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The Therapeutic and Biological Role of Zinc and Vitamin D-3 In Children's Dermatology

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Abstract: Our work reflects aspects of the study of the role of zinc and vitamin D-3 based on literature analysis.

Keywords: Dermis, function, layers, complications, vitamin.

Introduction: The skin is the largest human organ, consisting of water, proteins, fats and minerals. It protects against microbes, regulates body temperature and water balance. The structure of the skin includes three main layers: the epidermis, dermis and subcutaneous layer.

The skin consists of three main layers: the epidermis, dermis and subcutaneous fat, which, in turn, consist of several internal layers.

Skin appendages such as hair follicles, sebaceous glands, and sweat glands also help the skin perform its functions.

Lifestyle and external factors such as solar radiation and temperature changes have a destructive effect on collagen and elastin, as well as on the structure of the extracellular matrix.

As we age, our natural production of collagen and elastin slows down, and our skin's ability to retain moisture decreases. Skin loses tone and wrinkles appear. Learn more about what factors affect skin condition, why sun protection is needed, and how skin ages.

In the human body, the most important condition for maintaining homeostasis is the effective performance by the skin of at least two of its most important functions: barrier, preventing the penetration of foreign substances from the external environment into the internal environment of the body, and thermoregulatory, ensuring the temperature constancy necessary for the normal functioning of the body.

Numerous studies over the last three decades of the biological properties of vitamin D indicate its diverse effects on the human body. Vitamin D receptors have been found in all organs and tissues of the human body, which has led to the discovery of its non-calcemic (extraosseous) effects.

Research results have proven that a sufficient level of vitamin D in the body prevents various diseases and pathological conditions not only in the musculoskeletal system, but also ensures the effective functioning of the endocrine, cardiovascular, immune and other systems.

The studies conducted have shown that vitamin D deficiency occurs among people of different age groups, both in infants and young children, and in adolescents, and including adults and the elderly. In infants and young children, vitamin D deficiency is one of the leading causes of rickets, as vitamin D is necessary for the formation and maintenance of the skeletal system. Intensive growth of young children, high rate of skeletal modeling with insufficient intake the presence of phosphates and calcium in the body and the imperfections of their transport and metabolism pathways cause the rapid development of bone signs in infants and young children.

Although other functions of the skin (participation in maintaining water balance, in metabolism, in gas exchange, in immune reactions, ensuring the synthesis of vitamin D and regulation of calcium metabolism, protection from ultraviolet radiation, sensory function)

play a very important role in ensuring the sustainable functioning of the body.

It is important to take into account that the borderline position makes the skin very vulnerable to various external factors to which it is constantly exposed. The skin is protected from adverse effects can only be provided under the condition of maintaining its normal structure and adequate ability to perform functions - two main, inextricably linked components of the life process of any organ and organism.

The unity of structure and function denotes the secondary nature of functional disorders in relation to the corresponding morphological changes at various levels, from the organismic to the microstructural and biochemical.

Thus, the full functional activity of the skin as an organ is possible only on the basis of its normal structure. In providing this condition, in addition to genetic factors and the regulatory system, the state of the circulatory system plays a crucial role. The effect of zinc on physiological barriers has also been studied.

A striking example of zinc deficiency is enteropathic acrodermatitis, which combines severe skin lesions and diarrhea syndrome. As for the permeability of the gastrointestinal mucosa, zinc is able to regulate the formation of cAMP and cGMP, which activate protein kinase C.

In zinc deficiency, the process of protein kinase phosphorylation leads to dephosphorylation of myosin light chains, which leads to a reduction in enterocyte size and an increase in paracellular permeability.

In addition, zinc inhibits cAMP-induced chloride-dependent fluid excretion by inhibiting potassium channels, so when it is deficient, the secretion of chlorides and water into the intestinal lumen increases. During periods of exacerbation of the inflammatory process in the intestinal mucosa, the need for zinc increases (the microelement is mobilized from the blood), which ensures reparation and intensive renewal of the intestinal epithelium. Also, A.S. Prasad in his studies indicates an increase in the level of enzymes of the brush border of enterocytes when using zinc in conditions of diarrhea.

If the human body does not receive enough zinc, changes occur in the immune system. Thus, the activity of thymulin, which is produced in the epithelial cells of the thymus and ensures the maturation of lymphocytes, decreases.

It is also necessary to note the decrease in phagocytic activity, chemotaxis of macrophages. Precursors of B-lymphocytes practically do not suffer from zinc deficiency, since the level of their growth factor interleukin 4 (IL-4) does not decrease. With a significant deficiency of this element and a block in the development of cells in the bone marrow, the number of B-lymphocytes decreases.

Myelopoiesis also suffers with prolonged zinc deficiency and increased production of glucocorticosteroids, and the number of neutrophils decreases. Zinc is essential for DNA replication processes, as it plays a role in the functioning of more than 100 transcription factors. Zinc affects the activity of key enzymes at the basic stages of replication and transcription.

These include DNA polymerases, thymidine kinase, DNA-dependent RNA polymerase, aminoacyl transcriptase, RNA synthetase. A whole group of transcriptional regulators contain Zn-containing protein domains in their structure, known as "zinc fingers". Zinc also increases the level of insulin-like growth factor 1 - somatomedin, which is synthesized in the liver under the influence of somatotropic hormone.

Insulin-like growth factor 1 stimulates DNA replication (which is manifested by increased incorporation of thymidine into DNA), transcription, and translation in tissues that are targets of somatotropic hormone. Somatomedin deficiency leads to growth disorders in children.

The effect of reduced zinc concentrations on hormone levels has been proven: the activity of thymulin, a Zn-binding peptide produced by thymus epithelial cells, decreases. The role of thymulin is to ensure maturation, cytotoxicity, and IL-2 production by T-lymphocytes outside the thymus.

Zinc deficiency activates the hypothalamic-pituitary-adrenal system, which leads to hyperproduction of glucocorticosteroids, which cause apoptosis of T-lymphocyte precursor cells, thereby reducing their number.

Thymus involution occurs: in experiments conducted on mice that were given a zinc-free diet for 4 weeks, a reduction in thymus size to 25% of the original was demonstrated.

A decrease in the number of CD73 molecules, a membrane enzyme necessary for lymphocyte differentiation, was also noted on cytotoxic lymphocytes. T-lymphocytes, especially immature ones, die without factors survival – IL-2, interferon γ, colony-stimulating factor and zinc. When studying zinc deficiency in an experimental model, a decrease in the content of interferon γ and tumor necrosis factor produced by type 1 T-helpers was found, and an unchanged amount of IL-4, IL-6, IL-10 produced by type 2 T-helpers, i.e. an imbalance of Th1/Th2 arose.

Zinc levels affect the activity of phospholipase C, protein kinase, lymphocyte kinase, which are necessary for the maturation of peripheral lymphocytes in the thymus gland and their activation. This microelement can increase the levels of specific antibodies (this effect was shown in patients with shigellosis).

Zinc is a powerful antioxidant, preventing lipid peroxidation processes and thus protecting cell membranes from reactive oxygen species.

Formation of organic peroxides is the result of activation of free-radical oxidation reactions in biological systems, the main substrate of which are unsaturated fatty acids of membrane phospholipids. Activation of lipid peroxidation reactions is one of the biological mechanisms of damage to biostructures and development of cellular pathology.

Zinc is a powerful antioxidant, as it is part of superoxide dismutase, which catalyzes the reaction of superoxide dismutation into hydrogen peroxide and molecular oxygen. In addition, zinc stabilizes protein structures, preventing the combination of iron and copper ions and the emergence of a "site of cyclic radical formation" through multiple oxidations.

Iron and copper ions act as reversible electron donors. The microelement also has an indirect effect on antioxidant protection – by increasing the level of metallothioneins in the liver, kidneys, and intestines. The antioxidant properties of metalloproteins have been proven in radiation injuries and the use of antitumor drugs.

Zinc is able to block the synthesis of nitric oxide induced by IL-1, as well as suppress the activity of the nuclear transcription factor NF-kB. As a result, the production of IL-8, tumor necrosis factor α and other mediators of the inflammatory process decreases.

An important property of zinc is the stabilization of basophil and mastocyte cell membranes due to the formation of compounds with thiol groups of plasma membrane proteins. In addition to its effect on the immune system, zinc has a direct antiviral effect. Zinc salts inhibit the replication of rhinoviruses, poliomyelitis virus, enterovirus, and herpes simplex virus.

By binding to the surface structures of the virus, zinc prevents its interaction with the intercellular adhesion receptors ICAM-1. Zinc is involved in the induction of apoptosis in virus-transformed cells.

Zinc deficiency in children increases the risk of pneumonia, malaria, tuberculosis, measles, etc. At the same time, a decrease in resistance to the herpes simplex virus, Salmonella enteritidis, Lysteria monocytogenes, Candida albicans, Toxoplasma gondii has also been proven.

The use of zinc in these diseases is justified and, according to L.E. Gaulfield, R.E. Black (2004), can save the lives of 406 thousand children with pneumonia and 207 thousand children with malaria worldwide every year.

Based on the above effects on the immune system, it can be assumed that additional zinc administration is advisable in various infectious diseases. The success of such practice has already been confirmed in patients with malaria, tuberculosis and lower respiratory tract infections.

According to WHO and UNICEF recommendations (2004), zinc preparations should be included in treatment protocols for diarrheal diseases. According to research, zinc use reduces mortality from diarrhea by 23% in children under 5 years of age.

In addition, the use of zinc also has a preventive effect - it reduces the likelihood of diarrhea in the next 2-3 months. It has been shown that adding zinc to oral rehydration solutions has a beneficial effect.

However, excessive zinc intake in humans is also harmful, as it may be associated with Zn-induced copper deficiency. In particular, it is known that zinc administration at a dose of 300 mg/day for 6 weeks leads to a decrease in chemotaxis, phagocytic activity of neutrophils and lymphocyte response.

Zinc is one of the microelements that are essential for the human body. The daily requirement for zinc in infants is 3-5 mg/day, in adults - 10-25 mg/day. Zinc enters the body with food; its main source is animal protein (meat, fish, eggs, cheese, milk), as well as mushrooms, nuts, legumes, grains, but due to the presence of phytic acid in the latter, the absorption of zinc is significantly reduced. Zinc absorption occurs mainly in the small intestine, with the help of metallothioneins.

It should be noted that breast milk contains a low-molecular zinc-binding ligand, which increases the absorption of zinc by the child's body. Also, the intestinal absorption of zinc is increased by the presence of vitamin A, amino acids (lysine, cysteine, glycine) in food, and calcium, iron, and copper reduce it. Zinc is excreted from the body mainly with feces (90%), as well as urine and sweat. It should be noted that zinc does not accumulate in the body with age if it is consumed in excess 48% of the world's population is at risk of developing zinc deficiency conditions. Zinc deficiency condition (ZDC) occurs when the zinc concentration in the blood decreases to less than 13 µmol/l, and a zinc level of less than 8.2 µmol/l is considered prognostically unfavorable.

According to the conclusion of IZINCG (International Zinc Nutrition Consultative Group), zinc deficiency in the body correlates with growth retardation in school-age children, the prevalence of which > 20% is considered elevated and may indicate a problem of zinc deficiency in the population.

According to WHO data from 2000, in Ukraine this indicator is at the level of 22.9%. Premature babies, children with low birth weight, HIV-infected people, patients with chronic kidney diseases, as well as children weakened by other chronic diseases suffer especially from zinc deficiency.

There is a classification of CDS by time of occurrence (A.A. Zhavoronkov, 1991), according to which CDS that arose in the antenatal and postnatal periods is distinguished. Studies have shown that children born to mothers with zinc deficiency in the body had congenital heart and brain defects in 13-18% of cases.

They also had a decrease in the mass of the spleen, thymus, and impaired functional activity of lymphocytes. In the postnatal period, endogenous and exogenous zinc deficiency are distinguished, including iatrogenic and technogenic. The first group - endogenous deficiency - includes congenital diseases: enteropathic acrodermatitis and sickle cell disease anemia. Exogenous deficiency may be of alimentary origin (Prasad's disease); secondary to gastrointestinal tract, liver, kidney diseases; in pregnant women, etc. Iatrogenic zinc deficiency occurs with unbalanced nutrition, long-term treatment with cytostatics, L-histidine. Technogenic zinc deficiency is a consequence of excess of its so-called competitors in the environment - lead, cadmium, chromium.

According to the classification of R. Henkin, R.L. Aamodt et al. (1983), acute, chronic and subacute forms of CDS are distinguished. The acute form occurs rarely, with unbalanced parenteral nutrition; the chronic form is typical for people whose usual diet contains few products containing zinc (for example, true vegetarians).

Its morphology and functional activity determine the provision of all skin components with material resources necessary to maintain their normal vital activity, oxygen supply, energy and full participation in thermoregulation. Any disturbances in the blood supply to the skin lead to structural changes in its components from functional-compensatory to pathological(reversible and irreversible). Underestimation of the role of deviations in the blood supply system in the development of dermatoses leads to insufficient understanding of their etiological and pathogenetic mechanisms and, ultimately, hinders the prevention, early diagnosis and effective treatment of skin diseases.

In addition, it is necessary to take into account that the blood and lymphatic vessels of the skin are not isolated, but are part of the vascular system of the body and the blood supply to the skin directly depends on the state of the cardiovascular system as a whole.

In practice, few people think about secondary hemodynamic, and therefore trophic disorders in the skin, arising against the background of heart pathology or damage to the main vessels, creating conditions for the development of many skin diseases.

There is virtually no information about the possible prevention of these disorders, their role and significance in the pathogenesis of skin diseases, as well as when prescribing therapy, which naturally affects its effectiveness and safety.

On the other hand, many skin and systemic diseases are basically vascular in nature with predominant damage to the microcirculatory bed of the skin and mucous membranes, and the overwhelming majority of dermatoses are accompanied by pronounced changes in the microcirculatory bed of the skin, but the mechanisms of formation of these changes in most cases remain unexplored,

and their role in pathogenesis is underestimated and is not always taken into account when prescribing therapy. The reason for insufficient attention to the vascular component in the development of skin pathology and the obvious underestimation of vascular mechanisms in the pathogenesis and therapy of dermatoses and systemic diseases with involvement of skin and mucous membranes is the lack of safe, effective and accessible methods of objective assessment of the circulatory bed of the skin. Such widely used methods of vascular examination as ultrasound examination, as radiocontrast methods are able to effectively assess the state of the main blood flow.

Then the assessment of the intradermal vascular network, which performs primarily a nutritional function, is closely connected with the vital activity of all structural components of the skin and is of direct interest for understanding the processes occurring in the skin, remains beyond the capabilities of the indicated methods.

Meanwhile, the need to study microcirculatory processes in the skin is very relevant not only for dermatology, but also for other medical specialties: angiology, cardiology, rheumatology, endocrinology, neurology, combustiology, etc.

Thus, there is evidence that the level of structural changes and the degree of development of

microangiopathies in the skin in diabetes mellitus are a reflection of metabolic, vascular, neurological and immune disorders and allow us to assess the depth of these disorders.

Some authors have demonstrated the dependence of biochemical processes and the general molecular profile of the skin in diabetes on the level of systemic disorders, and a meta-analysis conducted by Fuchs D. et al. demonstrated a statistically significant relationship between the level of metabolic disorders in diabetes and dysfunction of the skin vessels.

There is evidence that the severity of some athological changes in the skin can serve as an indicator of the severity of the overall vascular lesion, in particular, as an indicator endothelial dysfunction, microvascular complications and early stages of atherosclerotic transformation of blood vessels, and in some cases act as an independent risk factor for the development of atherosclerosis of the carotid arteries.

Thus, due to the availability of skin as an optimal object for research, the creation of easily implemented, reliable and informative methods for assessing the morphological state of the skin and its vascular bed could contribute, on the one hand, to understanding the microcirculatory mechanisms of pathogenesis of cardiovascular, endocrine, neurological and other diseases, and on the other hand – early detection of prognostically important structural changes in the skin and diagnosis of angiopathies in various types of systemic pathology in order to organize timely prevention of irreversible vascular complications.

As for combustiology and surgery, the tactics and effectiveness of treating burn surfaces and wounds directly depend on the depth of damage to the skin and its vascular bed, so the creation of optimal objective methods for assessing the degree and effective monitoring of these injuries will be of decisive importance in the successful development of these medical areas.

Until recently, the main and practically the only objective method for studying the structure of the skin and its microcirculatory bed was biopsy. The main advantage of the histological method is the ability to study the structure of tissue, in particular the skin, at the cellular level, which provides high information content, which can be increased by using, in addition to standard special staining methods, various techniques, including injection of vessels for their better visualization.

The main disadvantage that prevents its widespread use and limits its capabilities in studying the vascular bed of the skin is its invasiveness.

Traumatization of tissue during biopsy sampling is inevitably accompanied by disturbances in the structure of the microcirculatory bed and ischemia, which can distort the actual state of the vessels. Subsequent fixation, preparation of sections and staining can radically change the architecture of the vascular bed and lead to an erroneous assessment of its conditions. In addition, this method completely excludes the possibility of studying the functional state of the vessels, which is often necessary for the most complete understanding of the nature of the process, and is capable of providing only static information corresponding to the histological picture frozen at the time of biopsy sampling.

Due to its invasiveness, biopsy practically excludes multifocal and repeated studies, which are necessary in some cases for accurate diagnosis and understanding of the underlying cause of the process. For the same reason, it seems difficult to conduct functional tests, dynamic observations of the development of certain processes and assessment effectiveness and the risk of developing side effects from the therapy. Although, in the literature there are individual reports, mainly concerning the study of the mechanisms of healing and the effectiveness of therapy for burn wounds based on the use of repeated biopsy, but all of them concern exclusively experimental studies carried out in laboratory conditions on simulated burn wounds using animals. In addition, the invasiveness of the biopsy study suggests a high risk of developing various complications (bleeding, severe pain, infectious complications, systemic reactions, delayed healing), residual tissue deformation and numerous contraindications (coagulation pathology, acute inflammation in the lesion, manifestations of pyoderma and systemic infectious processes, intolerance to anesthetics, etc.). It is precisely because of the high risk of residual deformation and technical difficulties in taking a biopsy, even in cases of urgent need, that a biopsy is practically impossible in such complex localizations of the process as the corner of the eye, eyelid, face, nail apparatus, genitals, etc. And among some contingents (children, pregnant women, elderly patients, patients with disorders coagulation, diabetes, etc.), the intervention turns out to be extremely undesirable or even impossible. At the same time, it must be recognized that the use of biopsy for dynamic observations and monitoring of structural changes in tissue, even with the availability of technical capabilities, cannot ensure the accuracy of the results, since. When examining each new biopsy, the esearcher observes new structures each time, while the original object of study is irretrievably removed when taking the first and subsequent biopsies.

Thus, zinc, vitamin D3 is important for the growth and development of the child's body, the functioning of the immune system, antioxidant protection, and the activity of all organ systems. Zinc deficiency in children leads to delayed growth and development, and increases the risk of various infections.

Thus, summing up the literature review, it can be noted that the problem of skin pathologies remains an open question.

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