Review article / Artykuł przeglądowy

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Hypothyroidism, skin changes, and methods of skin care

Niedoczynność tarczycy a zmiany skórne i metody pielęgnacji skóry

ABSTRACT

Hypothyroidism mainly affects adults. The improper functioning of the thyroid gland results in hormone deficiency, and the slowdown of the metabolism of the whole body and skin changes.

The study aimed to present, based on a literature review, skin symptoms occurring in hypothyroidism and substances that can reduce the adverse effects of thyroid hormone deficiency, and support skin care.

The cosmetics rich in moisturizing ingredients, antioxidants, keratolytic, and immunomodulating substances are recommended to strengthen the skin barrier.

Keywords: thyroid, hypothyroidism, trehalose, ceramides, nicotinamide, lycopene, β-glucan, urea, hemp oil

STRESZCZENIE

Zapadalność na niedoczynność tarczycy dotyczy głównie osób dorosłych. Skutkiem nieprawidłowego funkcjonowania gruczołu tarczycy jest niedobór hormonów, spowolnienie metabolizmu całego organizmu oraz zmiany skórne.

Celem pracy było przedstawienie na podstawie dostępnych źródeł, objawów skórnych występujących w schorzeniu niedoczynności tarczycy oraz substancji, które mogą zmniejszyć niekorzystne skutki niedoborów hormonów gruczołu tarczycowego oraz wskazanie substancji wspomagających pielęgnację skóry.

Zalecane jest, aby kosmetyki były bogate w składniki nawilżające, wzmacniające barierę skórną, przeciwutleniające, keratolityczne oraz immunomodulujące.

Słowa kluczowe: tarczyca, niedoczynność tarczycy, trehaloza, ceramidy, nikotynamid, likopen, β-glukan, mocznik, olej konopny

INTRODUCTION

The thyroid, or the thyroid gland (*glandula thyroidea*), is an unpaired endocrine gland, located at the bottom of the front of the neck. The thyroid gland is one of the largest endocrine glands in the human body. Its shape resembles the letter H, due to the presence of adjacent organs, because it does not have a specific shape. The thyroid gland consists of two lobes - the right and the left, which are connected by an isthmus. The weight of the whole organ is 15-50 g. The endocrine gland is surrounded by a connective tissue capsule, the strands of which penetrate the parenchyma and divide it into lobules. Within them, there are follicles, which are important and basic elements of the structure of this organ [1, 2].

The thyroid is supplied bilaterally by two arteries - the superior and inferior thyroid arteries. Blood vessels connect on the surface and inside the gland, thanks to which they form a dense network [2].

One of the basic functions of the thyroid gland is the synthesis and secretion of hormones, which maintain metabolism in tissues at an optimal level for their functions [3]. Follicular cells secrete hormones which are derivatives of the amino acid tyrosine - thyroxine (T4) and triiodothyronine (T3). Thyroid C cells are responsible for the production and secretion of calcitonin, which is involved in the regulation of calcium and phosphate metabolism [4]. A kind of reservoir of T3 and T4 is the protein thyroglobulin. The attachment of

iodine molecules to tyrosine residues is a significant step in the synthesis of thyroid hormones. Hormones circulating in the blood are in 99% bound to plasma proteins, but the free fraction is responsible for the biological effect. The biologically active hormone is T3, and its daily production is 10 times lower than T4. Most T3 comes from the conversion of T4 [5].

Thyroid hormones have a multidirectional effect:

- they regulate the processes of cell differentiation and maturation;
- they stimulate the basic metabolism;
- they regulate the metabolism of carbohydrates, fats, and proteins;
- in the correct concentrations, they have an anabolic effect [5].

HYPOTHYROIDISM

Hypothyroidism is defined as a clinical syndrome associated with a deficiency of thyroid hormones or, very rarely, resistance to their action at the cellular level. This disorder may be congenital or acquired. Children suffer 10 times less often than adults, and the highest incidence is among the elderly. A deficiency of thyroid hormones leads to a slowdown in metabolic processes [1, 6].

Depending on the cause hypothyroidism can be divided into subclinical, primary, secondary, and tertiary. The subclinical (latent) form is the mildest form of hypothyroidism, and its symptoms are difficult to notice. Primary hypothyroidism is caused by damage to the thyroid gland, which can originate, among others, from Hashimoto's disease, iodine deficiency, or its excess. In the secondary form, the pituitary gland is damaged as a result of a tumor, hemorrhage or trauma. Tertiary hypofunction is a rare phenomenon and is caused by hypothalamic disorders in the form of tumors or strokes [1, 5-7].

Thyroid hormones have a direct effect on the skin. This is due to the presence of the TR receptor on keratinocytes, fibroblasts, and sebaceous glands, but also on vascular endothelial cells, structures forming the hair follicle or smooth muscles within the hair [8].

SKIN CHANGES

Symptoms of hypothyroidism can vary by age and gender. The skin of people struggling with hypothyroidism is dry, rough, covered with the exfoliating epidermis, pale and cool. The decrease in skin temperature and its bright appearance is related to the direct influence of thyroid hormones on blood circulation. A typical symptom of hypothyroidism is dryness of the elbows and knees, which may resemble ichthyosis. The term "dirty elbows and knees" is often used. The described skin changes occur as a result of vasoconstriction, a decrease in lipid synthesis, and reduced activity of the sweat and sebaceous glands. As a result of increased keratin synthesis and thyroxine deficiency, there is an increase in transepidermal water loss (TEWL), hyperkeratosis, and developing skin dryness. In the case of long-term hypothyroidism, myxedema may occur due

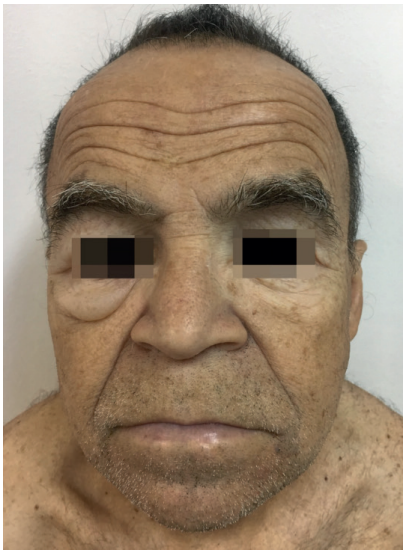

Fig. 1 Myxedema, periorbital edema, and pallor of the skin in a patient with primary hypothyroidism. **Source** [12].

to the deposition of mucopolysaccharides in the dermis, and the most common location is hands, feet or face. Histological examination confirmed thinning of the epidermis and hyperkeratosis [8-11] (Fig. 1).

A noticeable symptom of hypothyroidism is a change in skin color. People suffering from Hashimoto's thyroiditis, due to the lack of carotene metabolism in the liver, may have a yellowish color of the outer integuments. It most often manifests on the palms of the hands, soles of the feet, and nasolabial folds. The carotene accumulates in the stratum corneum, is excreted with sweat, and then accumulates mainly in the sebaceous glands. The presence of a marbled appearance of the skin is often described, which occurs as a result of a decrease in ambient temperature [11, 13].

In patients with hypothyroidism, slower hair growth is observed, and hair structure is dry and brittle. Half of the patients have localized or diffuse alopecia, which may be due to an excessive or insufficient release of T3 and T4 hormones. Slowing down the metabolic processes leads to the miniaturization of the hair follicles. Some patients may notice hair loss from the outer parts of the eyebrows. As a result of thyroid hormone deficiency, nails become dry, dull, and brittle, and longitudinal or transverse grooves may appear on their surface. Thinning of the nail plate may hinder everyday functioning and forces patients to regularly shorten these epidermal products. Onycholysis is a frequent defect of the nail plate in the course of hypothyroidism (Fig. 2, 3). It is the separation of the outer part of the nail plate from the nail bed. It usually starts in the distal part and gradually develops towards the proximal section [10, 11].

Haritha et al. conducted a study in which 100 people diagnosed with hypothyroidism, 76% were women and 24% men. The number of people with skin symptoms was 63, of which almost 86% were women. Dryness and extensive hair loss were the most common symptoms (38.1% and 34.8%).

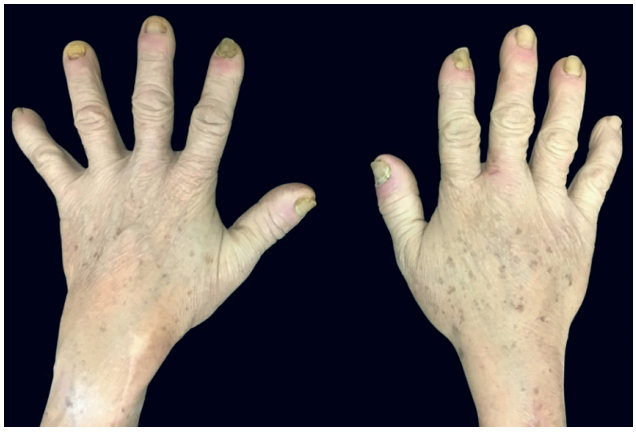

Fig. 2 Changes in the skin and nails in a person with primary hypothyroidism before treatment. **Source** [12]

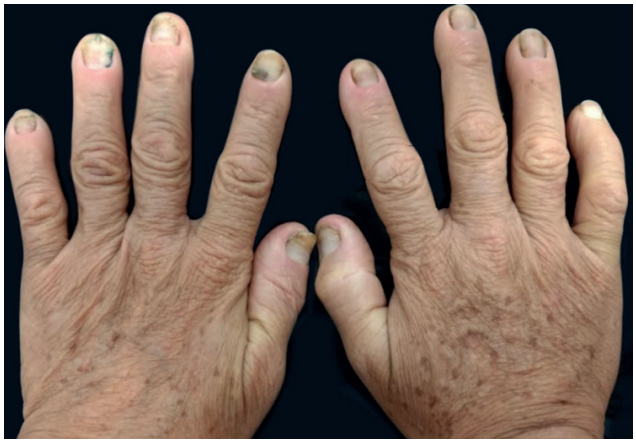

Fig. 3 Changes in the skin and nails in a person with primary hypothyroidism after 30 days of hormonal treatment **Source** [12]

Table 1. Percentage of symptoms and signs of clinical hypothyroidism

Symptoms	(%)	Signs	(%)
Tiredness	88	Dry, thick skin	90
Cold intolerance	84	Hoarseness	87
Dry skin	77	Periorbital edema	76
Hoarseness	74	Movement slowdown	73
Decreased hearing	40	Mental retardation	54
Somnolence	68	Bradycardia <60/min	10
Impaired memory	66		
Weight gain	72		
paresthesias	56		
Constipation	52		
hair loss	41		

Source: Own elaboration based on [15]

Other symptoms included: melasma (14.3%), chronic urticaria (14.3%), generalized pruritus (11.1%), skin eruptions (9.5%), fungal infections (7.9%). Other related skin conditions were: alopecia areata (6.3%), vitiligo (4.8%), lichen planus (3.2%), eyelid xerosis (1.6%) [14] (Table 1).

SUBSTANCES USED IN THE SKIN CARE

Trehalose

Trehalose (α-D-glucopyranosyl-(1→1)-α-D-glucopyranoside) is a disaccharide composed of two glucose molecules joined by an α-glycosidic bond. It is characterized by high hydrophilicity and chemical stability and is widely found in nature. Some isomers have been found in fungi, bacteria, nematodes, plants, and insects. It is considered a generally safe substance [16, 17].

Trehalose, an osmotically active compound, is involved in the physical and chemical protection of the integrity of cell structures, in particular membranes and enzyme proteins. This compound is responsible for the protection of molecules in stress conditions (high or low temperatures, dehydration). Due to the described properties, trehalose is used in medicine for cryopreservation of stem cells [16, 17].

Trehalose, due to its moisturizing features, is often used in cosmetology. It is a component of bath oils, lotions, deodorants, and hair growth preparations. It protects the outer layer of the epidermis against drying, but also against other skin irritants, e.g. high temperature, frost, or solar radiation. Due to the physical and chemical properties of trehalose, this compound affects the stabilization of proteins and allows them to maintain their proper structure during stress developed as a result of dehydration. It has been proven that trehalose can inhibit fatty acids degradation reactions, and enclose them in liposomes, which facilitates tissue penetration, resulting in the stimulation of autophagy - the process of catabolic digestion by the cell of dead and damaged elements of its structure [18-21].

15 people with very dry skin on limbs were invited to the research study to assess the effectiveness of moisturizing a 2% hydrogel containing trehalose and ceramides. They applied the recommended product twice a day for 4 weeks. Using appropriate instrumental methods, a statistically significant increase in skin hydration by 69.5% and a decrease in TEWL by 26.5% was observed [21].

Ceramides

In terms of chemical structure, ceramides are compounds of fatty acid connected by an amide bond with the amino group of sphingosine or dihridosphingosine [22]. They are classified as ingredients modulating the protective barrier of the epidermis and moisturizing ingredients. This group also includes cholesterol and essential fatty acids [23]. Ceramides are synthesized in lamellar bodies, and are released by exocytosis into the intercellular space and subjected to the action of enzymes [24]. Their production depends, among others, on age and weather conditions [25].

Ceramides present in the epidermis affect its cohesion and tightness. The mixture of lipids formed in the granular layer fills the intercellular spaces, which significantly affects the adhesion of corneocytes of the stratum corneum. For this reason, ceramides are a component of the so-called

intercellular cement. They participate in the growth and differentiation of keratinocytes, acting as specific intercellular messengers [22, 24].

An important role in maintaining the proper functioning of the epidermis is played by Ceramide I, to which linoleic acid is attached. It prevents the layers of intercellular cement from moving relative to each other. In the case of a deficiency of this compound, the viscosity of the lipid mixture decreases and the protective properties of the skin are impaired [21, 24]. However, the amount of Ceramide III is directly related to TEWL [24].

With a decrease in the ceramides in the skin, the epidermal barrier is weakened. In dry, skin there is a reduction in the ceramides: I, II, III, IV, V and VI, while in normal skin these compounds are present at a high level [25].

The absorption of ceramides in the skin after topical application is the subject of dispute among researchers. They are compounds of high molecular weight and high lipophilicity, which may be a factor that hinders penetration into the skin. For this reason, various types of carrier systems are used. The relationship between the amount of endogenous ceramide in the skin and the ability to penetrate was questioned. It is believed that dry skin containing little endogenous ceramide will easily absorb exogenous substances. In order to increase the penetration of ceramides into the skin, liposomes, microemulsions, microparticles, nanoparticles, and innovative carrier systems are used. Among these, microemulsions are considered the most effective due to the presence of surfactants in the preparation and an indirect increase in solubility [26].

Nicotinic acid amide

Nicotinamide, otherwise known as niacinamide, is the amide form of water-soluble vitamin B3. For the production on an industrial scale, *Rhodococcus rhodochrous* J1 bacterial cells are used. Nicotinamide exhibits the same vitamin activity as nicotinic acid but has different pharmacological effects and side effects. However, it has not been clarified whether the efficacy of nicotinic acid amide is related to direct or indirect effects on the skin. Currently, nicotinamide is a compound widely used in cosmetology and dermatology [27, 28].

The topical application of nicotinamide stimulates the synthesis of ceramides, free fatty acids, and cholesterol and reduces TEWL, thus supporting the functioning of the skin barrier. Anti-inflammatory effect and reduction of the release of pro-inflammatory cytokines: IL-1β, IL-6, IL-8 and TNF support the therapy of skin inflammation. Nicotinic acid amide also has an antioxidant effect which is related to the direct capture of reactive oxygen species, and also to the increase in the antioxidant capacity of cells [27, 29].

Nicotinamide is a compound often used to reduce skin hyperpigmentation. It inhibits the transport of melanosomes from melanocytes to keratinocytes, which results in a reduction in melanogenesis. Topical application of 5% nicotinamide for 4 weeks has been shown to effectively reduce skin discoloration [30].

The research emphasizes the photoprotective properties of nicotinamide. This compound taken orally effectively reduces the risk of developing non-melanoma skin cancers (NMSC). Nicotinamide is the best-known internal photoprotective substance recommended by dermatologists [31].

Nouh et al. studied the efficacy and safety of nicotinamide in the treatment of skin lesions in patients with Lupus Erythematosus. They compared the effects of 2% and 4% nicotinamide with a placebo trial. Preparations containing the described substance in their composition have proven to be effective with minimal side effects. Irritation occurred in 40% of patients using 2% nicotinamide and in 80% of patients using the higher concentration. The subjects were instructed on how to deal with side effects. It was recommended to wash the application site 2 hours after application of the preparation [32].

Lycopene

Lycopene is considered one of the most important representatives of carotenoids. It is classified as an organic compound that belongs to the group of linear unsaturated hydrocarbons. It is produced in the cells of plants and microorganisms, while animals cannot synthesize it. The source of lycopene is red vegetables and some fruits. It is well soluble in fats [33-35].

Lycopene has antioxidant properties twice as strong as β-carotene and ten times as strong as α-tocopherol. This compound is characterized by a high affinity to cell membranes, affecting their fluidity and permeability [36]. Its immunomodulatory effect has been proven by stimulating the production of defense cells [37].

In cosmetology, lycopene is used to produce sunscreens. By affecting the defense mechanisms of the human body, it supports the regeneration of the epidermis. It is a valuable component of anti-aging cosmetics, participating in the synthesis of procollagen and protecting hyaluronic acid from disintegration [36, 37].

β-glucans

β-glucans are a heterogeneous group of glucose polymers, in which the compounds are built of β-D-glucopyranosyl units joined by β-glycosidic bonds. They are found in food products such as cereals, seaweed, or mushrooms. β-glucans are polysaccharides that are also a component of dietary fiber. Depending on the raw material from which they were obtained, they differ in the type of bonds, branching, and molecular weight. β-glucans became very popular in cosmetology due to their wide application [38-41].

The immunomodulatory properties of β-glucans have been known for decades. The studies showed that they stimulate phagocytic activity and support the synthesis of

pro-inflammatory cytokines: TNF-α, IL-1 and IL-6. They also increase the activity of NK cells, which plays an important role in wound healing [39]. However, their use in cosmetology is much wider as β-glucans:

- support the healing of wounds and irritations;
- support the skin's natural defenses;
- reduce skin redness;
- easily penetrate the skin barrier and stimulate collagen synthesis;
- regenerate dry and flaky skin;
- have an antibacterial effect [38].

β-glucans as ingredients of emollients, have a moisturizing effect, creating a protective film on the skin and retaining moisture. Due to their properties, they can be used in skin care with symptoms of psoriasis or other chronic diseases. It should also be emphasized that β-glucans are widely studied compounds with a good safety profile [38].

Urea

Urea is an organic compound of low molecular weight. It is characterized by hygroscopic properties, due its ability to bind water. Urea, a component of the natural moisturizing factor (NMF), absorbs water in the epidermis and plays an important role in maintaining hydration and integrity of the stratum corneum. Due to its properties, it is widely used in diseases characterized by dry skin [42, 43]. It has moisturizing, softening, anti-pruritic and keratolytic properties. *In vivo* and *in vitro* studies have shown that urea affects the reduction of DNA synthesis in the basal layer along with the decrease in the number of cells, slowing down the mitotic divisions and thinning of the epidermis [44]. Urea can stimulate the production of lipids and induce the synthesis of antimicrobial peptides in the epidermis, which belong to the skin's immune system. Physiological doses of urea in the millimolar amount increase the expression of transglutaminase I, filaggrin, involucrin, and locrin, i.e. factors affecting the differentiation of keratinocytes and the synthesis of antimicrobial peptides [42].

The keratolytic effect of urea is often used in dermatology. As a result, the proteins of the intercellular matrix are dissolved, the cohesion of keratinocytes is reduced due to the breaking of hydrogen bonds, the epidermis is moisturized and the penetration of topical agents is improved. In the treatment of dermatoses with hyperkeratosis, urea at a concentration of 40-50% is most often used [45, 46].

Dysfunction of the skin barrier leads to increased TEWL, skin dryness, and the risk of allergen penetration. Urea is considered as a safe and effective moisturizer and TEWL-lowering substance, but to a lesser extent than ceramides. The moisturizing effect is associated with an increase in the amount of water in the epidermis in conditions of high humidity. For this purpose, preparations with urea at a concentration of ≤10% are used [47, 48] (Table 2).

Table 2. Local effects of urea on the skin

Effect of urea on the skin	Effect of urea on skin cells
Increased hydration of the stratum corneum	Reduced TEWL. Increased water retention. Increased the resistance of the stratum corneum to osmotic stress. An endogenous humectant in low humidity conditions.
Regulation of epidermal proliferation	Reduced DNA synthesis in the cells of the basal layer. Reduced number of epidermal cells.
Strengthening the barrier function of the skin and antimicrobial effect	Increased the expression of the antimicrobial peptide, calicidin, and β-defensin-2 genes. Increased the level of transglutaminase I protein, involucrin, and filaggrin. Stimulation of the synthesis of lipids. Regulation of the transcription of genes involved in the differentiation of the epidermis. Increased the amount of AMP.
Keratolytic action	Denaturation of keratin by breaking hydrogen bonds or changing conformation in the protein structure.
Increasing drug penetration	The transport of hormones through the skin and nails, antifungal drugs, and corticosteroids.

Source Own elaboration based on [43]

Hemp oil

The popularity of hemp oil dates back to antiquity. It is obtained from *Cannabis sativa* L. seeds, the plants are rich in cannabinoids and terpenes. Cannabinoids are lipophilic organic compounds, which include e.g. tetrahydrocannabidiol (THC), cannabidiol (CBD) or cannabinol (CBN). The presence of terpenes is responsible for their anti-inflammatory and antioxidant properties [49]. Hemp oil also contains vitamins A, E, K and minerals: sodium, potassium, zinc, magnesium, calcium, phosphorus, copper and iron [50].

The largest number of CB1 cannabinoid receptors is found in the central nervous system, and CB2 in the peripheral nervous, digestive, and immune systems. However, studies suggest that both types of receptors are also present in keratinocytes, melanocytes, dermal cells, eccrine sweat glands, and hair follicles [51]. Figure 1 shows the endocannabinoid system of the skin.

Hemp oil is characterized by low comedogenicity, which is why it can be successfully used in the care of oily skin prone to acne. Thanks to the high content of unsaturated fatty acids, it regulates the secretion of sebum, as it resembles a mixture of lipids produced by the sebaceous glands. The presence of omega-3 and omega-6 acids contributes to the alleviation and treatment of dermatoses characterized by dry skin. Hemp oil strengthens the structure of intercellular cement, and also reduces TEWL, thus improving the natural defenses

of the skin. The complex of vitamins A, E and K improves skin elasticity, prevents premature aging, stimulates regeneration processes, nourishes and strengthens the elasticity of blood vessels, and contributes to deeper penetration of active ingredients. In addition, vitamins A and E have a strong antioxidant effect [50].

Hemp oil can be supplied with the diet, as a food additive. The recommended dose is 1 teaspoon taken once or twice a day. Contraindications to oral supplementation are splenic insufficiency, stomach ailments, and diarrhea. Overdose can cause digestive upset [52].

SUMMARY

Thyroid hormones perform many important functions and in physiological conditions, they regulate the processes occurring in the tissues. This article presented the symptoms of hypothyroidism and active substances that should be components of cosmetic preparations used in the disease to eliminate skin changes. The skin of people struggling with hypothyroidism requires specialized care due to the slowdown of all processes in the human body. Dryness and hair loss are the most common skin symptoms of developing disorders, and general symptoms include fatigue, cold intolerance, and hoarseness. Trehalose, ceramides, nicotinamide, lycopene, β-glucan, urea, and hemp oil are compounds that meet the needs of the skin. Sealing intercellular cement, reducing TEWL, antioxidant, regeneration support, keratolytic, anti-inflammatory, and antimicrobial properties are just some of the many properties of these substances. Their presence in cosmetics can help to increase the natural protective barrier of the skin and improve its functioning.

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