

## Review Article

# The Perspective of Whole Body Cryotherapy in Rheumatic Diseases: A Narrative Review

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## Abstract

**Objective:** Whole Body Cryotherapy (WBC) consists in using cold application as a form of physical therapy to reduce pain and inflammation levels.

**Data source:** This narrative review reports data from trials studying the role of WBC in treating rheumatologic diseases such as Rheumatoid Arthritis (RA), Fibromyalgia (FM), Ankylosing Spondylitis (AS)

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and Chronic Pain. The systematic literature research was conducted on the past ten years. The main search keywords were "whole body", "cryotherapy", "cabin", "Rheumatoid Arthritis", "Ankylosing Spondylitis", "Fibromyalgia", "Psoriatic Arthritis", "Chronic Fatigue", "Rheumatic disorder", "Rheumatic disease".

**Data selection and data Extraction:** The sample size, subject's age and gender, year of publication, duration and temperature of exposition, physical activity and outcomes were extracted. Of all the articles examined, only 17 met the inclusion criteria.

**Data synthesis:** Data regarding 816 subjects aged between 17 to 80 were included in the review. The WBC protocols covered temperatures from -10 to -196 degrees Celsius, while exposure times ranged from 30 seconds to 3 minutes. WBC was usually paired with other kinds of physical therapies, such as Kinesiotherapy and physical exercise. WBC seems to be a safe procedure for all the groups of the population examined, with no major events to report.

**Conclusion:** WBC could be an "add-on therapy" useful in the management of several Rheumatic diseases, even though numerous aspects need to be clarified, as shown in the research agenda proposed in this review. Hence, further studies are necessary to establish standardized protocols.

**Keywords:** Whole body; Cryotherapy; Rheumatoid arthritis; Ankylosing spondylitis; Fibromyalgia; Psoriatic arthritis; Chronic fatigue; rheumatic disorder

## Introduction

Cryotherapy corresponds to the therapeutic application of cold to control inflammation and relieve pain in sports after traumas, often using cold packs to do so. Cryotherapy is often used as an additional therapy to control the level of inflammation in rheumatic diseases [1,2]. Cold has a positive effect in mitigating pain levels and allows the patients to increase physical activity [3]. Cryotherapy seems to downregulate the levels of pro-inflammatory cytokines [4]. Whole-body cryotherapy (WBC) is a short exposure to extremely cold air in a controlled cabin for time periods ranging from 2 to 5 mins. WBC was born in Japan during the '70s. Starting from Germany, it spread throughout Europe ten years later [5]. This technique requires exposure to a very low temperature (from -110°C to -160°C) in a dry environment for a short period of time, usually 1-3 minutes. Some studies demonstrated its efficiency in decreasing articular pain and supporting physical rehabilitation [6,7].

Some data show that WBC is able to reduce inflammation and to produce analgesic effects, therefore it has been explored in inflammatory musculoskeletal disorders such as rheumatoid arthritis and ankylosing spondylitis. It's been demonstrated that, as well as recovering after any form of heavy exercise, Cryotherapy determines an increase in white blood cells, antiinflammatory cytokines, ACTH, beta-endorphins, cortisol and catecholamines. Moreover, Cryotherapy is believed to cause immunostimulation, by increasing noradrenaline response to cold, reducing pain through the decrease of nerve conduction and increasing the level of plasma total antioxidant cytokines, therefore improving immune function in general. Also, while muscle

stress and inflammation increase the level of oxidants in the intercellular space leading to membrane damage and, ultimately, to an increase in inflammation, the cold has been suggested to reduce oxidant production by decreasing the level of inflammation.

In 1986 Yamauchi found that the effects of WBC with temperatures as low as  $-175^{\circ}\text{C}$  influences cortisol concentrations and has a direct analgesic effect in RA patients, while Samborski and Sobieska, in a cross over study (which compared the effects of WBC to hot mud pack), showed that WBC with temperatures at  $-150^{\circ}\text{C}$  could lead to an increase of the pressure pain threshold, decrease of the number of tenderpoints and pain levels in general in the short-term in patients affected by FM.

In 2000, Offenbächer reviewed treatment options in FM, considering cardiovascular fitness training physiotherapy, massage, acupuncture and trigger point injection, biofeedback, TENS and WBC, which may reduce localized as well as generalized pain in the short term. Even though there is no single best treatment for FM, a multidisciplinary approach combining physical therapy and these other treatment options is thought to be the most promising strategy. Also, in the same review, Offenbächer delved further into the use of WBC in previous research programs and its rationale as a treatment possibility for rheumatoid diseases [8]. In addition, some recent meta-analyses have confirmed the positive influence of cryogenic temperatures on patients with AS [9,10]. The effects of WBC on oxidative stress in healthy people [4,11,12] and AS patients [11,13] is under investigation, especially to establish and standardize treatment protocols [1].

The aim of this narrative review is to report trials and studies regarding the application of WBC in rheumatic diseases such as RA, FM, AS and CF in order to summarize and better understand its limitations and effectiveness in patients affected by rheumatic diseases.

## Methods

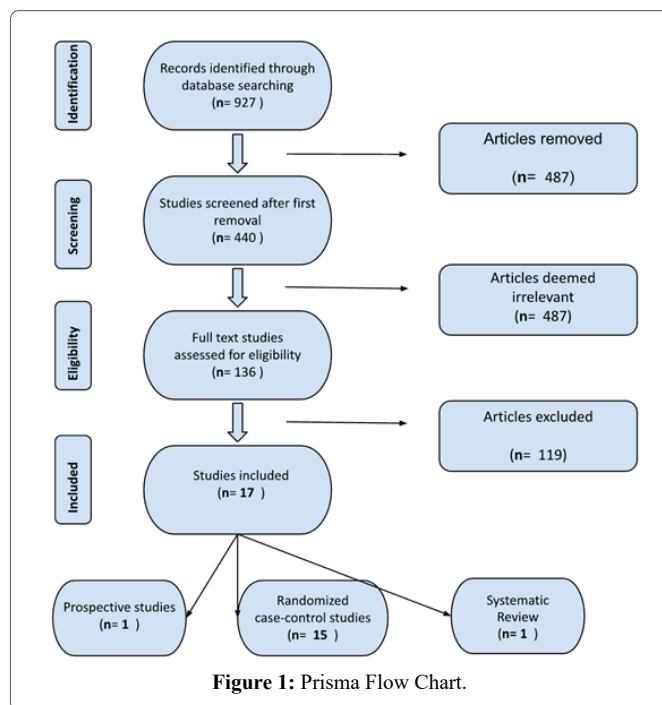
To conduct the electronic and systematic search, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Guidelines were followed and databases such as PubMed, Scopus and ScienceDirect were used. The main search keywords were “whole body”, “cryotherapy”, “cabin”, “Rheumatoid Arthritis”, “Ankylosing Spondylitis”, “Fibromyalgia”, “Psoriatic Arthritis”, “Chronic Fatigue”, “Rheumatic disorder”, “Rheumatic disease”. By doing so, the following data regarding the number and characteristics of participants (sample size, subject’s age, and gender) were obtained, as well as year of publication, description of the intervention (application characteristics, duration and temperature of treatment), level of activity, inclusion criteria, trial groups, outcomes, tools used to evaluate results and study results.

Results from the past ten years were investigated and 17 articles which met the criteria were found, after thorough research conducted by PMS, FM and AM. The search strategy is depicted in Figure 1.

Duplicated and irrelevant articles, wrong outcomes, incorrect patient population, incorrect intervention and topics were all criteria of exclusion.

## Results

The results are reported according to the specific disease explored in the study.



## Fibromyalgia

Fibromyalgia is a chronic widespread pain disorder in which the neurogenic origin of the pain, featured by allodynia and hyperalgesia, results from an imbalance in the levels of neurotransmitters and, consequently, of the peripheral pro- and anti-inflammatory mediators [13]. In 2018 Javier Rivera evaluated the efficacy of WBC to control pain and symptoms in sixty patients affected by FM in an open, randomized, crossover trial. Patients were divided into two groups: while one of them underwent 15 WBC sessions in 3 weeks ( $-60^{\circ}\text{C}$  (30s) plus  $-140^{\circ}\text{C}$  (3min)) with a Cryosense TCT cabin, the remaining acted as a control group. This first period of treatment was followed by a 1-week of washout during which the two groups were inverted, and another 3-weeks period of treatment. The Study measured change ( $\Delta$ ) in pain after 2 and 4 weeks, according to a visual analogue scale (VAS),  $\Delta$  burden of disease, evaluated by the FM Impact Questionnaire (FIQ), and severity of FM, measured by the Combined Index of Severity of FM (ICAF). It showed that outcomes were significantly larger in the WBC group after the first period of treatment. The authors concluded that WBC with a Cryosense TCT cabin may be a useful adjuvant therapy for FM [14]. In the same year, Vitnet randomized 24 patients with FM into 2 groups; 11 patients were treated with 10 sessions of WBC ( $-110^{\circ}\text{C}$ ) for 3 min, over a duration of 8 days in addition to usual care, while the control group (13 patients) received usual care. Patients in the WBC group reported a significantly improved quality of life compared to the control group, lasting up to a month after the exposure to cold [15]. Furthermore, in 2021 Klemm compared 23 FM patients to 30 healthy subjects (HC) after 6 serial sessions of WBC at  $-130^{\circ}\text{C}$  for 3 min, administered twice a week, evaluating both symptomatic outcomes (such as change in pain level and disease activity) and laboratories findings (like cytokine levels interleukin (IL)-1, IL-6, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and IL-10) after 3 sessions and 3 months after WBC exposition. The patients’ opinions about the satisfaction, effectiveness and relevance of WBC were also reported. Patients treated with WBC showed a significant

reduction in pain and disease activity after 3 and 6 sessions, without clinical benefits at 3 months follow up. However, patients in the WBC group reported high levels of satisfaction and considered WBC relevant and valuable. Laboratory findings showed that patients suffering from FM had a significantly different response of IL1, -6 and -10 to WBC compared to healthy subjects [16]. Taking all in consideration WBC could be a therapeutic option for FM patients.

## Rheumatoid Arthritis (RA)

In 2015, Gizinska compared the effects of WBC on 25 patients, exposed for 10 sessions in 2 weeks to  $-110^{\circ}\text{C}$  for 3 min, to 19 patients treated with a traditional rehabilitation program (TR). Systemic levels of IL-6 and TNF- $\alpha$  were evaluated. After therapy all patients exhibited similar improvement in pain levels, disease activity, fatigue and physical activity. The TR group showed significantly better results in HAQ only; similar important reduction in IL-6 and TNF- $\alpha$  levels were detected in both groups [17]. In 2017 H. Hirvonen investigated 60 RA patients, randomized into 3 groups: (1) WBC at  $-110^{\circ}\text{C}$ , (2) WBC at  $-60^{\circ}\text{C}$ , or (3) local cryotherapy. Each session was administered three times/day for 7 consecutive days and was combined with conventional rehabilitation. RA disease activity, daily plasma samples and total peroxyl radical trapping antioxidant capacity of plasma (TRAP) were evaluated before the first and after the last session. The authors report that only WBC at  $-110^{\circ}\text{C}$  induced a short-term increase in TRAP during the first treatment session and that the effects were short, being unable to maintain a significant improvement in oxidative stress or adaptation along 1 week [18]. Moreover, in 2019 Sadura compared the effects of WBC (administered for 20 days once a day at  $-140^{\circ}\text{C}$  for 3 min) and conventional rehabilitation (CR) in 50 RA patients divided into a study group (CT,  $n = 25$ ) and a control group (CR,  $n = 25$ ). The disease activity score (DAS28), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, serum concentrations of IL-6, TNF- $\alpha$ , macrophage migration inhibitory factor [MIF]) and IL-10 cytokines were measured. No statistically significant differences were observed between the two groups DAS28, morning stiffness and pain, as well as in the serum concentrations of tested cytokines after rehabilitation, nor between patient groups. Statistically significant improvements in CRP serum level were reported only in the CT group [19]. Finally, Klemm recently evaluated 56 patients affected by active RA undergoing a 16-day multimodal rheumatologic complex treatment randomized to either WBC (6 applications in 14 days at  $-130^{\circ}\text{C}$  for 3 min) or no treatment. Significant differences between the two groups regarding pain, disease activity, functional capacity, cytokine levels, and consumption of analgesics were assessed. After 12 weeks, the modification in pain scale remained significant, despite the disease activity score and functional capacity, which were still meaningful but not statistically significant [20].

## Ankylosing spondylitis

In 2015, Stanek investigated the capacity of WBC sessions to produce beneficial effects on index of AS disease Activity Index (BASDAI) and BASFI, pain intensity and spine mobility parameters in AS patients, after a WBC session (at  $-120^{\circ}\text{C}$ ) lasting 3 minutes a day with a subsequent 60 minutes of kinesiotherapy, compared with 60 minutes of kinesiotherapy only for 10 consecutive days. The authors reported that the WBC group with subsequent kinesiotherapy showed an average of about twice better results compared to the group treated only with kinesiotherapy [21].

In a study conducted in 2018 by Anna Straburzyńska-Lupa, sixty-five patients affected by AS were randomized to one of these three arms : WBC at  $-110^{\circ}\text{C}$ ,  $-60^{\circ}\text{C}$  (for 3 min each session, once a day per 8 days), or exercise therapy (non-WBC). The Bath BASDAI, AS Disease Activity Score (ASDAS-CRP), concentration of C-RP, and the concentrations of IL-8, IL-17, also the concentration of thiobarbituric acid reactive substances (TBARS) were assessed to determine the effect of WBC on oxidative stress. BASDAI, ASDAS-CRP, and the IL-8 concentration decreased in all the studied patients. At the end of the treatment the TBARS concentration was significantly increased in the group treated with WBC at  $-110^{\circ}\text{C}$ . After therapy BASDAI resulted significantly lower in the WBC at  $-110^{\circ}\text{C}$  group compared to the non-WBC group [22]. Moreover, Romanowski compared the effects of 3 regimens of treatment (WBC at  $-110^{\circ}\text{C}$  for 3 min combined with exercise, WBC at  $-60^{\circ}\text{C}$  for 3 min combined with exercise and exercise therapy alone) on disease activity and the functional parameters at the end of the 8-day treatment of the 92 patients with AS. All patients showed a significant reduction in disease activity, back pain, fatigue, duration and intensity of morning stiffness and a significant improvement in the patient's functional capacity, spine mobility and chest expandability, with no changes in the levels of CRP. The group that underwent cryotherapy at  $-110^{\circ}\text{C}$  manifested a significantly reduced BASDAI compared to exercise therapy only ( $p = 0.024$ ) [23]. In 2018, Stanek estimated the impact of WBC (at  $-120^{\circ}\text{C}$ ) lasting 3 minutes a day with a subsequent 60-minute session of kinesiotherapy on oxidative stress in 16 patients affected by active AS, compared to a session of kinesiotherapy alone. The parameters of oxidative stress (antioxidant enzymatic and nonenzymatic antioxidant status, lipid peroxidation products, total oxidative status (TOS), and oxidative stress index (OSI)) as well as BASDAI and BASFI indexes were calculated at baseline and one day after the sessions. In the WBC group, a significant decrease of oxidative stress markers (TOS and OSI) and a significant increase of total antioxidant status were detected. Also the BASDAI and BASFI indexes decreased significantly in both groups, but the differences between before and after treatment were significantly higher in the WBC group than in the control one [24]. Stanek also investigated the impact of WBC on cardiovascular risk factors in male patients with AS, by evaluating disease activity, markers of inflammation, oxidative stress, lipid profile, and atherosclerosis plaque after WBC sessions (administered at  $-120^{\circ}\text{C}$  for 3 min a day) with subsequent kinesiotherapy, or kinesiotherapy alone. In both groups, a decrease of the total cholesterol and LDL cholesterol, triglycerides, sCD40L, PAPP-A, and PLGF levels were observed, but the difference was higher in the WBC group. Similar results were found considering the BASDAI and BASFI indexes [10].

## Chronic fatigue

Bettoni, in 2013, evaluated a total of 100 fibromyalgic patients: 50 subjects underwent cryotherapy, and 50 did not. Patients treated with WBC (15 sessions in 3 weeks,  $-60^{\circ}\text{C}$  (30s) plus  $-140^{\circ}\text{C}$  (3min)) showed a higher improvement of the quality of life measured by Visual Analogue Scale, Short Form-36, Global Health Status and Fatigue Severity Scale, in comparison with the patients of the control group [14]. Also, in 2021 Kujavsky compared the functional interrelation of fatigue and cognitive, cardiovascular and autonomic nervous systems implications in a group of 32 patients affected by CFS with 18 healthy controls. The patients were treated with WBC ( $-120^{\circ}\text{C}$ ) combined with a static-stretching (SS) program with 5 sessions per week, for 2 weeks. In the CFS group an increased fatigue was found, related to baroreceptor function. After ten sessions of WBC with a static

stretching exercise, both groups showed an improvement regarding fatigue, cognitive function, cardiovascular and autonomic nervous systems [25]. Recently, the same author investigated the tolerability and effects of SS and WBC on fatigue, daytime sleepiness, cognitive functioning and autonomic nervous system functioning in 32 patients suffering from CFS compared to a control group (18 healthy subjects). All patients underwent a programme of five sessions per week for 2 weeks, composed by SS associated with WBC. A significant decrease in fatigue was reported in the CFS group. Moreover, some parameters of cognitive functioning, such as speed of processing visual information and set-shifting, also improved in both groups [26].

## Discussion

Rheumatic diseases are systemic disorders, affecting the organism as a whole, thus needing systemic therapy. In addition physical exercise is undoubtedly fundamental to produce beneficial effects on pain in these diseases [27], but it's not sufficient alone. For instance, low intensity exercise is the main therapy applied in rheumatic patients [28], but adjuvant therapies for muscular soreness are needed as well, such as cold therapy. Therefore, using WBC in addition to medications and physical therapy, could lead to a significant improvement in the patient's general well-being and quality of life and, at the same time, to a decrease of systemic collateral effects by reducing drug dosage. Data here indicates the importance of employing a combined therapeutic approach [27] of WBC to reduce pain in Rheumatic diseases when associated with physical activity. This combination seems to lead to adjunctive beneficial results, such as improvement in mood, promotion of a better pain adjustment and facilitation of physical and mental activities [18,19,24,27,29,30]. It is also suggested that this therapeutic association could improve the management of patients affected by AR, ameliorating the aerobic capacity and reducing their cardiovascular risk [31]. Different pathways and mechanisms of action have been investigated to explain WBC's positive effects on patients. Firstly, WBC is capable of significantly reducing oxidative stress and inflammation levels in the organism. This is the reason why it has been suggested for clinical use in all Rheumatic diseases [32]. Furthermore, WBC is able to regulate neurotransmission involved in pain perception, and also to balance pro- and anti-inflammatory cytokine levels in the body. Moreover, WBC has been used with a positive effect on other systemic diseases such as Atherosclerosis and dyslipidemia, proving itself to be a useful method of prevention [10].

WBC's positive effects on cardiovascular and autonomic functions have been shown by Kujavsky as well: his recent studies confirm that WBC is well tolerated by patients affected with CFS and leads to symptomatic improvements associated with cardiovascular health. Hence, given the preliminary data showing the beneficial effect of cryotherapy, its relatively easy application, good tolerability, and proven safety, it appears to be an approach worthy of attention [26].

Moreover, as shown by Guillot by pooling 6 studies including 257 RA patients, a significant decrease activity score after chronic cryotherapy was assessed. Also, local cryotherapy was demonstrated to induce intra-joint temperature decrease, thus down regulating mediators involved in inflammation and joint damage, such as cytokines, proangiogenic factors and cartilage-degrading enzymes [1].

WBC is also to be considered a safe therapy option (using temperatures spanning from -130°C to -60°C), as demonstrated by the lack of side effects in the rheumatic patients enrolled in the studies

taken into account in this paper. Similar results about safety have been found in healthy subjects and athletes as well as obese and/or old patients [33-36]. WBC seems also to have positive effects in the rheological parameters of blood in older women showing a significant decrease in erythrocyte elasticity and aggregation indices [35]. In particular, Kujavsky reported that in older subjects (aged > 55) with Mild Cognitive Impairment (MCI), WBC treatment determined a significant improvement of short-term memory, such as a reduction in IL-6 levels and an increase in BDNF release when whole blood was challenged with Aβ42 (Amyloid β-42) [36]. Considering all together we can argue that WBC can enhance performance and alleviate chronic conditions in older patients, combined with regular physical exercise. It could also represent a potential affordable treatment in conditions associated with cognitive dysfunction [25,26]. WBC could be proposed for clinical use in RA and other joint inflammatory diseases as an additional therapy to conventional or biological disease-modifying antirheumatic drugs (DMARDs), as well to corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) in order to decrease the dosage of systemic pharmacological treatments, minimizing the likely of severe related side effects [1].

Even if studies on cryotherapy were not numerous, the evidence suggesting the benefits on pain relief and disease activity is increasing. These results, however, need to be confirmed, because pain relief can be due to several factors and pain level is probably not the most specific parameter to evaluate the efficacy in the management of disease. In addition the duration of clinical benefit seems to be short. Unfortunately, the lack of literature concerning WBC and its protocols leads to questions about the intensity (temperature wise) and duration of the treatment, repetition of sessions or the most suitable time to perform WBC in addition to physical therapy. Finally, additional research is required to define the best moment to start WBC regarding the course and stage of the target disease. All these unanswered questions are reported in the Research Agenda. However, the impact and contribution of WBC to medical and physical therapy appears to be promising, but not yet completely defined [37,38], as it is equally not fully determined the comparison between the effects of systemic and local cryotherapy [37,39], because of the lack of studies comparing the effectiveness of WBC among other cryo-therapies (Table 1).

Research agenda
Standardization of protocols related to each specific disease is required
Personalization of protocols according to subject characteristics is necessary
Duration of exposure, range of temperature during exposure, frequency and number of sessions have to be defined
Determination of the appropriate timing of exposure in relation to physical therapy has to be determined
Determination of the appropriate timing of exposure in relation to the stage of disease needs to be investigated
Determination of the protocol based on disease's activity/inactivity is necessary
The gender difference in safety and clinical efficacy must be attentively reported

Table 1: Research Agenda.

To discern between PBC and WBC, it is helpful to refer to a study conducted by Bouzigon in 2016. In PBC treatment, the head region is excluded and a more moderate-sized mobile device is used than in WBC. The study also demonstrates that PBC is the preferred treatment in the sport recovery domain, since it can be easily performed

	Author	Article	Pathology	Diagnostic criteria	N. patients	Inclusion Criteria	Exclusion Criteria	Temperature/time (WBC group)	Temperature/time (control group)	Outcome	Results	Adverse events/Results
1	J.Rivera (2018)	RCT	FM	ACR	60	25-80yo FM for more than 1 year Reduced or no response to therapies Not pregnant	Cardiovascular or psychiatric comorbidity Cold intolerance Changes in pharmacological or non-pharmacological treatment during the study Body temperature over 37.5 °C.	10 sessions in 3 weeks -196 C° for 3min		Primary endpoint: changes in VAS and in FIQ. Secondary endpoint: changes in the severity of the disease (assessed by ICAF).	Improvement of: VAS, FIQ and ICAF	Tremors, stiffness, headache, vomiting, palpitations, sleep disturbances (8%)
2	P.Klemm (2021)	Prospective Control Study	FM	2010/11 diagnostic criteria of FM (revised in 2016)	53 (23 FM and 30 HC)	18 – 80yo FM	Pregnant Change of drug therapy in the last 4 weeks Other physical therapies Contraindications to WBC	6 sessions in 3 weeks -130 C° for 3min	No treatment	Primary endpoint: changes in VAS after 6 sessions. Secondary outcome: changes in VAS after 3 sessions of WBC and 3 months of discontinued therapy and in cytokine levels (IL-1, IL-6, TNF-a and IL-10)	Subjective satisfaction of WBC group. No changes: TNF-a. Reduction of: VAS, FIQ, IL-1, IL-6, IL-10)	Nausea (1%), Erythema (1%)
3	T. Sadurra-Kieklucka (2019)	RCT	RA	EULAR	50 (25 each group)	18-59yo Same therapy for at least 3 months.	Surgery within the last 6 months, prior cancer.	1 session daily for 20 days; 1 WBC session (for 3min at -140 C° for 20 days) + FKT + 30min of physical exercise	1 FKT session+ 30min of water exercise	Primary endpoint: changes in DAS28, changes in VAS and ESR.	Improved in both groups: DAS28, VAS.	None observed
4	Peres (2017)	Systematic Review	RA		683			WBC + local cryoT + physical activity		Primary endpoint: evaluation of disease activity and pain relief.	Improvement of: VAS, Unchanged: HAQ, ESR.	
5	M. Gizinska (2015)	RCT	RA	ACR	44 (25 and 19)	Post menopausal women Diagnosed >1 year of AR. mean age = 55.9, SD = 5.08, IQR = 51–60		10 sessions in 2 week (-10 C°) + (-60 C°) + (-110 C°) for 3min	Traditional rehabilitation program with other physical agents (i.e. magnetotherapy)	Primary endpoint: changes in DAS28, changes in VAS, physical function (measured by HAQ-DI) and 50-meter walking test	Improvement in both groups: disease status, functional performance, VAS, DAS28, TNF-a, IL-6. Decrease in: pain, fatigue, IL-6 and TNF.	None observed

6	H.Hirvonen (2017)	RCT	RA	Active AR ≥5 swollen and ≥5 tender joints VES ≥20, CPR>20, Morning stiffness > 30 min	60 (20, 20 and 20)	Active sero-positive AR	Hypertension Arhythmia Cardiovascular disease Pulmonary disease Raynaud's disease Cold allergy Cold broncho-spasm	20 sessions in a week First study group: sessions at -110 C°; Second study group: sessions at -60 C°	20 sessions in a week; local cryotherapy	Primary endpoint: changes in TRAP	Only WBC at -110° produced an increase in TRAP	Intolerance and side effects (15% in both study groups)
7	S. Kujavsky (2021)	RCT	CF	Fukuda criteria	50 (32 CF+ 18 HC)		Psychiatric disorders CF secondary to other causes	10 sessions every 2 weeks -110 C° for 30s increasing up to 150s during 2 weeks + stretching	10 sessions every 2 weeks (-110 C°) for 30s increasing up to 150s during 2 weeks + stretching	Primary endpoint: reduction of fatigue severity (measured by CFQ, FSS and FIS).	Improvement of: CFQ, FSS, FIS	None observed
8	M.Romanowsky (2020)	RCT	AS	Modified New York criteria	92 (32, 31 and 29)	18-65yo; stable pharmacotherapy (2wks for CC and NSAIDs, 12wks for DMARDS)	Presence of other chronic pathologies and contraindications to WBC	6 sessions in a week. First study group: sessions at -110 C Second study group: sessions at -60 C°. Each session followed by 30min of physical exercise	6 sessions in a week. Physical therapy only.	Primary endpoint: changes in BASDAI, ASDAS-CRP. Secondary outcomes: functional parameters (measured by BASFI and BASMI)	No difference between groups in: BASFI, BASMI, PCR. Best BASDAI and ASDAS-CRP for WBC	Respiratory infection (3%)
9	A. Straburzyńska (2018)	RCT	AS	Modified New York criteria	65 (23, 21 and 21)	BASDAI>4 Stable pharmacotherapy (2wks for CC and NSAIDs, 12wks for DMARDS)	Contraindications to WBC	6 sessions in a week. First study group: sessions at -110 C°; Second study group: sessions at -60 C°. Each session followed by 30min of physical exercise	6 sessions in a week. Physical therapy only.	Primary endpoint: changes in BASDAI, ASDAS-CRP, IL-8 and IL-17 levels, total antioxidant capacity measurement.	Improvement in (all): BASDAI, ASDAS-CRP, IL-8, PCR, IL-17, TBARS. Decisive improvement of BASDAI in WBC. No difference between WBC -110° and WBC -60°	None observed
10	C.Garcia (2021)		CP	Pain >3months								
11	M.Vitenet (2018)	RCT	FM	ACR	24 (11 and 13)	18 years or older	Modification of usual treatments during the experimentation Recent history of WBC treatment Diagnosis of coexisting diseases Potential contraindications for WBC procedures	10 sessions in 8 days; -110 C° for 3 min	No treatment	Primary endpoint: changes in pain and/or inflammatory processes, quality of life and perceived health	Improvement: health-reported quality of life	None observed

12	Klemm (2022)	RCT	RA	EULAR	56 (31 and 25)	18 years or older >3.6 or pain level >5 on a NRS and a DAS28 >3.2.	Body weight over 120 kg Intolerance to cold Any contraindication to cryotherapy Acute infection during the trial Change in pharmacological treatment or non-pharmacological treatment	6 sessions in 14 days; -130°C for 3 min	No treatment	Primary endpoint: changes in pain on an NRS, in DAS28, functional capacity (measured by HAQ), serum levels of IL-6, IL-10 and use of analgesics.	Improvement in: pain level, DAS28, functional capacity and disability, Reduction in: cytokine levels and use of analgesics	None observed
13	Stanek (2015)	RCT	AS	New York Criteria for AS	48 (32 and 16)	No associated pathologies- No treatment with DMARDs, biologic agents, or steroids.		1 session/day for 3 minutes, with a subsequent 60 minutes of kinesiotherapy	1 session/day for 10 days. 60-minute session of kinesiotherapy only	Primary endpoint: evaluation of BASDAI and BASFI Secondary endpoint: changes in pain intensity and chosen spine mobility parameters.	Reduction in: BASDAI, BASFI in the study group	None observed
14	Stanek (2018)	RCT	AS	Modified New York Criteria	32 (16 each group)	No associated pathologies- No treatment with DMARDs, biologic agents, or steroids		1 session/day for 10 days. 3 minutes a day with a subsequent 60-minute session of kinesiotherapy	1 session/day for 10 days. 60-minute session of kinesiotherapy only	Primary endpoint: evaluation of BASDAI and BASFI Secondary endpoint: changes in oxidative stress parameters	Improvement in: SOD, total antioxidant activity Reduction: oxidative stress markers; higher reduction of BASFI and BASDAI in study group	None observed
15	Stanek (2018)	RCT	AS	Modified New York Criteria	32 (16 each group)	No associated pathologies- No treatment with DMARDs, biologic agents, or steroids		1 session/day for 10 days. 3 minutes a day with a subsequent 60-minute session of kinesiotherapy	1 session/day for 10 days. 60-minute session of kinesiotherapy only	Primary endpoint: evaluation of BASDAI and BASFI; changes in markers of inflammation (i.e. IL-6), oxidative stress, lipid profile, and atherosclerosis plaque.	Reduction in: oxidative stress markers, BASDAI and BASFI, total cholesterol and LDL cholesterol, triglycerides.	None observed
16	Bettoni (2012)	RCT	CF/FM	ACR	100 (50 WBC + 50 no WBC)	Age range 17-70 years		15 sessions in 3 weeks; -60°C for 30 sec, then -140°C for 3 min	No WBC treatment	Primary endpoint: evaluation of VAS, of physical and SF-36, of health status, of FSS	Improvement: quality of life	None observed

17	S.Kujavsky (2022)	RCT	CF	Fukuda criteria	50 (32 + 18 HC)		Psychiatric/psychological impairment Fatigue not being the main complaint	10 sessions in 2 weeks; SS + -110/-160°C	10 sessions in 2 weeks; SS + -110/-160°C	Primary end-point: changes in fatigue, daytime sleepiness, cognitive functioning and autonomic nervous system functioning	Improvement in: some domains of cognitive functioning (speed of processing visual information and set-shifting). Reduction in: fatigue.	None observed
<b>Abbreviations</b>												
<b>WBC=</b>		Whole Body Chriotherapy					<b>ICAF=</b>		Combined Index of Severity of Fibromyalgia			
<b>RCT=</b>	<b>Randomized Trial</b>	<b>Control Trial</b>	Randomized Control Trial					<b>HAQ-DI=</b>	Health Assessment Questionnaire			
<b>FM=</b>	Fibromyalgia					<b>TRAP=</b>	Total peroxyl radical trapping antioxidant capacity of plasma					
<b>RA=</b>	Rheumatoid Arthritis					<b>CFQ=</b>	Chalder Fatigue Scale					
<b>AS=</b>	Ankilosing Spondylitis					<b>FSS=</b>	Fatigue Severity Scale					
<b>CF=</b>	Chronic Fatigue					<b>FIS=</b>	Fatigue Impact Scale					
<b>CP=</b>	Chronic Pain					<b>ASDAS=</b>	AS Disease Activity Score					
<b>ACR=</b>	American College of Rheumatology					<b>BASFI=</b>	Bath Ankylosing Spondylitis Functional Index					
<b>EULAR=</b>	European League Against Rheumatism					<b>BASMI=</b>	Bath Ankylosing Spondylitis Metrology Index					
<b>SD=</b>	Standard Deviation					<b>SF-36=</b>	Short Form Health Survey 36					
<b>IQR=</b>	Interquartile Range					<b>ESR=</b>	Erythrocyte Sedimentation Rate					
<b>NSAIDS=</b>	Non-steroidal anti-inflammatory drugs					<b>MIF=</b>	Macrophage migration Inhibitory Factor					
<b>DMARDS=</b>	Disease modifying antirheumatic drugs					<b>NRS=</b>	Numerical Rating Scale					
<b>BASDAI=</b>	Bath Ankylosing Spondylitis Disease Activity Index					<b>VAS=</b>	Visual Analog Scale					
<b>DAS=</b>	Disease Activity Score					<b>FIQ=</b>	Fibromyalgia Impact Questionnaire					

**Table 2:** Summaries of WBC studies.

in the field, or wherever needed, whereas WBC requires cabins and more stable and stationary equipment. This is the reason why WBC is more widespread in a rehabilitation context. Furthermore, WBC is a convenient option when more patients need to be treated at the same time. Of course there are limitations that seem to stand for both treatments: while PBC seems to be the least safe option (since direct contact with nitrogen is needed for the procedure), it is easier to exit a PBC cabin. Another limitation applies to energy consumption, which is high for both treatments, although it seems that PBC is the most economical one in terms of purchase. However, large quantities of nitrogen (which is expensive and hard to supply) is needed to perform PBC, while it is not used in WBC. Lastly, PBC exposes the user to temperature heterogeneity during the treatment, while there is not sufficient data about WBC cabins' temperature [2] (Table 2).

## Conclusion

WBC seems to be a safe and promising therapeutic option to add to systemic treatments and physical activity in order to improve quality of life in the management of numerous Rheumatic diseases, such as RA, AS, FM and Chronic Fatigue. Its positive effects on pain, oxidative stress, inflammatory response in the system and overall well-being of patients are encouraging. However many items need to be investigated in detail and further studies are necessary. Standardized protocols are not completely defined, considering the lack of literature on this matter. Hence, further studies are required

## Declarations of Interest

None



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