mg of zinc may be pro-inflammatory, and that treatment with zinc gluconate was suppressive rather than curative.[17,19] The dose-dependent inflammatory effect of zinc may be explained by zinc increasing innate immunity markers, though this is speculative.[17]

Oral zinc gluconate, zinc sulfate, and zinc oxide are the most common formulations available, with the most common side effect being gastrointestinal distress.[17] While zinc toxicity is rare, care should still be taken when supplementing because zinc intake exceeding the recommended dietary allowance may induce copper deficiency and symptoms of anemia and neutropenia.[14]

COPPER

Similar to zinc, copper has widespread functions in dermatology. For example, copper functions as an essential cofactor for the enzymatic reaction of *lysyl oxidase* in collagen synthesis.[2] Next, copper's crucial role in keratinization is evident in the "kinky" hair (*pili torti)* of children with Menkes syndrome, a genetic disorder of copper transport.[2] Interestingly enough, copper also plays an important part in mast cell regulation via gene expression.[20] Patients with MEDNIK syndrome, another disorder of copper transport, have a hyper-allergenic skin phenotype, including pruritus and dermatitis.[20] Patients with MEDNIK syndrome also have increased numbers of mast cells and higher numbers of chymase and tryptase in mast cells.[20]

In terms of treating dermatological conditions, skin products containing a copper tripeptide complex did not significantly improve carbon dioxide laser-resurface skin in the number of wrinkles, level of erythema, or overall skin quality, but patients who used copper-based products reported higher rates of satisfaction.[21] Copper's part in supportive skin care is evident by its success in wound care. Wound dressings that contain copper have been successful in promoting the healing of difficult-to-treat wounds, hypothesized by copper's role in healing by inducing vascular endothelial growth factor (VEGF) and angiogenesis.[22] Copper is also hypothesized to be beneficial in wound healing via inducing the expression of pro-wound healing genetic factors, promoting the formation of granulation tissue, and suppressing infections.[22] A factor contributing to the severity of wounds in patients with diminished peripheral blood supply is thought to be a low level of copper in the wound site.[22] Copper-containing socks have shown beneficial results in reducing the number of skin infections in diabetic patients.[23]

Though most of copper's role in dermatology remains topical, oral copper supplementation may have a therapeutic potential. Copper has been implicated in the pathogenesis of acne vulgaris in male patients; a lower zinc-to-copper ratio is seen in males with acne vulgaris with lower levels of antioxidative enzymes, suggesting that oral copper supplementation may prove substantial.[24] Additionally, in burn patients, combined parenteral Cu, Zn, and Se supplementation conferred a protective effect against pulmonary infections, though it is difficult to isolate each element's function.[25]

However, oral supplementation greater than 1.3 mg Cu/L should be cautioned due to acute side effects, including nausea, vomiting, abdominal pain, hepatocellular necrosis, and acute tubular necrosis.[26] Chronic copper toxicity is evident in Wilson's disease, an autosomal recessive metabolic disorder that results in impaired copper excretion.[26] Wilson's disease is characterized by severe neurological abnormalities, hemolytic anemia, renal tubular dysfunction, and cirrhosis.[26]

SELENIUM

Selenium plays an important role biologically, as it is an antioxidant and co-factor for the enzyme glutathione peroxidase, which is vital to regenerate metabolites that neutralize oxidative damage.[27] It is precisely selenium's antioxidant and regenerative function that has led to the wide discussion of selenium and cancer.[28] While early research suggested that selenium supplementation could protect against cancer,[28] results from the Nutritional Prevention of Cancer Trial showed that selenium supplementation was ineffective at preventing basal cell carcinoma and that it increased the risk of squamous cell carcinoma and total nonmelanoma skin cancer.[29] Still, basic science studies have suggested that selenium may play a role in protecting against aging, as aged keratinocytes require a higher concentration of selenium to repair DNA and prevent photoaging.[27] In terms of treating dermatological conditions, due to selenium's role in mediating oxidative damage, selenium supplementation with glutathione or a selenium-mung bean face mask, has been shown to lighten skin possibly via an inhibitory effect on tyrosinase, the enzyme responsible for producing melanin.[30] Patients with psoriasis reported no improvements after taking selenium supplement[31]; however, a selenium deficiency has been associated with psoriasis, skin cancer, and epidermolysis bullosa.[32] Overall, selenium supplementation should be cautioned as excess selenium can cause toxicity (selenosis).[33] Selenosis presents with hair loss, nausea, vomiting, fatigue, irritability, and paresthesias.[33]

SILICA

Silica has been suggested to play a role in connective tissue formation.[34,35] In a randomized controlled trial, supplementation with a bioavailable form of silicon for 20 weeks resulted in a significant positive effect on the skin surface, skin mechanical properties, and the brittleness of hair and nails.[34] A similar trial found that oral intake of bioavailable silicon had a positive effect on the tensile strength of hair, especially elasticity and break load, and resulted in thicker hair.[35] While no studies have been performed to evaluate the adverse effects of oral bioavailable silicon, caution should be taken in silica supplementation as exposure to

silica has been highly associated with connective tissue diseases such as lupus and scleroderma.[36,37]

CALCIUM

Calcium's synergy with vitamin D has been long described in the field of dermatology, as keratinocytes provide the body's primary source for vitamin D and metabolize vitamin D into active metabolites.[38] However, other perhaps less recognized roles of calcium in dermatology include calcium supplementation to treat the pustular psoriasis of pregnancy.[39] In this form of psoriasis, hypocalcemia is a result of the disorder rather than a trigger, but the exact role of hypocalcemia and psoriasis flares remains unclear.[39] Nevertheless, pustular psoriasis of pregnancy can be associated with severe hypocalcemia and can remarkably improve with calcium supplements.[39] Calcium may also play a role in reducing cancer risk, as calcium supplementation has been associated with a reduced risk of developing colon polyps, and one trial showed a significant reduction in total all-cancer incidence with calcium plus vitamin D supplementation.[40] Additionally, in women with a history of nonmelanoma skin cancer, calcium and vitamin D supplementation reduced subsequent melanoma risk.[40]

STRONTIUM

Strontium has an important physiological influence on the body, particularly in the ever-changing metabolism of bone.[41] Strontium acts through the Calcium-sensing receptor, inhibits osteoclasts, and may be involved in the future treatment of osteoporosis.[41,42] At the cutaneous level, strontium salts have been shown to inhibit sensory receptors and inflammation when applied topically.[43] Specifically, strontium inhibits histamine-dependent and histamine-independent pruritus.[44,45] While the exact mechanism of topical strontium inhibiting pruritus is unclear, a possible explanation is that strontium directly affects the sensory nerve C fibers that transmit pain and itch signals.[44] Pretreatment with topical strontium has shown to decrease the symptoms of itching, burning, and stinging in irritant contact dermatitis.[46]

CONCLUSION

Trace minerals play a key role biologically.[1] Thermal Spring Water and Dead Sea Mud are two treatment modalities that capitalize on the advantageous impacts of trace elements in dermatology.[5,11] No side effects or toxicities appear to be associated with either of these treatments.[5,10] Zinc and Copper are two trace elements that have crucial positions in collagen synthesis and wound healing.[2] Deficiencies of both these elements lead to abnormalities in the skin and hair, as well as other systematic manifestations.[2] Selenium has a diverse role: on the one hand, it is thought to have antioxidant properties important in reducing cancer; on the other hand, it can lighten the skin by inhibiting tyrosinase.[28–30] Silica can strengthen the connective tissue matrix, resulting in positive effects on the skin and hair, but supplementation should be cautioned due to the possible development of silicosis.[34–36] Calcium's interplay with vitamin D is vital to homeostasis of many functions, pustular psoriasis of pregnancy is associated with hypocalcemia and can improve upon calcium supplementation, and calcium may protect against cancer.[38–40] Topical strontium has shown to inhibit irritant receptors and decrease pruritus.[44–46] Overall, trace minerals are fundamental to the normal functioning of skin and hair by mediating oxidative damage, offering structural support, and altering the transcription of certain genes.[1,2] Deficiencies of trace minerals are associated with premature graying of hair,[47] increased inflammation, and systemic evidence of oxidative damage.[48,49]

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