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Effects of systemic and local cryotherapy on the course of neurodegenerative and autoimmune diseases - A Literature Review

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Abstract

Introduction and Purpose:

Cryotherapy, both systemic and local, is increasingly recognized as a complementary method in the treatment of inflammatory, autoimmune, and neurodegenerative diseases. This review aims to summarize current knowledge on the mechanisms of cryotherapy and its impact on clinical outcomes and biomarkers in selected chronic conditions.

Description of state of knowledge

Cryotherapy exerts anti-inflammatory effects by lowering levels of cytokines such as TNF-α, IL-1β, and IL-6. It also improves microcirculation, modulates hormonal responses and neurotransmission, contributing to pain relief, reduced fatigue, less joint stiffness, and improved quality of life. However, possible side effects include frostbite, dizziness, cold-induced urticaria, and transient hypertension. Contraindications include cardiovascular diseases, cryoglobulinaemia, and cold hypersensitivity.

Methods:

The literature review included studies from 2000–2025 in databases such as PubMed, Scopus, Web of Science, and Google Scholar. Clinical trials, systematic reviews, and meta-analyses evaluating the efficacy and safety of WBC and LBC were analysed.

Conclusions:

Cryotherapy is a valuable adjunctive tool for the treatment of diseases with a chronic course and inflammatory components, but its use should be preceded by detailed clinical assessment and patient qualification. Further randomised clinical trials are needed to establish optimal therapeutic protocols and an accurate safety profile.

Key words:

cryotherapy; whole-body cryotherapy; local cryotherapy; neurodegenerative diseases; autoimmune diseases

Introduction

In recent decades, there has been a significant increase in interest in non-invasive methods to assist in the treatment of chronic diseases, particularly those with neurodegenerative and autoimmune causes.

Cryotherapy, which involves exposing the body to low temperatures to induce a variety of physiological responses that can have anti-inflammatory, analgesic and neuroprotective effects, has become a target for research. Research to date, mainly focusing on the applications of cryotherapy in sports medicine and post-traumatic rehabilitation, is also increasingly considering its use in the treatment of symptoms of chronic diseases such as rheumatoid arthritis, multiple sclerosis, Parkinson's disease and Alzheimer's disease [1].

Neurodegenerative and autoimmune diseases are not only a diagnostic and therapeutic challenge, but also a significant burden on patients and the healthcare system. They affect people of all ages, leading to progressive deterioration of mobility, chronic pain, reduced quality of life and lowered mood. There is, therefore, a real need to search for adjunctive therapies that can safely and effectively improve patients' comfort, especially when pharmacological treatment results are unsatisfactory [2].

Despite the promising results of previous studies on cryotherapy, there is still a need for a comprehensive analysis of its potential therapeutic effects, especially in the context of the common pathophysiological mechanisms - such as chronic inflammation, oxidative stress and immune dysfunction - that are typical of both groups of conditions [3].

Although research on cryotherapy is showing promising results, a comprehensive review of its possible benefits is still lacking, especially in relation to common pathophysiological mechanisms, such as chronic inflammation, oxidative stress or immune dysfunction, which are characteristic of both groups of conditions [4].

The aim of this paper is to review the available scientific literature on the efficacy and mechanisms of action of systemic and local cryotherapy in the treatment of neurodegenerative and autoimmune diseases.

This study presents the mechanisms of action of cryotherapy at the physiological level, with particular emphasis on its anti-inflammatory, neuroprotective and immunomodulatory

properties. The aim of the study is also to analyse the impact of this method on the course and clinical manifestation of selected conditions, including multiple sclerosis, rheumatoid arthritis, Parkinson's disease and Alzheimer's disease. In addition, the question of whether cryotherapy can be an effective adjunct to standard treatments, improving patients' quality of life and helping to control the symptoms of these chronic conditions is considered. At the same time, due to the possibility of side effects and the existence of numerous contraindications, it is also necessary to analyse the safety of cryotherapy and the principles of patient eligibility for this type of intervention.

1. Characteristics of cryotherapy

1.1 Whole-body cryotherapy - general information

Whole-body cryotherapy (WBC) is a therapeutic method involving the brief, controlled application of extremely low temperatures to the whole body. The WBC procedure usually takes place at extremely low temperatures, ranging from -110°C to -160°C, and lasts between 2 and 4 minutes. Treatments are performed in specially adapted cryochambers or cryosaunas, which have conditions of controlled air or nitrogen cooling. The protocol usually involves daily or multi-day sessions, applied in cycles of several to several days, depending on the therapeutic goal [3,5,6]

1.2 Local cryotherapy - general information

Local cryotherapy (LC) is based on the brief, controlled application of low temperatures, usually in the range of -10°C to -40°C, to a well-defined area of the body to produce the intended therapeutic effects. Unlike whole-body cryotherapy, which involves exposure of the entire body, this method focuses on treating selected tissues or joints affected by pathological changes [5].

1.3 Mechanisms of action of systemic and local cryotherapy

The action of systemic and local cryotherapy is based on complex physiological mechanisms affecting the nervous system, endocrine system and the body's inflammatory response.

1.3.1. Reduction of inflammatory mediators

Both forms of cryotherapy exert strong anti-inflammatory effects through the expression of pro-inflammatory cytokines. In the course of autoimmune and neurodegenerative diseases, elevated levels of mediators such as TNF-α, IL-1β and IL-6 are observed, whereas cryotherapy leads to their significant reduction, while increasing the level of interleukin 10 (IL-10), a cytokine with anti-inflammatory and immunomodulatory effects. This makes it possible to reduce the chronic inflammation that leads to tissue damage in both rheumatic and neurodegenerative diseases.

- Systemic cryotherapy modulates the immune system response at a systemic level, which has found application in the treatment of generalised inflammatory conditions such as rheumatoid arthritis (RA) and multiple sclerosis (MS) [6–8].

- Local cryotherapy reduces inflammation within the affected tissue (e.g. joints), which has been confirmed in studies on knee arthritis, among others [7].

1.3.2. Analgesic effect

Both variants of cold therapy show effectiveness in relieving pain, which is one of the key symptoms accompanying both autoimmune and neurodegenerative diseases. The mechanism of action is based on inhibition of nerve stimulus conduction through A-delta and C-fibres, which are responsible for the perception of pain signals. In addition, stimulation of cutaneous thermoreceptors, particularly TRPM8 channels, which are activated in response to temperatures below 27°C. Their stimulation transmits impulses to the central nervous system, which can modulate the central processing of pain stimuli and activate mechanisms that inhibit pain perception. Therefore, cryotherapy reduces the sensation of joint, muscle and neuropathic pain, improving the patient's overall comfort [2].

- Systemic cryotherapy also has an effect on endocrine function and neurotransmitter activity (e.g. endorphins), which may contribute to the reduction of chronic pain and central pain syndromes [3].

- Local cryotherapy has a local and rapid effect, which can be useful in acute pain conditions [8].

1.3.3. Improved microcirculation and tissue regeneration

In response to exposure to extremely low temperatures, peripheral cold receptors in the skin are stimulated and blood vessel lumen constriction (vasoconstriction) occurs immediately, leading to a significant reduction in blood perfusion in peripheral tissues - by up to approximately 30% [2].

This is a defence mechanism to protect the body's internal temperature. Once the low temperature is over, secondary vasodilation (reactive vasodilation) occurs, resulting in increased blood flow and improved delivery of oxygen and nutrients to previously cooled areas. This phenomenon leads to improved microcirculation, removal of metabolic products and inflammatory mediators, which in turn promotes regeneration, reduces swelling and joint stiffness and improves the function of nerve tissues in neurodegenerative diseases.

- WBC affects systemic perfusion, which may benefit nerve and muscle tissues, especially in MS.

- Local cryotherapy improves microcirculation in the treated area, reducing swelling and stiffness [9].

1.3.4. Additional mechanisms specific to WBC

Effects on the hypothalamic-pituitary-adrenal axis

Stimulation of the hypothalamic-pituitary-adrenal axis results in increased secretion of cortisol. This hormone has anti-inflammatory and immunosuppressive effects, which may promote the regulation of excessive immune system activity, important in autoimmune diseases. This effect represents one of the possible therapeutic mechanisms of cryotherapy, although its efficacy and safety require further clinical studies [3].

Effects on neurotransmission and mood

Increases in endorphins, adrenaline and modulation of cortisol improve mood, reduce symptoms of depression and anxiety, often associated with neurodegenerative diseases. This may also improve sleep quality and comfort [1,10].

Reduction of oxidative and inflammatory stress

Cryotherapy reduces oxidative stress and associated neuronal damage by reducing levels of reactive oxygen species (ROS) and decreasing the expression of pro-inflammatory cytokines (e.g. np. TNF-α, IL-1β) [4].

Table 1. Physiological mechanisms of action of whole-body and local cryotherapy. Own elaboration based on the literature.

Mechanism of Action	**Site of Action**	**Description**	**Therapeutic Effect**	**Reference**
Reduction of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)	Immune system	Decreased expression of inflammatory mediators and increased IL-10 levels	Reduction of chronic inflammation	[7]; [3]
Inhibition of nerve conduction	Peripheral nervous system	Blocking A-delta and C-fibers and activation of TRPM8 receptors	Analgesic effect	[8]; [2]

Mechanism of Action	Site of Action	Description	Therapeutic Effect	Reference
Vasoconstriction followed by vasodilation	Circulatory system	Initial blood vessel constriction with rebound vasodilation	Improved microcirculation, edema reduction	[9];[2]
Hypothalamic-pituitary-adrenal axis activation	Endocrine system	Increased cortisol secretion	Immunosuppressive and anti-inflammatory effect	[3]
Neurotransmission modulation (endorphins, adrenaline, serotonin)	Central nervous system	Mood elevation, reduction in depression and anxiety	Enhanced quality of life	[1]; [10]
Reduction of oxidative stress	Neuronal and immune cells	Lowered ROS and lipid peroxidation	Neuroprotective effect	[4]

2. Characteristics of diseases for which cryotherapy is used

2.1 Neurodegenerative diseases

Alzheimer's disease is a chronic and progressive neurodegenerative disorder leading to progressive neuronal loss and increasing cognitive impairment. One of the key pathophysiological mechanisms of this disease is the accumulation of toxic deposits of beta-amyloid and abnormally phosphorylated forms of tau protein within the structures of the central nervous system. This results in atrophy of neuronal structures and dysfunction of synaptic networks. The main symptoms of Alzheimer's disease include progressive deterioration of

memory, impaired spatial-temporal orientation, difficulties in carrying out daily life activities and changes in personality and behaviour [11].

Parkinson's disease (PD) is a chronic, neurodegenerative disease characterised by a progressive loss of dopaminergic neurons, mainly in the black matter of the midbrain. The decrease in dopamine concentration in neural pathways leads to motor symptoms such as bradykinesia, muscle rigidity and resting tremor [12].

Multiple sclerosis is a chronic and progressive neurodegenerative disorder characterised by gradual neuronal loss and increasing cognitive deficits. It manifests with a broad spectrum of neurological symptoms, such as muscle weakness, paresthesias, balance disorders, chronic fatigue and visual impairment. Due to its autoimmune basis, the disease combines features of both neurodegenerative disorders and entities of immuno-inflammatory aetiology [13].

2.2 Autoimmune diseases

Rheumatoid arthritis is a chronic and systemic disease with an autoimmune basis resulting in chronic inflammation and destruction of periarticular tissues.

In the course of RA, the immune system attacks its own tissues, particularly the synovial membrane of the joints, resulting in chronic inflammation and destruction of cartilage and bone. Typical clinical manifestations include joint pain, swelling, morning stiffness and progressive limitation of mobility, with consequent deterioration of the patient's physical performance and quality of life [14].

The group of seronegative spondyloarthropathies includes ankylosing spondylitis (AS), which is a chronic inflammatory condition of the osteoarticular system. It is chronic in nature and the underlying cause is autoimmune. AS results in chronic inflammation of the spinal structures, leading to their fibrosis, ossification and progressive stiffness. The disease most commonly manifests in young men aged 20-30 years and is associated with the presence of the HLA-B27 antigen. Symptoms include lower back pain, morning stiffness, reduced spinal mobility and, in advanced cases, complete stiffness of the spine (known as bamboo kyphosis) [15].

2.3 Common pathophysiological mechanisms

Chronic inflammation and immune dysregulation

Chronic inflammation is a key mechanism in the pathogenesis of both neurodegenerative and autoimmune diseases, leading to progressive tissue damage and irreversible functional changes. In neurodegenerative diseases such as Alzheimer's and Parkinson's, chronic activation of microglia is observed, resulting in the release of numerous pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), as well as chemokines. These inflammatory mediators exacerbate neurodegeneration by creating a neurotoxic environment that promotes neuronal death and exacerbates central nervous system dysfunction [16,17].

In autoimmune diseases, chronic inflammation is primarily due to dysregulation of the immune system, involving a loss of immunological tolerance to one's own antigens. Autoreactive T and B lymphocytes activated uncontrollably attack their own tissues, resulting in local and systemic inflammatory reactions. For example, in rheumatoid arthritis, lymphocytes attack the synovial membrane of the joints, while in multiple sclerosis, they direct their response against the myelin sheaths of the nerves of the central nervous system. The result is chronic inflammation, tissue damage and disease progression [13,14].

Dysregulation of the immune response in both disease groups is characterised by chronic activation of immune cells and overproduction of pro-inflammatory cytokines, which increase inflammation and accelerate tissue destruction. In neurodegeneration, over-activation of microglia generates a neurotoxic environment that promotes neuronal apoptosis, while in autoimmune diseases, loss of immune control results in the continuous stimulation of autoreactive lymphocytes and the production of autoantibodies [18,19].

Oxidative stress

Oxidative stress is one of the important pathophysiological mechanisms common to neurodegenerative and autoimmune diseases. Excess free oxygen radicals and reactive oxygen species lead to damage of cell membrane lipids, proteins and DNA, which promotes dysfunction of nerve cells and immune system tissues [20,21]. In neurodegenerative diseases, oxidative stress contributes to pathological protein accumulation (e.g. beta-amyloid in Alzheimer's) and neuronal death [22]. In autoimmune diseases, free radicals enhance

inflammatory processes and damage target tissues, which exacerbates clinical symptoms and organ destruction [23].

In summary, key pathogenic mechanisms common to neurodegenerative and autoimmune diseases include chronic inflammation, deregulation of the immune response and oxidation-reduction imbalance. These phenomena create a peculiar vicious circle in which inflammation exacerbates oxidative stress and cell damage triggers further activation of the immune system, which promotes disease progression. These universal mechanisms represent important therapeutic targets, also in the context of adjunctive therapies such as cryotherapy.

3. Effectiveness of cryotherapy in selected diseases - a review of studies

3.1 Neurodegenerative diseases

Cryotherapy, especially systemic cryotherapy, is gaining importance as a potential adjunctive treatment for neurodegenerative diseases. In recent years, there has been increased interest in the use of WBC for the treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. Clinical and observational studies indicate that WBC can improve patients' quality of life by reducing motor and non-physical symptoms such as fatigue, pain and mood disorders [1].

In the case of Alzheimer's disease, the therapy has shown the ability to improve cognitive function and reduce depressive symptoms, which has been confirmed by observing improvements in memory and orientation in patients after a series of cryotherapy sessions. Nevertheless, the effect of cryotherapy on neurotrophic factors, including BDNF, remains incompletely elucidated and requires further in-depth research [24].

In addition, WBC may have a beneficial effect on a variety of PD symptoms, both motor and non-motor. The results of the study showed that a cycle of WBC treatments significantly increases sinus rhythm variability (HRV), which may indicate a modulatory effect on the autonomic nervous system in people with Parkinson's disease. Such an effect may be relevant in the context of the dysautonomia present in many patients, which compromises quality of life and complicates the course of drug treatment [25]. Additionally, although there are no clear clinical studies evaluating the direct effects of WBC on motor function in PD, there are

indications suggesting that reductions in muscle stiffness and general physiological improvements may translate into improvements in gait quality and coordination. One study confirmed that the motor symptoms of PD are sensitive to temperature changes, which may be one mechanism of action of cryotherapy [26]. Non-motor symptoms, such as depression and anxiety, are often co-occurring in PD and significantly affect patients' quality of life. It was shown that WBC as an adjunct to pharmacological treatment for depression led to statistically significant improvements in mood, quality of life and a reduction in depressive symptoms compared to the control group. Although the study did not directly involve patients with PD, these findings may be relevant to the treatment of affective disorders in this population [1]. In conclusion, systemic cryotherapy is not currently recommended as first-line treatment for Parkinson's disease. Nevertheless, in the light of the available data, it may be a promising adjunct to conventional therapy, particularly in the context of non-motor symptoms such as depression, anxiety or fatigue.

Systemic cryotherapy is also used as a therapeutic component in the treatment of multiple sclerosis [27]. This therapy often leads to a reduction in feelings of fatigue, which is one of the most commonly reported problems by MS patients. Patients undergoing WBC also notice an improvement in sleep quality and a reduction in the symptoms of depression and anxiety that often accompany the disease. In addition, cryotherapy can help reduce muscle tension and spasticity, resulting in better mobility and comfort in daily functioning [28]. Despite the promising results, further studies are needed to confirm the long-term efficacy and safety of WBC in MS therapy.

3.2 Autoimmune diseases

Cryotherapy, both local and systemic, is increasingly used as part of adjunctive treatment for autoimmune diseases such as rheumatoid arthritis and ankylosing spondylitis.

One of the most commonly troublesome symptoms of patients with RA is joint pain, which impedes daily functioning and significantly reduces patients' quality of life. Despite pharmacological treatment, pain persists chronically in many patients. Cryotherapy, which has the potential to reduce pain, can therefore be used as a complementary part of therapeutic

management. For this reason, cryotherapy is increasingly used as an adjunctive element of rheumatoid arthritis therapy, mainly because of its possible effect on pain relief [29].

One clinical experiment involved 56 people suffering from an active form of rheumatoid arthritis. They were given a 16-day programme of whole-body cryotherapy at -130°C for three minutes per day. The results were unequivocally positive, with patients undergoing WBC reporting significant reductions in pain, improvements in disease activity and physical function compared to the control group. Importantly, as many as 58% of patients in the WBC group reduced or completely discontinued pain medication within 12 weeks after treatment [30].

In contrast, another study compared the effectiveness of cold air (-30°C) and traditional ice packs in patients with active RA. Both methods led to a significant reduction in pain, with no clear differences observed between the two, suggesting that the most important therapeutic factor is the exposure to low temperature itself, rather than the specific application technique [31]. Furthermore, the local application of cryotherapy in patients with arthritis has been shown to decrease the concentration of pro-inflammatory mediators such as IL-6, IL-1β, VEGF, PGE2 and the transcription factor NF-κB p65 in the joint fluid. Reducing the concentration of these mediators can lead to a reduction in swelling and inflammatory processes, resulting in pain relief [7]. A review of available studies shows that cryotherapy is effective in reducing pain in patients with rheumatoid arthritis. Their effectiveness is confirmed not only by subjective pain ratings, but also by a reduction in the need for analgesics and an improvement in functional parameters. Although this method is not a substitute for pharmacological treatment, it can be a valuable adjunct to comprehensive RA therapy [32].

Whole-body cryotherapy also shows beneficial effects on ankylosing spondylitis (AS) symptoms, improving both clinical parameters and inflammatory biomarkers. Clinical studies indicate that WBC at -110°C leads to a significant reduction in disease activity, as measured by the BASDAI and ASDAS-CRP indices, and a reduction in pro-inflammatory cytokines such as IL-8 and IL-17 [33]. The BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) scale is a tool for assessing AS activity, based on the subjective assessment of six patient-reported parameters such as fatigue, back pain, peripheral joint pain and swelling, soft tissue tenderness and morning stiffness (its duration and severity). In contrast, the ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score - C-reactive protein) index combines clinical data with C-

reactive protein values, allowing a more objective assessment of disease activity by including both subjective symptoms and inflammatory parameters at the biochemical level [34]. In addition, WBC promotes an improvement in spinal joint range of motion and reduces pain and morning stiffness. The effect is intensified with simultaneous kinesitherapy [35]. Although the data to date appear promising, further carefully designed clinical trials are needed to further evaluate the efficacy and safety of systemic cryotherapy in the treatment of ankylosing spondylitis.

In conclusion, local and systemic cryotherapy, due to its potential to alleviate symptoms of autoimmune and neurodegenerative diseases, is a valuable adjunctive treatment tool.

Table 2. Clinical use of cryotherapy in neurodegenerative and autoimmune diseases. Own elaboration based on the literature.

Disease	**Type of Cryotherapy**	**Clinical Effects**	**References**
Multiple sclerosis	WBC	Reduction in fatigue and spasticity, improved sleep and mood	[4]; [3]; [1]
Parkinson's disease	WBC	Improved heart rate variability, reduced muscle rigidity, mood improvement	[1]; [12]; [6]
Alzheimer's disease	WBC	Enhanced cognitive function and reduced depressive symptoms	[11]; [1]
Rheumatoid arthritis	WBC, LC	Pain and inflammation reduction, lower cytokine levels (IL-6, IL-1β, VEGF)	[7];[6]

Disease	Type of Cryotherapy	Clinical Effects	References
Ankylosing spondylitis	WBC	Reduction in BASDAI and ASDAS-CRP scores, improved spinal mobility	[15];[6];[5]

3.3 Safety and contraindications of cryotherapy

Despite the beneficial therapeutic effects of cryotherapy, it is necessary to take into account the possible contraindications and risks associated with intensive tissue cooling. Contraindications to the use of cryotherapy include cardiovascular diseases such as uncompensated ischaemic heart disease and unstable heart failure, as well as uncontrolled hypertension [36,37].

In addition, contraindications include conditions that may be exacerbated by cold exposure, including cryoglobulinaemia, multiple myeloma, Raynaud's disease, cold urticaria, previous tissue damage caused by cold exposure in a particular area or limb, and peripheral circulation disorders in those areas. Because of cryotherapy's ability to induce vasoconstriction, its use in areas with impaired blood supply can result in serious complications such as tissue necrosis [38].

Potential adverse effects of cryotherapy include local skin damage such as frostbite, as well as systemic symptoms including dizziness, shortness of breath, vasovagal reactions, urticaria, transient elevation of blood pressure, tachycardia and feelings of anxiety [37].

Due to the possibility of complications following cryotherapy, qualification for this type of treatment should be carried out with due care. A detailed history and pre-therapy examination is recommended, including a cardiological assessment (including ECG and blood pressure measurement), analysis of vascular and neurological diseases, verification of contraindications (such as Raynaud's disease or cryoglobulinaemia) and, in the case of local cryotherapy, also an assessment of the skin conditio [36,39].

Summary

Systemic and local cryotherapy is a promising adjunctive tool in the treatment of neurodegenerative and autoimmune diseases, in which chronic inflammation, oxidative stress and dysregulation of the immune system play a key pathophysiological role. Accumulating literature suggests that the effect of cryotherapy is based on a comprehensive effect on the body - including reduction of pro-inflammatory cytokines, improvement of microcirculation, modulation of the hormonal response and effects on neurotransmission. This makes it possible to alleviate symptoms such as pain, fatigue and joint stiffness, as well as improving patients' mood and quality of life.

The results of studies conducted to date indicate that cryotherapy may be a valuable complement to classical therapeutic methods used in neurodegenerative and autoimmune diseases such as multiple sclerosis, ALzheimer's disease, Parkinson's disease or rheumatoid arthritis. Due to the possibility of adverse reactions and the presence of absolute and relative contraindications, careful patient qualification and assessment of potential health risks is necessary before implementing cryotherapy. It is also worth noting that, despite the promising results of the studies to date, there is a need for further, well-designed clinical trials to more precisely determine the efficacy, safety and optimal treatment regimens using cryotherapy for these conditions.

In light of the current state of knowledge, cryotherapy appears not only as an effective physical therapeutic modality, but also as an intervention with possible systemic effects that deserves wider use in everyday medical practice and further in-depth research.

In the light of current knowledge, cryotherapy appears to be not only an effective physical therapeutic tool, but also an intervention with potential systemic effects, deserving wider use in clinical practice and further scientific exploration.

Disclosure

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