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Extreme Exposure to Cold: A Method to Enhance Physical Wellness and Recovery

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Abstract

This paper reviews the current literature on Cryotherapy and its ability to enhance physical wellness and recovery. The paper details the proposed mechanisms of Cryotherapy as well as its various clinical applications regarding the treatment of numerous diseases and physical exercise recovery. The paper also details the possible limitations/detrimental effects of Cryotherapy usage.

Keywords

Cryotherapy, whole body cryotherapy, partial body cryotherapy, cold water immersion, extreme cold exposure

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Comments

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I. INTRODUCTION

The use of extreme cold exposure for medicinal purposes began early in human history. Specifically, in ancient cultures, it was one of the various methods in which individuals would treat physical suffering. In addition to its use in physical suffering, cold remedies including snow, ice, and water mixtures were also utilized to treat disease in ancient Greece, Persia, and the Roman Empire (Bouzigon et al. 2016).

In more recent times, extreme cold exposure therapies have been expanded to include overall wellness practices. For example, Nordic countries have begun to engage in the practice of winter-swimming, during which individuals will regularly bathe in ice-cold water, as they believe that winter-swimming improves their immune system and enhances their ability to cope with daily stress. As such, given its benefits, the tradition of extreme cold exposure treatments is being further developed in several domains including medicine, health/wellness, and sports (Bouzigon et al. 2016).

Two common methods of modern-day extreme cold exposure therapy treatments used for medicine, health, and sports are Partial Body Cryotherapy (PBC) and Whole Body Cryotherapy (WBC). Both of these methods expose the patient to extreme cold for a short duration using either a cryochamber or a cryocabin. More specifically, Partial Body Cryotherapy is performed in a partial cryocabin called a cryosauna. A cryosauna is an open tank in which the individual's entire body excluding the head and neck are exposed to the cold. Cryosaunas are extremely convenient, as they are easily turned on/off and easy to transport. These facts have made Partial Body Cryotherapy the predominant cold therapy remedy for sports events, as they allow the possibility of mobile chambers to be present at sports events (Bouzigon et al. 2016). Partial Body Cryotherapy creates cold exposure through direct contact between the patient and nitrogen.

Specifically, the cold environment is created by spraying nitrogen directed at the body of the patient inside the tank. It is the use of nitrogen that makes it necessary to refrain from having the head and neck exposed to the cold during a Partial Body Cryotherapy procedure due to the harmful effects of breathing nitrogen (Bouzigon et al. 2016).

In contrast to Partial Body Cryotherapy, Whole Body Cryotherapy allows the patient to be entirely exposed to the cold treatment. Whole-Body cryochambers are divided into two or three compartments of different temperatures with the following most common chamber temperatures: -10 degrees Celsius, -60 degrees Celsius, and -110 to -160 degrees Celsius. These chambers create cold air in two different ways. The first way involves large chambers with air compressors that divide oxygen and nitrogen in order to cool nitrogen. When nitrogen is sufficiently cooled, it is recombined with oxygen and injected into the chamber. The second way Whole-Body cryochambers create cold air is by circulating nitrogen in the walls of the chamber (Bouzigon et al. 2016). This second way makes Whole Body Cryotherapy a little safer than Partial-Body Cryotherapy, as the patient is never directly exposed to the nitrogen sprays. Unlike Partial-Body Cryotherapy, Whole-Body cryochambers are not mobile. As such, Whole-Body Cryotherapy is used primarily for rehabilitation in sports centers (Bouzigon et al. 2016).

A third common method of cryotherapy is Cold Water Immersion. Cold Water Immersion involves exposing parts of the body to cold water. Cold Water Immersion is often used to reduce hyperthermia by lowering core body temperature following exercise in hot environments. Cold Water Immersion specifically lowers core body temperature by inducing vasoconstriction of the blood vessels that ultimately limits blood from being exposed to the cold tissues, thereby, cooling them. When the cooling period is completed, the rewarming of the skin causes a peripheral vasodilation that enhances the flow of cooled blood from tissues toward the core. This results in further cooling of core body temperature (White and Wells 2013).

In the next three sections, both the mechanisms and applications of cryotherapy will be detailed. Such applications include clinical treatments of disease, as well as Physical Exercise Recovery pertaining to health/wellness and sports.

II. MECHANISMS OF CRYOTHERAPY

The mechanisms as to how Cryotherapy serves as a therapeutic agent to improve injury and disease recovery are not fully understood. However, there are three proposed mechanisms: a) Nerve transmission in pain fibers; b) Inflammation/edema; and c) Oxidative stress (Garcia et al. 2021). With regard to nerve transmission in pain fibers, exposure to the cold first induces a reduction in skin temperature. This reduction in skin temperature leads to a reduction in peripheral nerve temperature, which results in both a slowed nerve conduction velocity and acetylcholine formation, and subsequently, decreased pain (Bouzigon et al. 2016; Ernst and Fialka 1994). Interestingly, it has been shown that nerve conduction velocity is slowed in both sensory and motor nerves (Garcia et al 2021). This apparent decrease in pain from a slowed nerve conduction velocity is likely an effect of increased pain threshold and tolerance at the sight of Cryotherapy application (Garcia et al 2021). Although peripheral nerve conduction is slowed, cold exposure also stimulates the sympathetic nervous system effect of norepinephrine release. Norepinephrine is specifically released from the peripheral nerve endings and brainstem nuclei and reaches the spinal cord through the posterior supporting arteries. This is significant to pain relief as it is these posterior supporting arteries that supply the substantia gelatinosa, the area of the skin where the pain afferent nerves terminate (Bouzigon et al. 2016). Thus, by slowing the conduction of peripheral nerves and activating the sympathetic nervous system, cold exposure through Cryotherapy can potentially alleviate pain associated with physical injury and disease.

In addition to nerve transmission in pain fibers, another proposed mechanism of Cryotherapy's therapeutic effects on injury and disease recovery relates to the inflammation that commonly results from a musculoskeletal injury or chronic disease. Specifically, chronic inflammation often induces pain by either chemically or mechanically activating pain receptors and free nerve endings. Thus, researchers are interested in Cryotherapy's possible effect of reducing inflammation, and thereby, reducing the pain that results from inflammation. One key sign of inflammation is Edema, the entrance of fluid into the extravascular space due to vascular changes and increased vascular permeability that often result from an injury or chronic disease. It is the increased pressure in the extravascular space that partly leads to the mechanical stimulation of pain caused by inflammation. It is believed that Cryotherapy assists with this issue by both decreasing vascular permeability and restricting arterial and soft tissue blood flow through cold-induced vasoconstriction (Garcia et al 2021). In addition to helping reduce inflammation through reducing Edema, Cryotherapy also affects the main agents of inflammation, cytokines. Specifically, studies have shown that Cryotherapy decreases levels of the pro-inflammatory cytokine, TNF-α, and increases levels of the anti-inflammatory cytokine, IL-10. Interestingly, studies have also shown that Cryotherapy increases levels of the pro-inflammatory cytokine, IL-6. Despite this, Cryotherapy still reduces inflammation as IL-6 has been shown to possess some anti-inflammatory properties. For example, one study reported that patients with rheumatoid arthritis who were treated with Whole Body Cryotherapy demonstrated the best clinical outcome regarding joint swelling and pain despite having increased levels of IL-6 (Garcia et al. 2021).

Yet another proposed mechanism of the therapeutic effects of Cryotherapy is its ability to reduce oxidative stress. As a part of normal cell metabolism, cells produce free radicals and reactive oxygen species. These free radicals can potentially be harmful to the body as they will attack cellular components, particularly lipids, in a process called lipid peroxidation. This lipid peroxidation can result in the generation of more reactive oxygen species that can ultimately cause more cellular damage including membrane damage. Given this potential for cellular injury, the body has various methods of neutralizing free radicals including enzymes (e.g. superoxide dismustase, catalase, and glutathione) and non-enzymatic antioxidants. An imbalance between reactive oxygen species and antioxidants is termed oxidative stress (Bouzigon et al 2016). Studies have shown that acute and regular Whole Body Cryotherapy has a protective effect on oxidative stress as it causes an increase in plasma anti-oxidative capacity. For example, one study in which a series of thirty-six two-minute Whole Body Cryotherapy exposures at -110 degrees Celsius and a series of twenty three- minute Whole Body Cryotherapy exposures at -130 degrees Celsius were performed found that the Whole Body Cryotherapy exposures were able to increase anti-oxidative capacity by significantly lowering the level of plasma total oxidative status thirty minutes after exposure as well as the following day. In addition, the study also found that the body's level of anti-oxidative status initially decreased after exposure but increased the following day, implying that a repetition of Whole Body Cryotherapy exposures might lead to the activation of antioxidant defense mechanisms in the body (Bouzigon et al. 2016).

III. <u>CLINICAL APPLICATIONS OF CRYOTHERAPY</u>

A plethora of research has revealed numerous clinical applications of Cryotherapy. Several of these are discussed more fully below.

A. <u>Fibromyalgia</u>

Cryotherapy has been found to aid patients suffering from Fibromyalgia. Fibromyalgia is a chronic musculoskeletal pain disorder that is typically widespread in the body due to the allodynia (i.e. touch sensitivity) and hyperalgesia (i.e. increased sensitivity/response to pain) resulting from the disease (Bouzigon et al. 2016; Rivera et al. 2018). This neurological pain results from issues with the body's pain modulation system including nociceptive receptor hyperexcitability, decreased inhibitory response, an imbalance in neurotransmitter levels as well as pro-inflammatory and anti-inflammatory mediator levels (Bouzigon et al. 2016; Rivera et al. 2018; Klemm et al. 2021). Disturbances in the hypothalamic-pituitary-adrenal axis and cytokine dysregulation are other causes of Fibromyalgia (Klemm et al. 2021). The pain of Fibromyalgia often leads to fatigue, sleep disorders, anxiety and depression, joint stiffness, and headaches (Bouzigon et al. 2016; Rivera et al. 2018; Klemm et al. 2021). Fibromyalgia also results in several symptoms of comorbid mental disorders including the subjective sensation of swelling, concentration difficulties, and memory impairment (Bouzigon et al. 2016; Rivera et al. 2018; Klemm et al. 2021). The pain of Fibromyalgia becomes disabling in some individuals, and thus, results in adverse effects on their daily lives including a decreased ability to work and engage in activities (Rivera et al. 2018). Due to the fact that there is no definitive cure for this disease, research has been attempting to find effective and safe therapies to relieve symptoms (Rivera et al. 2018).

It has been discovered that Cryotherapy is an effective therapeutic treatment to relieve the symptoms of Fibromyalgia. For example, one study in which Whole-Body Cryotherapy was conducted on fifty Fibromyalgia patients found an overall improvement in the patients' quality of life. Specifically, researchers employed fifteen sessions of Whole-Body Cryotherapy with each session consisting of thirty seconds at -60 degrees Celsius and three minutes at -140 degrees Celsius for a duration of three weeks. Researchers measured changes in the patients' pain with a Visual Analogue Scale, a global health status questionnaire to assess the patients' disease activity, a Short Term Health Survey to assess changes in the patients' physical and mental health, and a Fatigue Severity Scale to measure changes in patients' fatigue. The researchers ultimately found a positive effect of Whole-Body-Cryotherapy on the daily life of Fibromyalgia patients as there were improvements in all of the above qualitative indices. With regard to the mechanism of these improvements, the researchers speculated that these improvements were due to the effects of Cryotherapy on the balance between pro-inflammatory and anti-inflammatory mediators in the body's pain modulation system (Bouzigon et al. 2016).

Further research has also corroborated the previous study's findings of Cryotherapy's positive effects on the quality of life of Fibromyalgia patients. Specifically, another study assessed Cryotherapy's potential benefits in the control of Fibromyalgia pain and the impact of disease. This study compared the effects of a Cryosense TCT cabin and pure rest on change in pain (measured through a Visual analogue scale), change in burden of disease (measured through the Fibromyalgia impact questionnaire), and change in severity of Fibromyalgia (measured through the Combined Index of Severity of Fibromyalgia) among sixty Fibromyalgia patients. Patients assigned to the Cryosense TCT cabin were subjected to three minutes of Whole-Body-Cryotherapy at -196 degrees Celsius. Ultimately, the researchers found that Whole-Body-

Cryotherapy had a significant effect on pain, impact of disease, and disease severity. Similar to the previous study, the researchers stated that these positive effects could be attributed to Whole-Body Cryotherapy’s effect of reducing oxidant levels as a reduction in oxidant levels could decrease muscular damage and accelerate recovery after normal bouts of physical activity. The researchers also postulated that Whole Body Cryotherapy’s ability to alleviate stress due to its activation of neuroendocrine and metabolic functions was beneficial to Fibromyalgia patients as stress is an important component to the disease (Rivera et al. 2018).

A third study also supported the previous studies’ results regarding Cryotherapy’s aid in pain alleviation. However, this study also assessed the molecular effects of Whole Body Cryotherapy by assessing changes in cytokines as a result of Cryotherapy treatment given Cryotherapy’s documented effects on cytokines. It also assessed how long the clinical effects of Whole Body Cryotherapy on Fibromyalgia symptoms last. Specifically, researchers compared the effects of Whole-Body Cryotherapy on Fibromyalgia patients exposed to six sessions of Whole-Body Cryotherapy at -130 degrees Celsius for a duration of six weeks. Changes in pain level after six sessions, changes in disease activity and pain after three sessions and after three months of discontinued therapy, and changes in cytokine levels (i.e. IL-6, Tumor Necrosis Factor Alpha, and IL-10) were measured. The researchers ultimately found that Whole Body Cryotherapy resulted in a significant reduction in pain and disease activity after six and three sessions respectively. In addition, with regard to the amount of time Cryotherapy benefits lasted, researchers found that Whole Body Cryotherapy had no clinical benefit on Fibromyalgia patients three months after its discontinuation (Klemm et al. 2021).

Regarding the molecular effects of Whole Body Cryotherapy on Fibromyalgia patients, researchers found significant differences in the levels of IL-1, IL-6, Tumor Necrosis Factor Alpha, and IL-10 after Whole Body Cryotherapy when compared to healthy individuals subjected to Whole Body Cryotherapy. In fact, levels of IL-1, IL-6, and IL-10 were significantly altered over time in Fibromyalgia patients. This was significant as pain induction and maintenance is prolonged by an imbalance between pro-inflammatory and anti-inflammatory cytokines. This imbalance is known to be altered in Fibromyalgia patients. Additionally, this was also significant as the cytokine, IL-1, itself or in combination with the cytokine, Tumor Necrosis Factor Alpha, increases inflammation and lowers the pain threshold in peripheral nerves, thereby, increasing the pain experienced by Fibromyalgia patients. Moreover, IL-1 and IL-6 also cause various symptoms of Fibromyalgia including fever, headaches, myalgia, and arthralgia, hyperalgesia, depression stress, and fatigue. In contrast, the cytokine, IL-10, works against inflammation by increasing the pain threshold. Given these cytokines' important effects on both pain and Fibromyalgia symptoms, the fact that Whole Body Cryotherapy changes the levels of these cytokines in Fibromyalgia patients is an indicator of its efficacy as a treatment (Klemm et al. 2021).

B. <u>Chronic Low Back Pain</u>

Another pain disorder for which Cryotherapy has been shown to be a potential therapeutic treatment is Chronic low back pain. Chronic low back pain is a common, musculoskeletal pain syndrome that can impact the quality of life (Bouzigon et al. 2016). Due to its long-lasting nature, Chronic low back pain can cause significant movement limitation, especially in physical exercise. One possible cause of Chronic low back pain is the involuntary processes of aging that result in deterioration of the functional capabilities of the human body. Another possible cause of Chronic low back pain is lumbar spine ailments that limit the abilities of people with low back pain due to health issues associated with motor organs (Giezma et al. 2014). One study performed on outpatients suffering from Chronic low back pain that utilized three perceptual scales reported pain relief in patients suffering from chronic low back pain. Specifically, researchers reported that chronic low back pain patients showed pain relief when subjected to ten three minute Whole Body Cryotherapy exposures at both -65 degrees Celsius and -5 degrees Celsius. Interestingly, pain relief usually occurs when skin temperature is below 13.6 degrees Celsius. However, skin temperature never reached this threshold when chronic low back pain patients were exposed to Whole Body Cryotherapy in this study. As such, researchers postulated that this pain relief could be explained by a lessening of nerve transmissions over a large area of the body or by humoral mechanisms (Bouzigon et al. 2016).

Another study performed on adults aged sixty-five to seventy-seven years old also documented Whole Body Cryotherapy as an effective therapy for enhancing the mobility and electrical stimulation of the muscles of patients suffering Chronic low back pain. Specifically, this study compared the effects of Whole Body Cryotherapy performed on Chronic low back pain patients twice a week to Whole Body Cryotherapy performed on Chronic low back pain patients everyday of the week. Patients were exposed to -120 degrees Celsius air over the course of therapy. The researchers measured lumbar spine mobility and EMG measurements. Ultimately, the researchers reported that those Chronic low back pain patients that were exposed to Whole Body Cryotherapy everyday of the week experienced significantly lower values of active potentials for the erector spinae muscles in the lumbar part of the spine and a significant increase in the mobility of the lumbar spine. The researchers attributed these positive results to the positive effects of Whole Body Cryotherapy including a decrease in pain, a reduction in inflammation, and the values of the action potentials of erector spinae muscles in the lumbar part of the spine. Given these positive results, researchers further found that the analgesic effects, anti-inflammatory effects, and decrease in muscle tension from Whole Body Cryotherapy allowed Chronic low back pain patients to increase their workload and intensity of their performed exercises, thereby, allowing researchers to conclude that Whole Body Cryotherapy was an effective treatment to improve their overall condition (Giezma et al. 2014).

Yet another study also purported the effectiveness of Whole Body Cryotherapy as a therapeutic treatment for Chronic low back pain. Specifically, this study utilized a quasi-experimental trial on Chronic low back pain patients between eighteen and sixty-five years of age in order to assess Whole Body Cryotherapy's effects on pain, disability, and inflammatory markers. Patients were subjected to twenty sessions of Whole Body Cryotherapy at -120 degrees celsius for a duration of five weeks. During treatment, researchers measured pain and disability measures through the Pain Numerical Rating Scale, the Oswestry Disability Index, and the Roland Morris Questionnaire. Researchers utilized patient blood samples to assess inflammatory markers levels.   Researchers' results indicated that there was a significant decrease between initial and final questionnaire results with a significant reduction in the Pain Numerical Rating Scale results found after just four cryotherapy sessions. With regard to inflammatory markers, results indicated decreasing values of the pro-inflammatory marker, IL-2, and decreasing values of the anti-inflammatory marker, IL-10 (Salas-Fraire et al. 2021).   This study was significant as it showed a possible mechanism as to how cryotherapy was able to decrease pain and increase mobility in patients with Chronic low back pain.

C. <u>Multiple Sclerosis</u>

A neuro-degenerative disorder for which Cryotherapy has also been shown to be a potential therapeutic treatment is Multiple Sclerosis. Multiple Sclerosis is an autoimmune, degenerative disease of the central nervous system that is characterized by inflammation, demyelination, and axonal loss (Kalsatou and Flouris 2019). At the onset of the disease, individuals experience relapsing neurological deficits followed by partial or full remission. As the disease progresses, individuals enter a second progressive phase in which neurologic symptoms worsen resulting in disability (Kalsatou and Flouris 2019). Multiple Sclerosis is an unpredictable, heterogeneous disease that manifests itself through a variety of symptoms including paralysis, ataxia, spasticity, incontinence (i.e. lack of voluntary control over urination or defecation), and fatigue syndrome. Fatigue syndrome has been found to be the most prevalent of Multiple Sclerosis symptoms as it occurs in 70-80 % of Multiple Sclerosis patients. Fatigue syndrome also has the most significant impact on the quality of life of Multiple Sclerosis patients as it often affects their social, physical, and occupational well-being (Bouzigon et al. 2016). Multiple Sclerosis also affects individuals' way of life due to thermoregulatory failures from exercise-induced hyperthermia or exposure to heat that result in exacerbated neurological symptoms. In fact, the neurological symptoms of Multiple Sclerosis patients can be exacerbated by as little as a 0.5 degree Celsius increase in body temperature (Kalsatou and Flouris 2019).

Studies have shown that Whole Body Cryotherapy is an effective treatment for the neurodegenerative processes associated with Multiple Sclerosis due to its antioxidative effects as it has been established that individuals with Multiple Sclerosis have a significantly lower Total Antioxidant Status (TAS) when compared to healthy individuals. Specifically, researchers compared the antioxidative status and antioxidative enzyme activity of various antioxidative enzymes (i.e. SOD, and CAT in erythrocytes) of patients with Multiple Sclerosis to a control group of healthy participants. Participants with Multiple Sclerosis had ten two-three minute exposures of cryotherapy that went from -120 degrees celsius to -110 degrees celsius as well as exercises to complete after their cryotherapy. In contrast, healthy participants were given only exercises to complete. Ultimately, researchers found that patients with Multiple Sclerosis had higher Total Antioxidant Status (TAS) after treatment with Whole Body Cryotherapy when compared to the healthy participant control group. However, researchers found no increase in antioxidant enzyme (i.e. SOD and CAT) activity after Whole Body Cryotherapy when compared to healthy subjects (Miller et al. 2010). This finding was confirmed by a later study performed by the researchers in which a long-lasting effect of uric acid, the main antioxidant in the blood, was observed in Multiple Sclerosis patients subjected to ten three minute sessions of Whole Body Cryotherapy at -130 degrees Celsius (Bouzigon et al. 2016). These findings were significant as oxidative stress is a hallmark of the negative symptoms of neurodegenerative disorders such as Multiple Sclerosis. This oxidative stress can be combated with antioxidants as antioxidants are reducing agents that neutralize oxidative compounds before they cause damage to various biomolecules. Thus, the positive effect of an increased level of Total Antioxidant Status despite the stagnant level of antioxidant enzymes suggested that Whole Body Cryotherapy is an effective adjuvant therapy for patients suffering from Multiple Sclerosis (Miller et al. 2010).

Additional research has shown that another type of Cryotherapy, Cold Water Immersion, can help increase the functional capacity of Multiple Sclerosis patients due to its ability to eliminate the thermoregulatory issues of Multiple Sclerosis that ultimately result in an increase in body temperature. Specifically, one study performed thirty minute pre-cooling sessions with lower limb water immersion in a 16 degrees to 17 degrees Celsius water bath on both Multiple

Sclerosis patients and healthy participants in order to assess fatigue, gait, and water temperature. The study ultimately found that after forty minutes of continuous exercise, pre-cooling led to an improvement in the physical performance and functional capacity of Multiple Sclerosis patients. In addition, pre-cooling led to a heat deficit of 128 W, and by the end of the exercise sessions, body heat storage amounts were near resting values. he researchers attributed this improvement to the observed 1 degree Celsius decrease in rectal (core) body temperature after the exercise protocol. In contrast, researchers found that healthy participants had an overall significant increase in body heat storage amounts. The researchers attributed this improvement to the observed 1 degree Celsius decrease in rectal (core) body temperature after the exercise protocol (Kalsatou and Flouris 2019).

Functional capacity of Multiple Sclerosis has also been improved by utilizing Cryotherapy to improve Fatigue Status. Researchers have found that after ten three minute Whole Body Cryotherapy exposures between -110 degrees Celsius and -130 degrees Celsius, Multiple Sclerosis patients had an overall improvement in both fatigue status and functional capacity (Bouzigon et al. 2016).

D. Ankylosing Spondylitis

Research has also indicated that Cryotherapy can serve as a therapeutic treatment for individuals suffering from inflammatory rheumatic diseases due to its ability to both decrease pain and joint inflammation (Guillot et al. 2013). One example of an inflammatory rheumatic disease for which Cryotherapy could serve as a beneficial treatment is Ankylosing Spondylitis. Ankylosing Spondylitis is a chronic autoimmune-related, progressive, inflammatory rheumatic disease that affects the axial skeleton as well as the sacroiliac joints. Chronic inflammation results in a complete fusion of the vertebrae in the spine called Ankylosis and can result in a complete loss of mobility of the spine. In addition to the axial skeleton and sacroiliac joints, Ankylosing Spondylitis can also affect the peripheral joints, skin, eyes, bowels, and lungs. The main symptom of Ankylosing Spondylitis is pain and stiffness in various parts of the body including the lower back, upper buttock area, the neck, and remaining regions of the spine (Bouzigon et al. 2016; Straburzynska-Lupa et al. 2018). The pathophysiology of Ankylosing Spondylitis is unknown, but research has shown that genetic, immunological, and inflammatory factors, particularly proinflammatory cytokines and chemokines, are the most important factors in the onset of the disease (Straburzynska-Lupa et al. 2018).

Research regarding Cryotherapy and Ankylosing Spondylitis has shown that Whole Body Cryotherapy improves both disease activity and functionality indices among Ankylosing Spondylitis patients. Specifically, a study performed by Stanek et al. (2015) that compared the effects of Ankylosing Spondylitis patients receiving Whole Body Cryotherapy (i.e. 3 seconds in a -60 degrees Celsius chamber and 3 minutes in a -120 degrees Celsius chamber) in addition to kinesiotherapy to Ankylosing Spondylitis patients receiving only kinesiotherapy reported a 40 % decrease in the Bath Ankylosing Spondylitis Disease Activity Index in the group of participants who received Whole Body Cryotherapy. In addition, researchers also reported that the scores of participants who received Whole Body Cryotherapy in addition to kinesiotherapy corresponded to an “inactive disease” score. Researchers also reported a 30 % decrease in pain as indicated by the Bath Ankylosing Spondylitis Functional Index as well as “inactive disease” scores among participants who received Whole Body Cryotherapy in addition to kinesiotherapy (Bouzigon et al. 2016; Stanek et al. 2015). Similar results were reported in a study conducted by Straburzynska-Lupa et al. (2018) in which the effects of Whole Body Cryotherapy at -110 degrees Celsius, -60 degrees Celsius, and no Whole Body Cryotherapy at all on Ankylosing Spondylitis patients were compared. Similar to Stanek et al. 2015, the researchers reported significantly decreased postherapy disease activity according to a combined function of the Bath Ankylosing Spondylitis Disease Index and the Ankylosing Spondylitis Activity Score. The researchers also reported those who received Whole Body Cryotherapy at -110 degrees Celsius had a significantly lower Bath Ankylosing Spondylitis Disease Index than those who received no Whole Body Cryotherapy (Straburzynska-Lupa et al. 2018).

The study conducted by Straburzynska-Lupa et al. (2018) also examined the effects of Whole Body Cryotherapy on the levels of proinflammatory cytokines. The researchers specifically reported a significant decrease in IL-8 concentration after Whole Body Cryotherapy. This was a significant finding as IL-8 is a proinflammatory chemokine that causes neutrophil influx and inflammation.

E. Diabetes

Another prevalent disease for which Cryotherapy serves as a potential therapeutic treatment is Diabetes. Diabetes is characterized by a progressive dysregulation in energy de-partitioning that can lead to organ complications. Previous research has suggested mild cold exposure as a therapeutic approach to target this characteristic metabolic dysfunction. Research has shown that cold exposure can increase energy exposure as well as whole body glucose and fatty acid utilization. Furthermore, repeated cold exposures can lower fasting glucose levels, lower insulin levels, and improve dietary fatty acid handling, resulting in increased glucose tolerance (Bukowieki 1989; Ivanova and Blondin 2021). A study performed by Bukowieki et al. (1989) found that cold exposure reverses the diabetic effects of high-fat intake, and that nutrition-induced insulin resistance is amplified in sedentary animals living close to thermoneutral temperatures. Similar results were also determined by a study performed by Ivanova and Blondin (2021) in which cold exposure elicited a catecholamine-induced, intracellular, lipolysis of triglycerides (i.e. fats) that resulted in an increased rate of fatty acid oxidation. Ivanova and Blondin (2021) also purported that cold exposure led to decreases in both glucose levels and insulin levels in the blood. Similar to Bukowieki et al. (1989), Ivanova and Blondin (2021) also determined that cold exposure's effects on fat metabolism and glucose metabolism were temperature-dependent.

Mechanistically, Bukowieki et al. (1989) determined that cold exposure has the same role as insulin as it promotes glucose uptake in skeletal muscle as well as both white and brown adipose tissue. Thus, cold exposure stimulates glucose uptake by enhancing glucose oxidation through insulin-independent pathways (Bukowieki et al. 1989). Ivanova and Blondin (2021) furthered this assertion in two studies they performed on men with obesity and overweight men diagnosed with Type II Diabetes. Researchers found that daily cold exposure specifically stimulated basal glucose transporter protein, GLUT-4's, translocation to the cell membrane of muscle cells. Thus, researchers purported that the improvements in glucose levels in the blood due to cold exposure were a result of shivering/muscle contraction mediated GLUT-4 translocation that ultimately resulted in the body's enhanced ability to transport glucose into skeletal muscles (Ivanova and Blondin 2021).

F. <u>Depression and Anxiety</u>

A newly-discovered clinical application of Cryotherapy is the treatment of Depression and Anxiety disorders. A study by Rymaszewska et al. (2008) performed on outpatients aged eighteen to sixty-five years with existing depressive and anxiety disorders compared the effects of treatment with a cryogenic chamber and the typical psychopharmacotherapy for three weeks to treatment with just the normal psychopharmacotherapy for three weeks. The researchers utilized Hamilton's Depression Rating Scale and the Hamilton's Anxiety Rating Scale to assess patients' depression and anxiety levels. The researchers ultimately found at least a 50 % decrease in the Hamilton's Depression Rating Scale scores of 34.6 % of those who received cryogenic chamber treatment in addition to psychopharmacotherapy and 2.9 % of those who only received psychopharmacotherapy. Researchers found similar results with the Hamilton's Anxiety Rating Scale. Specifically, researchers found at least a 50 % decrease in the Hamilton's Anxiety Rating Scale scores in 46.2 % of those who received cryogenic chamber treatment in addition to psychopharmacotherapy. Researchers attributed these positive Cryotherapy effects to Cryotherapy's effects on the body's HPA axis and endogenous opioids. Specifically, previous research has stated that the body's opioid peptide systems play a significant role in motivation, attachment behavior, response to stress and pain, and the control of food intake, and that Cryotherapy activates this opioid peptide system to neutralize both internal and external pain. Thus, a multi-system reaction elicited by Cryotherapy could play a role in the treatment of mental disorders (Rymaszewska et al. 2007). Later research has also found positive effects of Cryotherapy on individuals' mental state. A study performed by Szczepańska-Gieracha et al. found that Whole Body Cryotherapy had a significant influence on improving the well-being and mood of patients with spinal pain syndromes and peripheral joint reprise with the strongest effects on patients with spinal pains and depressive symptoms. In fact, researchers found that the worse the mental state of the patient before Cryotherapy was, the stronger its positive effects were (Szczepańska-Gieracha et al. 2013).

IV. PHYSICAL EXERCISE RECOVERY

While Cryotherapy is used extensively as clinical treatment of diseases, perhaps the most common application of Cryotherapy is Physical Exercise Recovery regarding health/wellness and sports. There are three main methods of administering Cryotherapy for the purpose of Physical Exercise Recovery: a) Ice; b) Whole Body Cryotherapy and Partial Body Cryotherapy; and c) Cold Water Immersion.

The application of ice to an injury is a primary treatment for exercise injuries such as sprains, contusions, fractures, and acute musculoskeletal soft tissue injury. Ice is typically applied immediately after an injury to alleviate pain at the site of the injury by inhibiting nerve conduction velocity and to prevent edema or swelling in the injured area. Applying ice immediately after an injury has occurred is extremely important as it limits hemorrhage formation and secondary cell death. Despite these positive effects of ice, research has shown ice to be an ineffective treatment for exercise recovery. Specifically, research assessing the effects of a single application of ice reported no effect on soreness. Similarly, a meta-analysis also concluded that ice did not reduce soreness or accelerate the recovery strength following exercise. In addition, ice is also considered an ineffective mode of treatment due to the manner in which it must be administered. Specifically, the fact that ice is applied locally and is limited to a duration of thirty minutes means that it is most effective when it is administered repeatedly at frequent intervals as this will enhance the magnitude of cooling. This mode of treatment is extremely demanding, and thus, athletes are not likely to comply with it. Furthermore, studies assessing the effectiveness of repeat applications of ice were inconclusive. A few studies have shown positive effects on soreness and blood markers of muscle damage. However, other studies have shown no significant effect on recovery of soreness or blood markers of muscle damage (Kwiecien and

McHugh 2021). For example, one study performed by Howatson et al. (2005) assessed the effects of repeated applications of ice massage on indirect markers associated with muscle damage (i.e. creatine kinase and myoglobin) and other aspects of muscle function including muscle soreness, limb girth, and range of motion. Howatson et al. (2005) concluded that there was no significant difference in levels of indirect markers associated with muscle damage or measures of muscle function (i.e. muscle soreness, limb girth, and range of motion) between one group treated with repeated ice application and another group treated with no repeated ice application. From these results, the researchers ultimately concluded other studies have shown either no effect or a delay in soreness recovery and adaptation to exercise training (Howatson et al. 2005).

The second method of administering Cryotherapy for the purpose of Physical Exercise Recovery is Whole and Partial Body Cryotherapy. Previous research has shown that Whole and Partial Body Cryotherapy has effects on the body's normal inflammatory response to muscle damage, the Autonomic Nervous System, and Oxidative Stress. First, regarding the body's Inflammatory response, research has shown that intense exercise training can induce muscle damage, and subsequently inflammation (Bouzigon et al. 2016). Specifically, muscle strain experienced during contractions in response to increased mechanical stress result in a loss of structural integrity to the sarcolemma and contractile system. This disruption of sarcolemmal integrity and disruption of the contractile system leads to increased cell permeability and swelling as well as impaired force-producing capability (White and Wells 2013). This ultimately results in muscle soreness and reduced function (Bouzigon et al. 2016; White and Wells 2013). Thus, Cryotherapy is utilized to lessen undesirable reductions in muscle performance and increases in muscle soreness that often manifest immediately after exercise (White and Wells

2013; Kwiecien and McHugh 2021). It is specifically thought that Cryotherapy acts as an anti-inflammatory that reduces the stimulus activating pathways that could cause secondary damage to the muscle (White and Wells 2013). One such pathway that Cryotherapy acts upon is that of the inflammatory cytokines/proteins. A study performed by Pournot et al. (2011) that subjected eleven well-trained runners to Whole Body Cryotherapy at -110 degrees Celsius ultimately found that Whole Body Cryotherapy performed immediately after exercise enhanced muscular recovery by restricting the inflammatory process elicited by low to moderate muscle damage. The researchers specifically found that Whole Body Cryotherapy was able to restrict the inflammatory process by reducing the increase in the anti-inflammatory cytokine, IL-1β and inflammatory protein, CRP (Bouzigon et al. 2016).

Regarding the autonomic nervous system, research has shown that Whole and Partial Body Cryotherapy affects heart rate variability through its stimulation of the Parasympathetic branch of the Nervous system, which is known to be related to exercise recovery and a decreased risk of cardiovascular incidents (Bouzigon et al. 2016; Partridge et al. 2021). Specifically, researchers have reported that after one exposure to Whole or Partial Body Cryotherapy (i.e. Whole Body Cryotherapy at -110 degrees Celsius for three minutes and Partial Body Cryotherapy at -160 degrees Celsius for three minutes), cold exposure enhanced Parasympathetic Nervous system activation through cold stimulation in the trigeminal brainstem in forty young men (Bouzigon et al. 2016). Another study performed by Westerlund et al. (2006) on ten females reported an increase in parasympathetic activity during moderate physical activity after a single, two minute Whole Body Cryotherapy exposure at -110 degrees Celsius (Bouzigon et al. 2016).

Regarding Oxidative stress, exercise induces an enhanced formation of Reactive Oxygen species due to the fact that Reactive Oxygen species formation is closely correlated with muscle action intensity. Whole Body Cryotherapy's apparent oxidative stress benefits have been directly applied to physical exercise as it has been discovered that Whole Body Cryotherapy applied prior to training can reduce the risk of oxidative stress, and thus, reduce the extent of muscle injuries induced by intense exercise. One particular study that highlighted this was a study performed on six elite rowers in which the activity of superoxide dismutase and glutathione peroxidase in participants exposed to Whole Body Cryotherapy and not exposed to Whole Body Cryotherapy was measured. The study found that the activity of superoxide and glutathione peroxidase in the blood was lower after the third day of training in the participants who received Whole Body Cryotherapy when compared to participants who did not receive Whole Body Cryotherapy. In addition, the study also found that Whole Body Cryotherapy exposure before training led to a decrease in the circulation of peroxidation products in elite rowers whereas there was an increase in the circulation of peroxidation products in elite rowers who were not exposed to Whole Body Cryotherapy (Bouzigon et al. 2016).

The third and final method of Cryotherapy utilized for Physical Exercise Recovery is Cold Water Immersion. Specifically, research has shown that Cold Water Immersion accelerates recovery for several types of exercise including eccentric exercise, endurance exercise, resistance exercise, laboratory cycling protocols, and team-sports exercise. The physiological mechanisms of how Cold Water Immersion influences Physical Exercise recovery are unclear. However, research has attributed Cold Water Immersions's influences to the removal of body heat, reduced tissue temperature, and hydrostatic pressure effects (Tipton et al. 2017). Similar to Whole and Partial Body Cryotherapy, research has shown that Cold Water Immersion reduces muscle soreness following exercise. In fact, a meta-analysis of Cold Water Immersion reported that Cold Water Immersion reduces soreness for up to ninety-six hours after exercise. Research has also shown that Cold Water Immersion reduces blood markers for muscle damage such as creatine kinase and inflammation as well as improves the recovery of functional performance (Kwiecien and McHugh 2021; Tipton et al. 2017). However, research remains ambiguous as to Cold Water Immersion's role in accelerating recovery of strength loss following exercise. Researchers attribute this ambiguity to the variability in immersion temperatures and the variability in immersion duration. Specifically, Cold Water Immersion temperatures range between 5 degrees Celsius and 20 degrees Celsius. Although some researchers have purported that lower Cold Water Immersion temperatures benefits physical exercise recovery, research has demonstrated that decreasing water temperature does not elicit any recovery benefits. In fact, research has shown that reducing water temperature likely results in decreased discomfort. In addition, Cold Water Immersion duration is also limited by lower water temperatures due to the potential for cold-induced injuries or hypothermia if duration exceeds thirty minutes. Given these limitations, research has shown that Cold Water Immersion is most beneficial to physical exercise recovery if applied at frequent intervals of approximately ten minutes (Kwiecien et al. 2021).

Although Whole Body and Partial Body Cryotherapy and Cold Water Immersion are considered to be more effective forms of Cryotherapy for Physical Exercise Recovery than ice, it is unclear which method is more effective. One study assessing the effectiveness of both methods on exercise recovery after a marathon found that Whole Body Cryotherapy had a harmful effect on muscle function when compared to Cold Water Immersion. Additionally, Whole Body Cryotherapy positively influenced perceptions of training stress compared to Cold

Water Immersion. However, researchers also reported that neither cryotherapy method positively influenced blood markers of inflammation or structural damage (Wilson et al. 2017).

V. <u>LIMITATIONS/DETRIMENTAL EFFECTS OF CRYOTHERAPY</u>

Despite the numerous benefits of Cryotherapy as treatment for both disease and Physical Exercise Recovery, Cryotherapy does have some potential limitations and detrimental effects. One potential detrimental effect is that Cryotherapy impedes the healing process of injuries due to reducing the body's inflammatory response. Although the body's inflammatory response can cause secondary damage, it is also vital to the structural and functional repair of damaged tissues. Thus, many researchers have argued against Cryotherapy due to its potential to delay or impair the regeneration process or natural healing process that occurs following injury and exercise ((Kwiecien and McHugh 2021).

Additionally, another potential detrimental effect of Cryotherapy, especially, Cold Water Immersion, is its potential detrimental effects on muscle mass and strength gains as well as its impairment of muscle protein synthesis rates, especially if Cryotherapy is applied regularly as a part of an individuals' post-exercise regime. Researchers attribute these potential detrimental effects to Cryotherapy's ability to reduce intramuscular temperature and its ability to reduce blood flow to the exercised muscle (Kwiecien and McHugh 2021).

The limitations of Cryotherapy, particularly Whole Body Cryotherapy and Partial Body Cryotherapy, are primarily mechanistic. Specifically, one of the largest limitations of both of these methods of Cryotherapy is the lack of standardization in Whole Body Cryotherapy and Partial Body Cryotherapy protocols regarding exposure temperature and technology used. This results in difficulty determining the validity and practicality of the two methods (Bouzigon et al. 2016).

VI. CONCLUSION

The use of Cryotherapy has advanced significantly since its first use during the ancient civilizations and has proven to be a significant contributor to the disciplines of medicine, health/wellness, and sports. Current research has primarily focused upon Cryotherapy's roles in the improvement of both mental and physical health of patients suffering from inflammatory and mental diseases as well as the improvement of Physical Exercise Recovery of healthy individuals (Bouzigon et al. 2016). As its use expands, further research should focus upon precisely identifying mechanisms of Cryotherapy's benefits, increasing the types of diseases that could be treated by Cryotherapy, as well as determining how Cryotherapy could potentially increase physical performance during exercise (Partridge et al. 2021).

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