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Review article

Physical medicine modalities most frequently applied in the lower limbs chronic wounds treatment in Poland

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ABSTRACT

Introduction: Chronic wounds are the ones that present no healing progress for more than three months. The most common reasons for the chronic wound development in the lower limbs include long-lasting diabetes mellitus, venous insufficiency and peripheral arterial disease. However, it is estimated that 15%–20% of the lower limb chronic wounds are of mixed etiology. Standard treatments such as pharmacotherapy, debridement or skin grafting may be supplemented with physical medicine modalities.

Aim: The aim of the paper was to indicate the utility and biological effects of the physical medicine modalities frequently applied in chronic wound treatment.

Discussion: The physical medicine modalities widely used in the lower limbs chronic wounds treatment are variable magnetic fields, low-level laser therapy and hyperbaric oxygen therapy. Those modalities are proved to stimulate various biological reactions which may promote chronic wound healing. Stimulation of angiogenesis and collagen proliferation are factors that promote histological wound maturation and closure. Local circulation improvement mediated by hypocoagulation and vasodilatation is a factor accelerating wounds healing. Modalities-mediated pain reduction is a result of anti-inflammatory activity as well as of endogenous endorphin secretion. Modalities-mediated bacteriostatic and bactericidal effects are also observed. All those effects are mediated by activation of the immune system. An anti-inflammatory effect is due to the inhibition of pro-inflammatory cytokines secretion and the increase in interleukins activity.

Conclusions: Variable magnetic fields, low-level laser therapy and hyperbaric oxygen therapy are modalities revealing various working mechanisms. The significance of their administration in chronic wounds treatment can be attributed to a variety of their biological effects.

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1. Introduction

Chronic wounds are defined as remaining unhealed for more than three months. The most common reasons for chronic wound development in the lower limb are long-lasting diabetes mellitus, venous insufficiency and peripheral arterial disease (PAD).[1–3]

PAD is a medical condition arising from defused atherosclerotic plaques leading to obstruction or occlusion of arteries with secondary blood flow impairment.[4,5] Routinely this term refers to the arteries of the human body located distally to the aorta bifurcation, except for the coronary and cerebral vessels. However, the diagnosis of PAD correlates with a higher risk of myocardial infraction or stroke.[5–8] PAD is estimated to affect 10%–15% of general population, and the frequency of occurrence rises with age. In Europe and the United States there are about 27 million people diagnosed with PAD.[6] Almost 50% of the patients remain asymptomatic for a long time, which may lead to the diagnosis and treatment delay. What is more, some researchers point to inadequate general practitioners' awareness of PAD.[4–6,8,9] Patients may present diverse symptoms depending on the PAD stage, but the most common one is intermittent claudication.[6] PAD leads to different functional impairments including physical effort and exercises intolerance, gait disturbances, or limitations in activities of daily living. It may also increase the distress level and lower the quality of life (QOL).[3,10] The failure of standard and endovascular treatments may lead to amputation.[9]

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by an elevated glucose level in blood serum resulting from impaired insulin secretion or/and insulin resistance.[2,11,12] The number of people with DM is presumed to rise, particularly in developing countries. The World Health Organization estimates that about 347 million people worldwide are diabetic, where 90% suffer from type 2 diabetes.[2,13] DM may be complicated by cerebral, vascular, renal, ocular or muscular insults; skin pathologies are equally threatening.[14,15] Diabetic foot ulcers (DFUs) are the main reason for hospitalization in the diabetic population.[16] Peripheral autonomic, motor and sensory neuropathies are common factors predisposing to DFUs. Gait abnormalities in diabetic patients are consequences of the lower extremity muscles hypotrophy, range of motion limitations and foot deformations.[2,17,18] PAD correlates with DFUs. DM worsens the prognosis in patients with PAD, and DFUs may be escalated by PAD.[19] DFUs decrease the QOL and increase costs associated with long-lasting treatment. DFUs are the major cause of non-traumatic lower limb amputations.[18,20]

Venous leg ulcers (VLUs) are skin lesions resulting from venous insufficiency occurring mainly in the lower leg region.[21] They are found to be the most common chronic wounds with recurrence tendency.[21,22] It is estimated that VLUs affect 1% of adults and 3% of the elderly. VLUs develop more frequently in people with vascular and metabolic diseases.[21,23–27] Superficial and perforator vein valve impairments result in venous hypertension and blood stasis. In VLUs pathophysiology two theories have been considered: the fibrin cuff hypothesis and leukocyte trapping. Actually, the most probable mechanism assumes chronic inflammation leading to tissue destruction.[21,28,29] In patients with VLUs the decrease in QOL is correlated with functional limitations. However, it is important to indicate psychological consequences of VLUs, which may include feelings of isolation and resentment, or symptoms of depression.[23,26,27,30]

About 15%–20% of lower extremity ulcers are of mixed etiology (venoarterial). If the arterial component overweighs, compression therapy may be contraindicated. However, according to some researchers supervised compression with reduced pressure may be helpful in arterial disorders.[29,31–33]

DFUs treatment requires multidisciplinary approach, which may lead to reducing both the amputation rate and expenditure, and to improving the QOL. The most important aspect of DFUs therapy is glycaemia control, which should be supported by the patients' education.[18,34] Common local therapeutic procedures include dressings, debridement, decompression, vascular or non-vascular surgeries or skin grafting.[18,20,34,35] DFUs infections may complicate the treatment. Physicians may deal with osteomyelitis, deep tissue infections or even gangrene. Frequently DFUs infection treatment requires combined drug therapy. Sometimes pharmacotherapy must be associated with surgical interventions. Ultimately, amputations must be performed.[35,36]

VLUs treatment strategy is based on compression bandaging and this seems to be the most effective conservative method.[37,38] However, to increase the effectiveness of compression bandaging pharmacotherapy is introduced. Pentoxifylline, aspirin and antibiotics are frequently administered drugs.[39] The aims of VLUs debridement are bacteria and necrotic tissue removal and wound healing enhancement. Additionally, wound healing is promoted by dressings pre-moistened in antiseptics, chlorhexidine or silver sulfadiazine.[40]

Circulation assessment is a crucial aspect of arterial lower extremity ulcer therapy. Standard treatment is based on the foot offloading, debridement or skin grafting. Multidrug therapy is aimed at the local circulation improvement and bacteriostatic effect if the wound is infected.[41]

Physical medicine is an integral branch of medicine applying physical factors in prophylaxis and therapy. Frequently enumerated advantages of physical medicine modalities are minimal or absent side effects, low costs of treatment and patients' acceptance. This militates for physical medicine modalities application in chronic wound treatment.[42–44]

2. Aim

The aim of the paper was to indicate the utility and biological effects of physical medicine modalities frequently applied in chronic wound treatment.

3. Discussion

3.1. *Variable magnetic fields*

Variable magnetic fields may be applied as magnetotherapy or magnetostimulation, depending on the parameters used. Magnetotherapy is characterized by high values of magnetic

induction (above 100 μT) and low-frequency impulses (below 100 Hz). The impulses may have rectangular, triangular or sinusoid shape. Magnetostimulation, on the contrary, is an application using low values of magnetic induction (below 100 μT) with high-frequency impulses (above 3000 Hz).[44–47] Variable magnetic fields are willingly applied in VLUs, DFUs and arterial ulcers treatment.[46,48]

In chronic wound treatment various mechanisms of variable magnetic fields action may be identified. Two of them deal directly with blood vessels. Nitric oxide release leads to extensive vasodilatation, which is followed by blood flow enhancement and oxygen utilization increase. Magnetic fields stimulate angiogenesis, which is a crucial aspect of chronic wound healing.[46,48] The vascular endothelial growth factor (VEGF) is an agent playing the key role in angiogenesis regulation. However, according to available research, it may not be the most important agent stimulating magnetic fields-mediated angiogenesis. Fibroblast growth factor 2 (FGF-2) is suspected of being responsible for stimulating angiogenesis, yet the role of other angiogenetic proteins and cytokines is also claimed to be significant.[49]

Application of magnetic fields is proved to cause hypocoagulation.[46,48] Magnetostimulation also influences some blood rheological properties, leading to plasma viscosity and erythrocyte aggregation decrease. In animals, the thrombocyte number and aggregation decrease has also been observed.[46,50] A non-direct biological effect of magnetic fields action concerning patients with DFUs and PAD is the cholesterol and lipids level reduction, which may have impact on the treatment course.[51]

Increased oxygen diffusion and binding to hemoglobin, associated with parallel cytochromes activity, are factors associated with oxygen utilization improvement and internal breathing rate rise mediated by magnetic fields.[48] This process hastens adenosine triphosphate (ATP) synthesis and elevates the metabolic rate. What is more, interleukins (ILs) synthesis, particularly IL-1 and IL-6, promotes genes expression.[47,51]

Variable magnetic fields activate enzymes promoting the conversion of fibrocytes into fibroblasts. Collagen synthesis and deposition facilitate re-epithelialization and wound closure. Chronic wounds are frequently infected with diverse bacteria. Magnetic fields may be adjuvant to systemic therapy and antiseptic dressings because of their bacteriostatic effect. Orally administered antibiotics require a period of time to reach therapeutic concentration whereas the magnetic fields-mediated bacteriostatic effect occurs immediately after the application.[34–36,40,41,48,52–54] A magnetic fields anti-inflammatory effect is a result of the inhibition of pro-inflammatory cytokines release. Management of inflammation is associated with pain relief and edema reduction.[46,48,53,54] The above-mentioned effects correlate with the QOL improvement frequently observed in patients.[55] In diabetic patients, peripheral neuropathy symptoms improvement is an effect of neural tissue metabolism rise and reparative processes hastening. Additionally, in DFU treatment magnetic fields provide a hypoglycaemic effect.[51,53]

Constant technological development has resulted in a possibility of simultaneously applying magnetostimulation and low-energy light. A beam of light emitted by generators may be coherent (magnet-laser-therapy) or non-coherent (magnet-led-therapy). Magnet-laser-therapy and magnet-led-therapy apply red (wave length: 630 nm) or infrared light (wave length: 855 nm). What is more, magnet-led-therapy allows for simultaneous application of red and infrared light.[44,51,53,55–57]

Both modalities are aimed at the homeostasis regain due to various working mechanisms. They are proved to improve microcirculation and cause hypocoagulation. Vascular effects of those modalities include vasodilatation and angiogenesis. Magnet-laser-therapy and magnet-led-therapy promote oxygen utilization and ATP synthesis causing the cell cycle progression and acceleration. Boosted collagen production contributes to histological wound maturation. The immune system activation is manifested by the rise of lymphocyte proliferation. Both modalities provide an anti-inflammatory effect with secondary edema and pain reduction. However, the magnet-led-therapy analgesic effect is also associated with activation of the endogenous antinociceptive system and beta endorphin secretion.[44,51,53,55–57]

3.2. *Low-level laser therapy*

Lasers are devices generating electromagnetic radiation by stimulated emission. It ensures laser beam properties: coherence, parallelism and monochromaticity. A commonly applied wavelength range is 600–1100 nm. It corresponds to the skin optical window, which is defined as the greatest skin permeability for optic radiation. Light delivered to the skin is transmitted to tissues but biological effects may be elicited only by the absorbed light. Chromophores, located in mitochondria, are photon absorbers. Cytochrome c oxidase plays an important role in the respiratory chain, thus formerly absorbed radiation may stimulate various reactions.[58,59] During low-level laser therapy the tissue temperature rise does not exceed 1°C and thus is called non-thermal. This shows that biological effects of low-level laser therapy (LLLT) are a consequence of photochemical reactions.[58,60]

LLLT is proved to cause various biological effects, thus is willingly applied in numerous medical conditions. The most frequently listed effects include management of inflammation, edema reduction and analgesia.[61] LLLT stimulates re-epithelization due to increased collagen synthesis. New blood vessels growth, microcirculation improvement and hypocoagulation are effects influencing chronic wound healing. A wide range of benefits militates for LLLT application in chronic wound therapy.[61–65]

The LLLT anti-inflammatory effect is associated with peripheral histamine and prostaglandins secretion. Prostaglandins, being precursors of the inflammatory process, require the presence of cyclooxygenase 2 (COX-2). It particularly concerns prostaglandin E2 (PGE2), whose secretion inhibits COX-2 feedback production with secondary inflammation resolution.[61,66] What is more, bradykinin and interleukin activity inhibition also leads to inflammation reduction. Bradykinin-dependent angiogenesis is associated with the inflammatory process. However, LLLT-mediated new blood vessels growth has a different working mechanism.[61,67,68] It is associated with the increased activity of VEGF and hypoxia inducible factor (HIF-1α), and decreased activity of matrix metalloproteinase (MMP-2).[65,69] LLLT is proved to increase

nitric oxide production, which promotes vasodilatation and accelerates wound healing.[70–73]

The mechanism of LLLT analgesia is not fully understood. However, three hypotheses may be indicated: endogenous endorphin secretion increase, pain threshold rise, and conduction velocity decrease or inhibition.[70,72,74] Besides, local circulation improvement increases pain reduction in irradiated areas.[72]

LLLT-mediated fibroblasts proliferation is an important aspect of chronic wound treatment.[75] Intracellular calcium increase (Ca^{2+}) stimulates DNA and RNA synthesis, followed by protein production.[62] In irradiated fibroblasts MMP-2 activity rise and growth factor release are observed.[76,77] These mechanisms prove LLLT efficacy. Additionally, keratinocytes activity increase, collagen deposition, and soft tissue growth promote epithelization and wound closure.[78–80]

An LLLT-mediated bacteriostatic effect depends on features of the light applied (wave length and intensity).[81] Reactive oxygen species (ROS) activation leads to bacteria killing. Such an effect has been observed in *Staphylococcus aureus* and *Escherichia coli* colonies irradiated with 415 nm wavelength.[76,82] Commonly applied infrared light is reported to stimulate *S. aureus* growth while red light inhibits *S. aureus* MRSA proliferation.[81,83] What is more, LLLT activates the immune system. T lymphocyte activity rise is accompanied by macrophage phagocytic activity increase.[84,85]

3.3. *Hyperbaric oxygen therapy*

Hyperbaric oxygen therapy (HBOT) is a modality applying pure oxygen at high pressure (above 1 atmosphere absolute) in numerous medical conditions.[86–88] HBOT properties can be explained by Henry's law. Hyperbaric conditions increase the concentration of oxygen dissolved in blood plasma and oxygenation of hemoglobin.[86,89] Chronic wounds are proved to be hypoxic. HBOT-mediated blood hyperoxygenation ensures tissue oxygenation despite blood vessels occlusion or poor blood rheological properties.[90] In chronic wound treatment stimulation of new blood vessels growth is important. HBOT-dependent neovascularization may occur in two ways. Synthesis of VEGF stimulates new blood vessels growth and this process influences progenitor cells activity and blood vessels formation de novo.[86–89,91,92] What is more, HBOT promotes synthesis of nitric oxide synthase (NOS), and nitric oxide is essential for VEGF-stimulated angiogenesis.[86,92–94] HBOT induces angiogenesis via increased activity of the basic fibroblast growth factor (bFGF).[89,92,95]

An HBOT-mediated anti-inflammatory effect is a consequence of a diminished level of pro-inflammatory cytokines. Interleukins and tumor necrosis factor (TNF) levels are noted to be decreased after HBOT application.[87,96] Heme oxygenase-1 and heat shock protein activity mediates the anti-inflammatory effect via decreased cytokines production by macrophages.[91,92] Furthermore, HBOT stimulates the synthesis of IL-10, a cytokine production inhibitor.[97] Another HBOT anti-inflammatory mechanism is supposed to be based on leukocytes adhesion, rolling and activity decrease.[89,98]

Chronic wounds are frequently complicated by infections. Hypoxic conditions lead to neutrophils and macrophages activity impairment.[99] HBOT stimulates immunological reactions. Phagocytosis and leukocyte-killing activity increase result in a bactericidal effect. A well-reported bacteriostatic effect of HBOT was observed in *S. aureus* and *Pseudomonas aeruginosa*. Free radicals influence anaerobic bacteria whereas ROS inhibit aerobic ones.[100] HBOT acts synergistically with antibiotics, strengthening their bactericidal activity.[97–99,101–103]

Chronic wound treatment may be attributed to HBOT-mediated fibroblasts proliferation rise and collagen synthesis acceleration.[104,105] Chronic wounds may affect superficial or deep muscle groups. Available research reveals that HBOT stimulates the expression of insulin-like growth factor 1 (IGF-1), regulating satellite cells proliferation and their differentiation in muscles.[106] Increased concentration of IGF-1 promotes keratinocytes mitosis.[107]

HBOT provides pain relief.[108] It stimulates endogenous antinociceptive activity via opioids secretion. In neuropathic pain HBOT-mediated analgesia is an effect of NOS expression.[109]

4. Conclusions

Variable magnetic fields, low-level laser therapy and hyperbaric oxygen therapy are modalities presenting various working mechanisms. The significance of their administration in chronic wound treatment can be attributed to a variety of their biological effects.

Conflict of interest

None declared.

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