Application of Hyperbaric Oxygen Therapy in Skin Disease Treatment

Zastosowanie tlenoterapii hiperbarycznej w leczeniu chorób skóry

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Key words
HBOT, atopic dermatitis, psoriasis, diabetic foot, burns

Abstract
Introduction: Hyperbaric oxygen therapy (HBOT) involves the use of 100% pure oxygen in conditions of increased pressure, exceeding atmospheric pressure. This allows the supply of several times more oxygen to the internal organs and blood serum than when using standard pressure. HBOT has proven to support the treatment of autoimmune skin diseases, complications of metabolic diseases and burns, as confirmed by clinical studies. In addition, this therapy can also be used to improve the physiological condition of the skin after cosmetology procedures.
Objectives: The aim of this work is to review information on the therapeutic effects of hyperbaric oxygen therapy in the treatment of skin diseases, especially atopic dermatitis, psoriasis, diabetic foot, 2nd-degree burns and complications following cosmetic procedures.
Method: The review was based on the works published in the last 20 years (1999-2019), available in the following databases: PubMed, Google Scholar and PEDro.
Results and conclusions: The use of HBOT is becoming more common in the treatment of skin complications related to diabetes, as well as burn wounds. It is estimated that HBOT reduces the risk of foot ulcers and amputation in diabetic foot syndrome. In addition, HBOT promotes faster healing of burn wounds, also with the use of allogenic skin grafts. By increasing the level of reactive oxygen species (ROS), hyperbaric oxygen therapy significantly supports the treatment of psoriasis and atopic dermatitis. Despite this, the exact mechanisms of hyperbaric oxygen are still poorly understood, and the use of HBOT in the treatment of skin diseases has not yet been included in treatment protocols.

Słowa kluczowe
HBOT, atopowe zapalenie skóry, łuszczyca, stopa cukrzycowa, oparzenia

Streszczenie
Wprowadzenie: Tlenoterapia hiperbaryczna (HBOT) polega na zastosowaniu 100% czystego tlenu w warunkach zwiększonego ciśnienia, przekraczającego ciśnienie atmosferyczne. Pozwala to na dostarczanie kilkakrotnie większej ilości czystego tlenu do narządów wewnętrznych i surowicy krwi, niż w przypadku zastosowania standardowego ciśnienia. HBOT posiada udowodnione działanie we wspomaganiu leczenia autoimmunologicznych chorób skóry, powikłań chorób metabolicznych i oparzeń, co potwierdzają badania kliniczne. Ponadto terapia ta może być również wykorzystywana w celu poprawy kondycji fizjologicznej skóry po zabiegach kosmetologicznych.
Cel: Celem niniejszej pracy jest przegląd informacji na temat roli HBOT w procesie leczenia chorób skóry, ze szczególnym uwzględnieniem atopowego zapalenia skóry, łuszczycy, tzw. stopy cukrzycowej, oparzeń II stopnia oraz powikłań po zabiegach kosmetycznych.
Metoda: Przegląd wykonano w oparciu o prace opublikowane w ostatnich dwudziestu latach (1999-2019), dostępne w bazach: PubMed, GoogleSchoolar, PEDro.

The individual division of this paper was as follows: A – research work project; B – data collection; C – statistical analysis; D – data interpretation; E – manuscript compilation; F – publication search

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Wyniki i wnioski: Zastosowanie HBOT staje się coraz powszechniejsze w leczeniu powikłań skórnych cukrzycy, a także ran pooparzeniowych. Szacuje się, że tlenoterapia hiperbaryczna zmniejsza ryzyko wystąpienia owrzodzeń stóp oraz amputacji kończyn dolnych w przypadku zespołu stopy cukrzycowej. Ponadto HBOT sprzyja szybszemu gojeniu się ran oparzeniowych, również przy zastosowaniu przeszczepów allogenicznych skóry. Zwiększając poziom reaktywnych form tlenu (RFT), tlenoterapia hiperbaryczna istotnie wspomaga leczenie łuszczycy i atopowego zapalenia skóry. Pomimo tego dokładne mechanizmy działania tlenu hiperbarycznego są nadal słabo poznane, a zastosowanie HBOT w leczeniu chorób skóry nie zostało do tej pory ujęte w jednoznaczne protokoły leczenia.

INTRODUCTION

The skin, as the external covering of the body, is the main barrier to pathogens and provides protection against the adverse effects of external factors. Direct exposure to pollution, changes in temperature or air humidity not only cause loss of skin hydration and elasticity, but also disrupts gas exchange. In addition, an inadequate lifestyle: poor diet, low physical activity, stress or excessive drug abuse also lead to physiological and structural disorders of the skin[1]. The consequence of disturbances in homeostasis in predisposed persons may be the occurrence of chronic allergic changes, manifested by skin symptoms, as well as damage to the continuity of the skin.

Hyperbaric oxygen therapy (HBOT) has been successfully used for many years as an element of the therapy for metabolic diseases, poisoning and infections. In 2016, the European Commission of Hyperbaric Medicine revised and updated the list of indications for hyperbaric treatment, including diseases in which HBOT should be used as the primary treatment method or is suggested as an optional method, due to the small amount of evidence supporting its effectiveness[2]. The continuous increase in interest around HBOT is connected with numerous studies that still expand the potential scope of application regarding this therapy in supporting the treatment of other disease entities. In addition to the absolute indications for the use of HBOT (such as carbon monoxide poisoning, infections caused by anaerobic bacteria or complications of diabetes), hyperbaric oxygen therapy can also be used to improve the physiological condition of the skin, both in diseases, burn treatment and after procedures in the area of aesthetic medicine[3-6]. At the same time, HBOT is used in the treatment of autoimmune skin diseases such as atopic dermatitis or psoriasis[7-11].

OBJECTIVE

The aim of this study is to review information on the influence of hyperbaric oxygen therapy in the treatment of skin diseases, in particular atopic dermatitis, psoriasis, diabetic foot and burn wounds.

METHODOLOGY

This review is based on the works published in the last 20 years (1999-2019) available in the following databases: PubMed, Google Scholar and PEDro. In order to search for specialised topics, the following keywords were used: hyperbaric oxygen therapy, hyperbaric chamber, HBOT, HBO, HBO2, atopic dermatitis, psoriasis, burns, diabetic foot.

RESULTS

Research regarding the effects of hyperbaric oxygen therapy on the body

Hyperbaric oxygen therapy consists in administering 100% pure oxygen under conditions of increased pressure, exceeding the atmospheric pressure of 1 ATA (usually, 2.5-3 ATA)[12]. This enables the efficient delivery of several times more pure oxygen to the internal organs and blood serum than when standard pressure is applied, which is especially important in the case of hypoxic tissues[13-15]. In their research, Boerema et al.[16] demonstrated that 1 litre of blood serum contains 3 ml of oxygen. Breathing oxygen under normal pressure conditions increases the oxygen content to 20 ml, while when the pressure value exceeds 2.5 ATA, the amount of oxygen reaches even 50 ml per 1 litre of blood serum[16,17]. Moreover, it has been shown that as pressure increases, the volume of gas bubbles decreases and the blood vessels contract. Oedema at the site of the damaged tissues is inhibited.

The beginnings of using compressed air to treat pulmonary diseases date back to the 17th century (as early as 1662, C. Henshaw designed the "*Domocilium*" chamber). Since then, oxygen therapy has been primarily used to eliminate diseases among divers, as well as in the treatment of cardiovascular system diseases. However, the main precursor of modern hyperbaric oxygen therapy was the Dutch cardiac surgeon Ite Boerema, who, in an animal model, proved that in the conditions of a hyperbaric chamber, oxygen dissolved in plasma is sufficient to support life processes[16,18]. He also performed the first cardiac surgery in a hyperbaric chamber. Further experimental studies on animals in the 1970s were focused on the possibility of inhibiting the immune response at the cellular level after exposure to hyperbaric oxygen (HBO)[7]. Twenty years later, Saito et al.[19] suggested that the action of oxygen in the hyperbaric chamber influences the activity of B and T lymphocytes as well as the inhibition of immune response, reduction of the inflammatory reaction of the organism by a decrease in the amount of synthesised interferon and interleukins 1 and 12[9,20-23]. In other studies, it has been suggested that HBO can stimulate the production of anti-inflammatory cytokines (e.g. IL-10)[8,9,24].

During HBOT, the increase in the level of oxygen among cells is closely related to the formation of larger amounts of reactive oxygen species (ROS), which is a typical reaction also during inflammation in the

body[24,25]. ROS, although they react with proteins, lipids or carbohydrates (which can cause damage to them), in low concentrations, they play a key role in many pathways of cell-signalling, including those physiological reactions related to, among others, wound healing[26-29]. In addition, they exhibit bactericidal activity, which also remains an important factor in the treatment of skin infections.

Hyperbaric chambers and therapeutic procedure

Currently, there are both single- and multi-person hyperbaric chambers, the former usually used at private centres, while hospitals usually use group therapies in larger chambers, in which each patient has a separate oxygen mask. Single-session oxygen exposure typically lasts from 60 to 120 minutes at 1-3 ATA. During therapy, the patient assumes a horizontal position, but may perform other activities such as reading books or watching films on screens placed in the chamber. Before starting the treatment, the patient must change into specialised clothing made of 100% cotton[14].

Indications for hyperbaric oxygen therapy of skin diseases

Indications for the use of hyperbaric oxygen therapy were divided into acute and chronic disorders. The first group of skin diseases and lesions included thermal burns (2nd degree in children, 3rd degree in adults), for which immediate therapeutic intervention is required[30]. On the other hand, indications including chronic disorders, the therapy of which may be spread over time, include: diabetic foot syndrome, ulcers resulting from prolonged immobilisation, infections and wounds that heal poorly, radiation damage to the skin and inflammation of the skin and subcutaneous tissue[31].

Contraindications to hyperbaric oxygen therapy and threats

Despite the fact that HBOT is a relatively safe procedure, as evidenced by many years of clinical practice, qualification for a treatment in a hyperbaric chamber always requires meticulous assessment of the patient's current health condition and analysis of disease history. There are known cases of the toxic effect regarding oxygen under high pressure, especially with longer exposure durations[24,25]. In extreme cases, increased oxygen content may result in damage to the lung tissue, in consequence, leading to a situation that threatens the patient's health and life[13]. The excess of oxygen in the tissues can cause oxidative stress resulting from the accumulation of reactive oxygen species. However, over the exposure time and due to pressure values used in therapy, this condition is transient and does not result in permanent tissue changes[7,35]. Thus, in the absence of contraindications, the risk of HBOT adverse effects on homeostasis of the body is relatively low[24,33,34]. Nevertheless, before deciding to use HBOT, it is crucial to pay attention to comorbidities. An absolute contraindication to the use of HBOT is the presence of pneumothorax in the patient or treatment with cytostatics[13]. It has also been proven that oxygen therapy can lead to the progression of latent tuberculous infection into an active form of the disease. Therefore, in the case of patients at higher risk, it is imperative to perform a tuberculin skin test before the therapy is applied[32]. Relative contraindications for HBOT use also include upper respiratory tract infection, pregnancy, fever, epilepsy, emphysema or diagnosed cancer[13].

Possible health risks and complications of HBOT

Exposure to an excessively high dose of HBO may, in rare cases, cause pulmonary and central nervous system toxicity[36]. With the use of 2 ATA pressure, the first symptoms of poisoning appear about 6 hours after the procedure, and with 3 ATA, even after 2 hours, thus much faster than when the body is exposed to 100% oxygen under normal pressure. These symptoms include swelling in the nasal mucosa, discomfort in the trachea and larynx, as well as pain in the larynx. Prolonged cough may occur in response to continued HBO exposure, and at higher blood pressures, muscle tremors around the eyes, mouth and hands are characteristic[36].

Complications resulting from the use of HBOT therapy include barotrauma occurring in the area of the lungs, paranasal sinuses or the middle ear. In studies conducted so far, it has been shown that about 20% of people using hyperbaric chambers indicate ear pain, and in patients undergoing HBOT, despite upper respiratory tract infections, pressure injury in the paranasal sinuses may occur[17].

The group of complications within the organ of vision includes myopia and, less frequently, cataracts. These complications concern about 20% of people using HBOT, but these symptoms usually disappear up to 3 months after the completion of therapy[37]. It is also unclear how HBOT influences the course of cancer diseases. Currently, there are still disputes between specialists in the field of hyperbaric oxygen therapy regarding the harmful effects of therapy on the development of tumours[38].

HBOT in the treatment of atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory disease that significantly impairs patients' quality of life. As civilisation progresses, the problem with atopic dermatitis becomes more and more serious, and it is caused by incorrect lifestyle, eating habits, excessive consumption of drugs and the socio-economic situation[39]. Atopic dermatitis in Western Europe affects at least 9-24% of children and 1-3% of adults[40].

In clinical research by Olszański et al.[7], it has been confirmed that the use of the HBOT cycle results in a reduction of IgE level and the C3 complement component among humans. In all patients, improvement in general clinical condition and skin lesions and, at the same time, reduction of pruritus were noted, which allows considering HBOT as adjunctive therapy, especially in patients resistant to standard therapy with hydroxyzine and other antihistamines. In the application of HBOT during

AD treatment, it seems important to properly select exposure duration and pressure value in the hyperbaric chamber[7,22,41]. The number of studies conducted so far is still small, requiring deeper verification and development of treatment procedures[42].

In research carried out on a mouse model, it has been indicated that after exposure of animals to 100% oxygen, at a pressure of 2.5 ATA for 90 minutes, the amount of IgE and mast cells in the serum of mice with AD was reduced, and the symptoms of inflammation were alleviated. There was also a significant expression of indoleamine-2,3-dioxygenase (IDO), an enzyme that reduces the number of T lymphocytes, which partially explains the positive effect of HBOT on the course of AD treatment. This also allows to emphasize the importance of ROS in the manifestation of AD symptoms mediated by disturbed T lymphocyte activity[42].

HBOT and skin psoriasis

Psoriasis is a chronic inflammatory disease that compromises the immune system. It is one of the most common dermatological ailments, although the scale of the disease varies in different parts of the world. In Poland, it affects about 2% of the population, but in Russia, for example, it has effects on up to 10% of the population[43]. A significant problem of people suffering from psoriasis is, in addition to troublesome symptoms, long-term and expensive treatment.

Hyperbaric oxygen therapy may play a supporting role in the treatment of psoriasis, which is related to an increase of RTF level in the tissues. In the research by Kim et al.[44], it was shown that, as in the case of AD, modulation of T_{reg} regulatory T lymphocyte activity is a key issue in the treatment of autoimmune psoriatic disorders. The effectiveness of HBOT in this disease is confirmed in the study by Butler et al.[45]. In the first patient suffering from pustular psoriasis and arthritic psoriasis, the use of HBOT (60 minutes, 2.8 ATA) after 6 sessions – resulted in reduction of itching, and after 8 sessions – reduction of joint pain. However, after 18 months of intensive therapy, psoriasis completely remitted. The second patient suffering from psoriasis vulgaris manifested in skin erythema, itching sensation and bilateral leg ulceration, experienced a significant relief of itching and a reduction in the intensity of erythema after 6 HBOT sessions (90 minutes, 2 ATA). No side effects were reported in any of the patients[45].

Treatment of so-called diabetic foot

Diabetes as a civilisation disease of the 21st century affects an increasing part of the population, and according to forecasts, in 2030, the number of patients world-widewill reach 552 million[46]. Failure to treat diabetes properly can lead to so-called diabetic foot syndrome and severe disability of the ill person. Diabetic foot syndrome is characterised by lower limb ischaemia and an infectious condition extending into deep tissue, often accompanied by widening ulcerations. It is estimated that amputation in diabetic foot syndrome occurs in approximately 1% of patients[47]. Ischemia significantly impairs the healing of existing wounds and promotes the development of infection. Additionally, in psoriasis, there is a general reduction in immunity through damage to T lymphocytes, which also significantly impedes the healing process[48].

The use of HBOT promotes the healing of lower limb ulcers resulting from diabetes, while significantly reducing the number of partial amputations[49-51]. In the studies by Andrade et al.[50] and Kaplan et al.[51], it has been indicated that the effectiveness of HBOT (i.e. relieving disease symptoms or completely curing it) occurred mainly in the group of patients with chronic diabetic foot syndrome. The Kaplan et al.[51] study included 146 patients with diabetic foot syndrome who were treated with 100% oxygen at a pressure of 2.5 ATA for 120 minutes. Patients were monitored for a period of 3 years (recovery or amputation). Furthermore, 69.6% of patients had completely healed diabetic foot and 17.9% significantly improved. The effectiveness of HBOT in the treatment of diabetic foot syndrome was confirmed in the research by Knefel et al.[52] who conducted observations among 24 people. Before initiating the therapy, all patients underwent treatment aimed at balancing blood glucose levels, water and electrolyte disturbances and kidney dysfunction. The sessions in the hyperbaric chamber consisted of 2 to 60 treatments, the exposure lasting 70 minutes at a pressure of 2.5 ATA. The authors demonstrated that the symptoms of diabetic stop syndrome were reduced in all patients and that 5 were completely healed. Among the patients, 4 underwent amputation in the area of the toes and the metatarsus.

In turn, research in an animal model allowed to note that the use of HBOT in rats with induced diabetic foot results in a significant increase in the level of hemoglobin and its oxygen saturation in blood vessels. In animals subjected to HBOT, a significantly increased resistance of healthy (by 27%) and damaged (by 19%) skin to tearing was also observed[49].

It should be mentioned, however, that in the research by Fedorko et al.[53], it has been suggested that the use of 12-week HBO therapy did not reduce the number of patients qualified for amputation due to the diabetic foot. However, in this trial, the number of performed amputations was not considered, but only qualification for amputation based on the Wagner classification[53].

Treatment of skin burns

Burn syndrome is diagnosed as severe damage to the body integument and includes damage to the skin, deep tissues and organs, along with full impairment of function. The main factor in determining the severity of a burn is its depth. Usually, burns caused by chemical or electrical factors damage the skin along its entire thickness, while thermal burns depend on the temperature and duration of the stimulus action[54]. The extent of the lesion indicates the percentage chance of healing the patient, and as the area of the burn increases, so does the risk of mortality.

The use of hyperbaric oxygen therapy reduces the infection rate due to the bacteriostatic action of oxygen, and also facilitates the neutralisation of exotoxins by increasing the oxygenation of the damaged tissue[55,56]. HBO therapy can effectively destroy bacterial biofilm, which is important in the treatment of chronic infection associated with skin damage[57].

In studies carried out on an animal model, it has been shown that HBOT facilitates wound healing after 2nd degree burns in rabbits, which the authors associate with increased migration of inflammatory (in the inflammatory phase) and epithelial cells[58]. On the other hand, in rats, the use of HBOT resulted in shortening of wound healing time and the appearance of scars was improved[58]. Exposure to HBO for at least 45 min reduces the adhesion capacity of neutrophils to target tissues, which further decreases the number of inflammatory cells in deep wounds while, at the same time, not causing a reduction in the antimicrobial activity of neutrophils[59,60]. The results of studies regarding the influence of HBOT on the rate of epithelial regeneration after 2nd-degree burns are not unequivocal, however, in the research by Hatibie et al.[58], acceleration of the epithelialisation process in patients undergoing HBOT was noted, which may be associated with an increase in the rate of mitosis and migration of epithelial cells in conditions of high oxygen availability. At the same time, the use of HBOT facilitates the treatment of sepsis in patients with burns, compared to therapy without the use of HBO[61].

Hyperbaric oxygen therapy also shows promising results in the case of skin transplantation[5]. Rapid loss of water through the wound and the formation of edema leads to tissue hypoxia and accumulation of cellular metabolites. Therefore, proper tissue oxygenation is very important in this case, as it stimulates the process of epithelialisation and angigenesis[62,63]. The implementation of HBOT improves vascular permeability, enables the activation of neutrophils, enhances collagen synthesis, and the resulting ROS stimulate the proliferation and differentiation of keratinocytes, fibroblasts and myofibroblasts[24,64,65]. For this reason, the simultaneous use of HBOT with the application of allogeneic skin enables complete closure of the wound without the need to perform an autogenous transplant[5], which confirms the reduction of hospitalisation time in patients with burns treated via HBOT[66]. According to the data provided by Misiuga et al.[5], complete healing of wounds through allogeneic transplantation was achieved in 14 out of 20 patients undergoing HBOT, while in the control group, this was only 7 out of 20 patients.

With regard to electrically-induced burns, in the research by Knefel et al.[67] no mortality or complications after skin transplantation were noted in the group of patients undergoing HBOT as opposed to the control group. This suggests that supporting the standard treatment procedure with hyperbaric oxygen therapy allowed to achieve the expected results.

Use of HBOT in the treatment of complications regarding treatments in aesthetic medicine

One of the methods for eliminating wrinkles, scars as well as skin discoloration and, at the same time, a cleansing treatment, increasing the production of collagen and elastin is a chemical peel, one of the forms of which is so-called deep peeling, is performed, among others using phenol. Redness and soreness of the skin lasting up to several weeks are common symptoms after such treatment. The use of HBOT after deep chemical peeling reduces the severity of erythema and itching symptoms, as well as peeling of the skin after treatment, as while shortening the time of skin regeneration[68]. Also, in the treatment of complications after cosmetic procedures related to the injection of dermal fillers, HBOT may show positive effects[6]. The use of calcium hydroxyapatite, despite the relatively low risk, leads to partial skin necrosis in some cases as a result of obstruction in the blood vessels. As shown by Uittenbogaard et al.[6], the use of 6-month HBO therapy in a patient with the above symptoms allowed for a good cosmetic effect, despite the lack of effectiveness of previous treatment with hyaluronidase and warm compresses.

CONCLUSIONS

Each year, the use of HBOT in the treatment of skin diseases is confirmed by an increasing number of clinical trials. The majority of scientific reports concern the use of HBOT in the treatment of diabetes-related skin complications, as well as the treatment of burn injuries (also with the use of allogeneic skin grafts). In this case, more effective treatment of wounds and necrotic skin lesions is possible, among others, by increasing angiogenesis factors and improving blood flow in the area of hypoxia and the production of extracellular matrix components. Oxygen therapy is also important in supporting the treatment of autoimmune diseases such as atopic dermatitis or psoriasis, which is associated with an increased synthesis of ROS and modification of T_{reg} cells. The use of HBOT in the treatment of skin diseases has not yet been included in consistent and unambiguous treatment protocols, and the exact mechanisms of HBO action are still poorly understood. Despite this, HBOT seems to be a very effective therapy supporting other targeted methods of treating chronic wounds and skin diseases.

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