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ORIGINAL ARTICLE

Effects of 15 consecutive cryotherapy sessions on the clinical output of fibromyalgic patients

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Abstract 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. Whole body cryotherapy is a peculiar physical therapy known to relieve pain and inflammatory symptoms characteristics of rheumatic diseases, through the regulation of the cytokine expression. The aim of this study was to qualitatively evaluate the effects of cryotherapy on the clinical output of fibromyalgic patients. A total of 100 fibromyalgic patients (age range 17–70 years) were observed; 50 subjects were addressed to cryotherapy, while the second group (n=50) did not underwent to the cryotherapic treatment. All subjects kept the prescribed pharmacological therapy during the study (analgesic and antioxidants). The referred health status pre- and post-observation was evaluated with the following scales: Visual Analogue Scale, Short Form-36, Global Health Status and Fatigue Severity Scale. Fibromyalgic patients treated with cryotherapy reported a more pronounced improvement of the quality of life, in comparison with the non-cryo treated fibromyalgic subjects, as indicated by the scores of the qualitative indexes and sub-indexes, that are widely recognized tools to assess the overall health status and the effect of the treatments. We speculate that this improvement is due to the known direct effect of cryotherapy on the balance between pro- and anti-inflammatory mediators having a recognized role in the modulation of pain.

Keywords Fibromyalgia · Pain · Quality of life · Whole body cryotherapy

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Introduction

Fibromyalgia (FM) is a chronic widespread pain disorder estimated to affect 0.5 to 5 % of adult Western populations [1]. It is a persistent and debilitating condition with potentially devastating effect on people's quality of life, limiting their daily activities and, thus, imposing large economic burdens on society [2].

In 2010, the American College of Rheumatology (ACR) adopted new clinical criteria for diagnosing FM, based on a widespread pain index and a symptom severity scale and improved the previously used tender point examination [3, 4].

The most important symptom of FM is represented by the chronic widespread pain, and recent researches showed its neurogenic origin; moreover, neuroimaging studies showed that FM is associated with aberrant processing of painful stimuli in the central nervous system [5]. Indeed it has been postulated that the pain sense is the result of a neurochemical

imbalance in the central nervous system that leads to a "central amplification" of pain perception, with consequent allodynia (heightened sensitivity to stimuli that are not normally painful) and hyperalgesia (increased response to painful stimuli) [2]. At the molecular level, this imbalance is due to a relative change in the level of neurotransmitters and their receptors leading to a hyperactivation of the ascending (pro-nociceptive) pathways and, consequently, a depression of the descending (anti-nociceptive) pathways [6]. In FM patients have been found high cerebrospinal fluid levels of neurotrophins, i.e. nerve growth factor, and tachykinins, i.e. substance P, which are known to enhance the sensitivity of nociceptors and are also involved in the inflammatory regulation [7]. Consequently, high levels of the pro-inflammatory cytokines interleukin (IL)-6, IL-8 and those of the anti-inflammatory IL-1ra, have been found in the peripheral blood and skin of FM patients [8]. Particularly, IL-8 activates the sympathetic branch of the nervous system and it increases nociceptive sensitivity [9].

Studies on pain showed that FM patients complain pain at a lower threshold than healthy controls in response to pressure (dolorimetry) on some body area [2, 10].

Cold-based therapies are commonly used for relieving pain symptoms, particularly in case of inflammatory diseases, injuries and overuse symptoms, and in these two latter cases, mainly in the field of sports medicine [11]. A peculiar form of cold therapy or stimulation, namely whole body cryotherapy (WBC), was proposed 30 years ago for the treatment of rheumatic diseases: it consists of a brief exposure (2 to 3 min) to very cold air (−110 to −160 °C) in special temperature-controlled cryochambers, preceded by a 30-s-long preconditioning at −60 °C [11, 12].

Into the chamber, subjects are minimally dressed by wearing shorts (bathing suit), socks, clogs or shoes, surgical mask, gloves, and a hat (or headband) covering the auricles to avoid frostbite and they are invited to move their fingers while walking and avoid holding their breath [11].

The treatment is applied to relieve pain and inflammatory symptoms caused by numerous disorders, particularly those associated with rheumatic conditions, and it is recommended for the treatment of arthritis, fibromyalgia and ankylosing spondylitis. WBC has been shown to be not deleterious neither to lung function [13] nor to circulatory function [14]. Despite the wealth of literature on rehabilitation techniques, published data on WBC in physiology or rehabilitation programmes are very poor.

Conventional pharmacological treatments for FM are based to chronic or cyclical assumption of anti-inflammatory drugs to relieve symptoms associated with neuromodulatory agents (i.e. tertiary amine tricyclics) acting at the central nervous system level by diminishing the nociceptive signalling [15]. Parallel, non-pharmacological treatment, mainly based on the association of physical activity and cognitive-behavioural therapy have garnered good evidence of effectiveness in relieving pain symptoms [16].

Cold exposure has an immunostimulating effect due to the enhanced noradrenaline response to cold which is dependent on the relationship between core temperature decrease and duration of exposure. Limited are, instead, the evidences of immunosuppression from short- or long-term cold exposure [17]. WBC seems to act on the paracrine signalling rather than on systemic immune functions. In fact, WBC treatment is associated with an increase in the anti-inflammatory cytokine IL-10, and a decrease in the pro-inflammatory cytokines IL-2 and IL-8, supported by the decrease in intercellular adhesion molecule 1 (ICAM-1). The observation of a parallel decrease in prostaglandin E2, synthesized at sites of inflammation where it induces vasodilation and the increase of vascular permeability, confirmed the anti-inflammatory protection [18]. Lubkowska and colleagues demonstrated that following ten consecutive WBC sessions increases in leukocytes number, IL-6 levels, total oxidative and antioxidative status occurred, indicating that cryotherapy increases immunity [19]. More recently, the same group confirmed the finding on IL-6 and on the positive anti-inflammatory effects of WBC [20].

To our knowledge, there are very few works analysing the possible beneficial effects of WBC treatment on FM. In a 12-year-old review, Offenbächer and G. Stucki [21] reported the results of two studies in which, besides the different temperatures used, −150 °C [22] and −67 °C [23], the cold therapy ameliorate symptoms better than hot-based therapies. However, some considerations need to be taken into account about these studies: the optimal duration of the treatment (number of exposures) and temperature of exposure.

According to this background, with this study, we aimed to evaluate the eventual beneficial effects of a cycle of exposure to cryotherapy in a group of FM patients on a series of qualitative parameters indexes of morbidity and of quality of life.

Material and methods

Subjects and treatment protocol

The subjects involved in this study were submitted to the treatment as specifically prescribed by their physician.

The study population was composed of 100 consecutive subjects (94 females and 6 males), age range 17–70 years; all patients had a primary diagnosis of FM (in agreement with the ACR 2010 criteria[3, 4]). Two homogeneous groups were constituted based on the medical prescription to WBC or not: the first, named WBC+, was composed of 50 subjects (46 females and 4 males; age range, 17–67 years)

who underwent WBC while the second, named WBC−, was composed of 50 subjects (46 females and 4 males; age range, 19–70 years) who did not underwent to the WBC treatment.

The WBC treatment protocol consisted of 15 sessions consecutive sessions of WBC, as prescribed, performed in a period of time of 3 weeks. The cryochamber functioning was based on a heat exchanger cooling the air (previously dehumidified) by using liquid nitrogen. Every single session consisted of a preconditioning of 30 s at −60 °C and a 3-min-long exposure at −140 °C. During the exposure, the subjects were minimal clothed and to avoid frostbite they wore shorts (bathing suit), socks, clogs or shoes, surgical mask, gloves, and hat (or headband) covering the auricles. Any sweat was dried before entering the cryochamber, where the air was clear and dry. While in the cryochambers, subjects were asked to walk within the chamber, to maintain the fingers in motion and to avoid breath holding. The system was automatically controlled, and security personnel was always present. Each treatment was compulsorily followed by 30 min of aerobic exercise (cycloergometer or treadmill).

During the study, all subjects were allowed to continue the treatments (pharmacologic and/or antioxidants) they were subjected to, before the observation.

The clinical features of the two groups of patients and the WBC treatment protocol are summarized in Table 1.

Qualitative indexes

The following qualitative indexes were used to evaluate the clinical output of the patients.

Visual Analogue Scale (VAS) is a well recognized tool measuring the chronic pain intensity [24], visually representing the amplitude of pain that the subject believed to warn.

A qualitative score of physical and mental health of FM patients, at recruitment and following or not to WBC, was obtained with the Short Form (SF)-36 (Medical Outcomes Trust, Boston, MA), Italian version 1.6, a multipurpose, short-form health survey composed of 36 questions, yielding an eight-scale profile of scores on the quality of life [25].

Global Health Status (GH) is a self-assessment of the healthy status based on a visual analogue score (0=best, 100=worst) used to calculate the "Disease Activity Score" for various rheumatic diseases [26].

The Fatigue Severity Scale (FSS) [27] is addressed to evaluate, through 9 items and 7 levels of agreement, physical, social, or cognitive effects of fatigue (e.g., function, work, motivation).

Statistical analysis

Statistical analysis was performed by GraphPad Prism v5.0 software (GraphPad Software Inc., La Jolla, CA, USA). Normally distributed values, in the descriptive analysis, are expressed as the mean ± SD while not parametric values are described by median and range (5th–95th percentile). Normal distribution of values were assayed by Kolmogorov–Smirnov normality test. The within-group comparisons (pre-treatment vs. post-treatment) and between-groups comparisons (WBC treated vs. not treated for both time-points) were performed by two-tailed paired *t* test for normally distributed values, while Wilcoxon's matched pairs test was used for not-normally distributed values.

The significance level was set at 0.05.

Results

First of all, the two groups (WBC+ and WBC−) were not significant different for mean age. The median VAS score at the start of the study was 90.0 (76.0–100.0) in the whole population while it was 90.0 (78.5–100.0) in the WBC+ group and 90.0 (75.0–100.0) in the WBC− group, without evidencing any difference ($p=0.086$). At the second time-point both group showed a decrease in VAS ($p<0.0001$). The decrease was significantly greater in WBC+ than in WBC− ($p<0.0001$).

The median FSS and GH scores were 57.5 (44.0–63.0) and 90.0 (85.0–100.0), respectively, for the whole population, 58.0 (44.0–63.0) and 90.0 (87.3–100.0) in the WBC+ and 57.0 (48.0–63.0) and 90.0 (85.0–100.0) in the WBC−, without any difference between the two groups ($p=0.757$ and $p=0.630$). Following the treatment, in the WBC+ group, both scores recorded significant decreases, to 27.0 (15.0–38.0), $p<0.0001$, the FSS, and to 30.0 (5.0–60.0), $p<0.0001$, the GH; the same was for the WBC− group (FSS: 46.0 (38.0–56.0), $p<0.0001$; GH: 80.0(55.0–95.0), $p<0.0001$). However, the decreases in the WBC+ were significantly greater ($p<0.0001$ for both scores). The trends in VAS, FSS and GH scores are summarized in Fig. 1.

The SF-36 score kept the same tendency toward improvement for almost all the items: a substantial homogeneity between the two groups at recruitment, an improvement in the scores, for both groups, at the second time-point, a better improvement in the WBC+ group observed after the treatment. A summary of the trends in the SF-36 items is reported in Fig. 2.

Discussion

Physiologically, the perception of pain involves two groups of neural pathways. the ascending pathways through, the peripheral nerves, transmit sensory signals, including nociceptive signals, to the spinal and, thus, to the brain for processing. Nociceptive signals are emitted by nociceptors,

Table 1 Clinical features of the patients

WBC+ group					WBC− group				
ID	Age	Gender	Diagnosis	Secondary diagnosis	ID	Age	Gender	Diagnosis	Secondary diagnosis
1	43	F	FM	Pollinosis, disc hernia	1	49	M	FM	Arthrosis, cephalgia
2	45	F	FM	/	2	33	F	FM	/
3	55	F	FM	Arthrosis, diabetes, hypertrophic arthritis arterial hypertension	3	56	F	FM	Arthrosis, hypothyroidism
4	33	M	FM	Spondyloarthropathy, disc hernia	4	46	F	FM	Hypothyroidism
5	49	F	FM	Arthrosis, osteoporosis	5	53	F	FM	Hypothyroidism
6	50	F	FM	CFS	6	58	F	FM	CFS
7	52	F	FM	Sicca syndrome, lactose intolerance	7	32	F	FM	CFS
8	44	F	FM	Arthrosis, hypothyroidism	8	66	F	FM	Hypothyroidism, arthrosis
9	42	F	FM	Hypothyroidism	9	56	F	FM	/
10	58	F	FM	Arthrosis, cephalgia	10	45	F	FM	/
11	30	F	FM	Cephalgia	11	52	F	FM	Arthrosis
12	53	F	FM	Hypothyroidism	12	19	F	FM	Hypothyroidism
13	61	F	FM	MCS, spondyloarthropathy	13	45	F	FM	Spondyloarthropathy
14	28	F	FM	/	14	33	M	FM	Seronegative oligoarthritis
15	17	F	FM	/	15	26	F	FM	/
16	49	F	FM	Lactose intolerance, discopathy	16	30	F	FM	/
17	32	F	FM	/	17	56	F	FM	Radiculopathy
18	36	F	FM	/	18	56	F	FM	/
19	60	F	FM	GER, seronegative oligoarthritis	19	45	M	FM	Arterial hypertension hypertrophic arthritis
20	57	F	FM	Diabetes, CFS, arterial hypertension hypertrophic arthritis	20	38	F	FM	/
21	34	M	FM	/	21	62	F	FM	Arterial hypertension hypertrophic arthritis
22	21	F	FM	Seronegative oligoarthritis	22	23	F	FM	/
23	57	F	FM	/	23	49	F	FM	Arthrosis
24	67	F	FM	Osteoporosis, nasal polyposis	24	70	F	FM	Discopathy
25	52	F	FM	Undifferentiated connectivities	25	59	F	FM	Arterial hypertension hypertrophic arthritis, osteoporosis
26	58	M	FM	Arthrosis, chronic gastropathy	26	24	F	FM	/
27	52	F	FM	Arterial hypertension hypertrophic arthritis	27	26	F	FM	/
28	37	F	FM	Bronchial asthma	28	32	F	FM	CFS
29	64	F	FM	Arterial hypertension hypertrophic arthritis	29	35	F	FM	Arterial hypertension hypertrophic arthritis
30	18	F	FM	/	30	45	F	FM	/
31	35	F	FM	/	31	44	F	FM	Diabetes
32	60	F	FM	/	32	41	F	FM	/
33	40	F	FM	/	33	43	F	FM	/
34	39	F	FM	/	34	49	F	FM	Arthrosis
35	42	F	FM	CFS	35	48	F	FM	Hypothyroidism, arthrosis
36	37	M	FM	/	36	50	F	FM	Diabetes
37	58	F	FM	Arterial hypertension hypertrophic arthritis	37	54	F	FM	/
38	41	F	FM	/	38	56	F	FM	/
39	49	F	FM	/	39	48	F	FM	Hypertrophic arthritis
40	53	F	FM	Hypothyroidism, arterial hypertension hypertrophic arthritis	40	47	F	FM	MCS
41	54	F	FM	/	41	45	F	FM	/
42	56	F	FM	/	42	32	M	FM	Celiac disease
43	46	F	FM	Hypothyroidism	43	46	F	FM	/

Table 1 (continued)

WBC+ group					WBC− group				
44	50	F	FM	Arthrosis	44	40	F	FM	Diabetes
45	51	F	FM	Seronegative oligoarthritis	45	55	F	FM	/
46	47	F	FM	/	46	45	F	FM	/
47	31	F	FM	Seronegative oligoarthritis	47	34	F	FM	/
48	35	F	FM	/	48	45	F	FM	/
49	43	F	FM	/	49	23	F	FM	/
50	30	F	FM	/	50	47	F	FM	Arthrosis, hypothyroidism

FM fibromyalgia, *CFS* chronic fatigue syndrome, *MCS* multiple chemical sensitivity, *GER* gastro-esophageal reflux

specialized receptors in the peripheral nerves, are activated by physical stimuli (i.e., changes in temperature, pressure, impact). Descending pathways send modulatory signals (facilitatory and/or inhibitory) from the brain throughout the spinal cord to the periphery, tuning the ascending nociceptive signals reaching the brain. A number of neurotransmitters and neurochemicals are involved in these signal transmission (e.g., norepinephrine, serotonin) [28, 29].

In FM, these two pathways operate abnormally, resulting in central amplification of pain signals, a phenomenon named *central sensitization*. Indeed, many studies of FM-related pain and hyperalgesia advocated the involvement of spinal mechanisms, accordingly to the finding of enhanced responses to somatic and cutaneous stimuli throughout the pain matrix of the brain, including the thalamus, in FM [30, 31]. The pathogenesis of the pain amplification process is not fully understood but is certain to be multifactorial. An important role is surely played by the peripheral nociceptors, but a number of findings strongly suggested a central nervous system involvement that is or becomes largely independent of peripheral nociceptive input [2]. However, it is still unclear whether these are due to facilitating mechanisms within the brain (central *amplification*), spinal sensitisation maintained by the input of tonic impulses from somatic tissues, or abnormal mechanisms of descending facilitation from the brain toward periphery [9]. Central amplification is likely determined at least partially by genetics and modified by environmental influences [32].

While in general population, perception of pain displays a normal distribution on a bell curve, in FM population it is skewed to the right: the more one moves to the right along this distribution, the higher the "volume control setting" and pain intensity becomes, irrespective of peripheral nociceptive input [2, 6].

An imbalance of pro- and anti-inflammatory cytokines is assumed to play a role in the induction and maintenance of pain. IL-1, IL-6, and IL-8 are pro-inflammatory cytokines are known to mediate induction and maintenance of pain and also in pain syndromes [33], whereby IL-8 promotes sympathetic pain and IL-6 induces hyperalgesia, fatigue, and depression [34]. Therefore, it is likely that FM patients, who suffer from generalized pain, may have an innate or acquired imbalance in cytokine production and secretion.

A recently published systematic review of the literature revealed that, even with some uncertainness, FM patients had higher serum levels of IL-1ra, IL-6, and IL-8, and higher plasma levels of IL-8, compared to controls [35]. In two recent papers, Lubkowska and colleagues demonstrated that WBC affects the inflammatory status by inducing an imbalance towards the anti-inflammatory side. Particularly, consecutive sessions of cryotherapy increased IL-6 and IL-10 levels and lowered the IL-1α levels [19, 20]. Although IL-6 is generally considered a pro-inflammatory cytokine, it is known to induce the expression of anti-inflammatory mediator (i.e. IL-1ra, IL-10) [19]. Furthermore, the authors reported an increased leukocytes count and an improved oxidative status after WBC, indicating an overall immune activation [19].

Based on the link between the central pain with the imbalance between pro- and anti-inflammatory molecules and, thus, with the general referred status of the subject, parallel to the know anti-inflammatory effects of WBC [11], we speculated that consecutive sessions of cryotherapy could have a positive impact on the referred qualitatively measured pain.

Another possible explanation of the positive effects of WBC, on the referred pain sensation, could be attributed to changes in the nerve conduction induced by cryogenic temperatures. It has been, indeed, postulated that cold therapy could reduce pain via an alteration in nerve conduction velocity. In their protocol setting, Algafly and George [36], analyzed the effects of ice bath on nerve conduction and pain sensation in healthy sportsmen. The results indicated

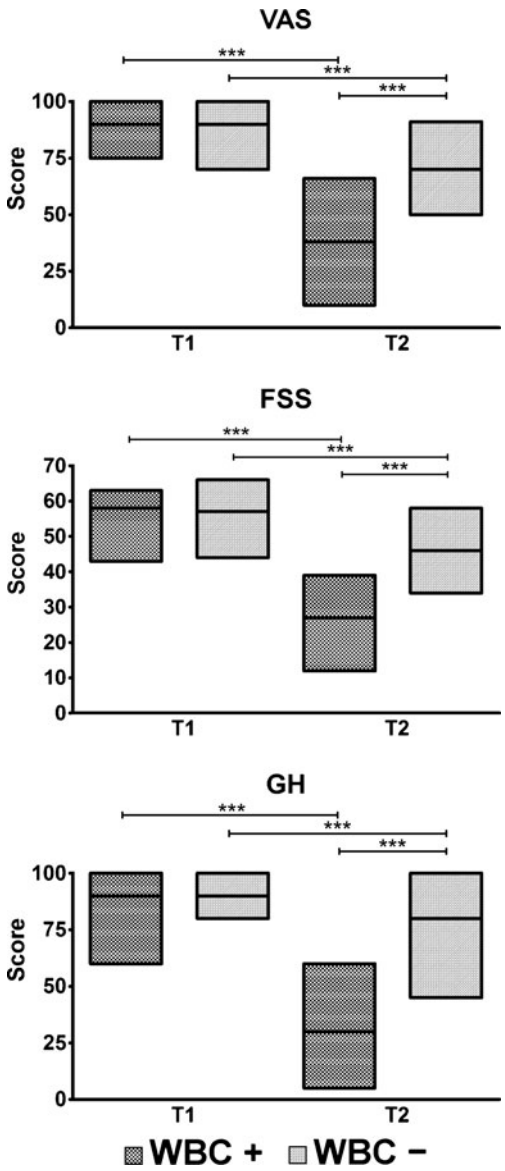

Fig. 1 Trends in VAS, FSS and GH scores. The figure shows the scores differences between the two groups pre- and post-observation and the score modification between the two observations. *Asterisks* indicate the level of statistical significance (*$p<0.05$; **$p<0.01$; ***$p<0.001$)

that the data suggest that cryotherapy can increase PTH and PTO at the ankle and this was associated with a significant decrease in NCV.

The SF-36 measure physical, mental and social functioning. It is generic health status instruments that permit comparisons across groups with different health conditions and they have been widely applied in studies worldwide [37]. SF-36 can currently be considered the most confidently recommended qualitative scale to measure physical function in rheumatoid arthritis for most research purposes even if it has recognized limited content coverage [38]. It is important to understand the health status burden of people with FM. Health status data quantify impairments in physical, mental and social functioning.

Such information can highlight areas where people with FM experience particular difficulty and where healthcare providers may be able to effect change in clinical status [39].

The VAS is the simplest method for assessing pain and fatigue and was clinically relevant in more than 76 % of patients with FM [40].

In our study, we found, despite a certain homogeneity between the two groups at recruitment, a more pronounced improvement of all the scores in the groups submitted to WBC compared to the WBC− group. Particularly, the perception of pain and fatigue, scored by the VAS scale, decreased of 58 % in the WBC+ group while only 22 % in the WBC− group. Reductions of the same magnitudes were manifest for FSS and GH scores.

For what concern the SF-36 scores, the same tendency was overall evident.

The item 3 group (A to J), giving a score for the "physical functioning" by analysing the daily activities, was improved in both groups with the WBC+ group showed a better output. However, the median scores of the two groups already differed at recruitment: 23.0 (17.0–29.0) for WBC+ and 24.0 (20.0–30.0) for WBC−. The item 4 group (A to D) assign the "role-physical" score and they followed the trend of item 3, as for items 7 (pain-magnitude) and 8 (pain-interface), grouped as "bodily pain" scores.

The items 1 and 11 are intended to evaluate the "general health": item 1 (EVGFP scale), indicating if the patient health is excellent, very good, good, fair, or poor, and items 11C (health to get worse) and 11B (health excellent) significantly differed between the time-points in both groups and between the groups at the second time-point; item 11A, sick easier, ameliorated only in the WBC+ group, after the treatment, even if the two groups were not significantly different at both time-point; item 11B, as healthy, never changed. Items 1, 3, 4, 7, 8 and 11 are used to evaluate the overall "physical health"; the other items are, instead, intended to the definition of the "mental health".

Vitality is defined by the items 9A (full of life), 9E (energy), 9G (worn out), 9I (tired): all of them did not differed between the groups at recruitment, were improved at the second evaluation with a greater positive effect in the WBC+ group. Social functioning, items 6 (social-extent) and 10 (social-time) showed an identical trend, as well as the item 5 group (A, B, C) analysing the "role-emotional" and the "mental health" item 9 group (B, C, D, F, H), even if in the case of items 9C and 9D the starting point was already different in the two groups, in favour of the WBC+ group.

In conclusion, with this study we found a positive effects of WBC on the quality of life of a group of FM patients as indicated by the improvement of a number of qualitative

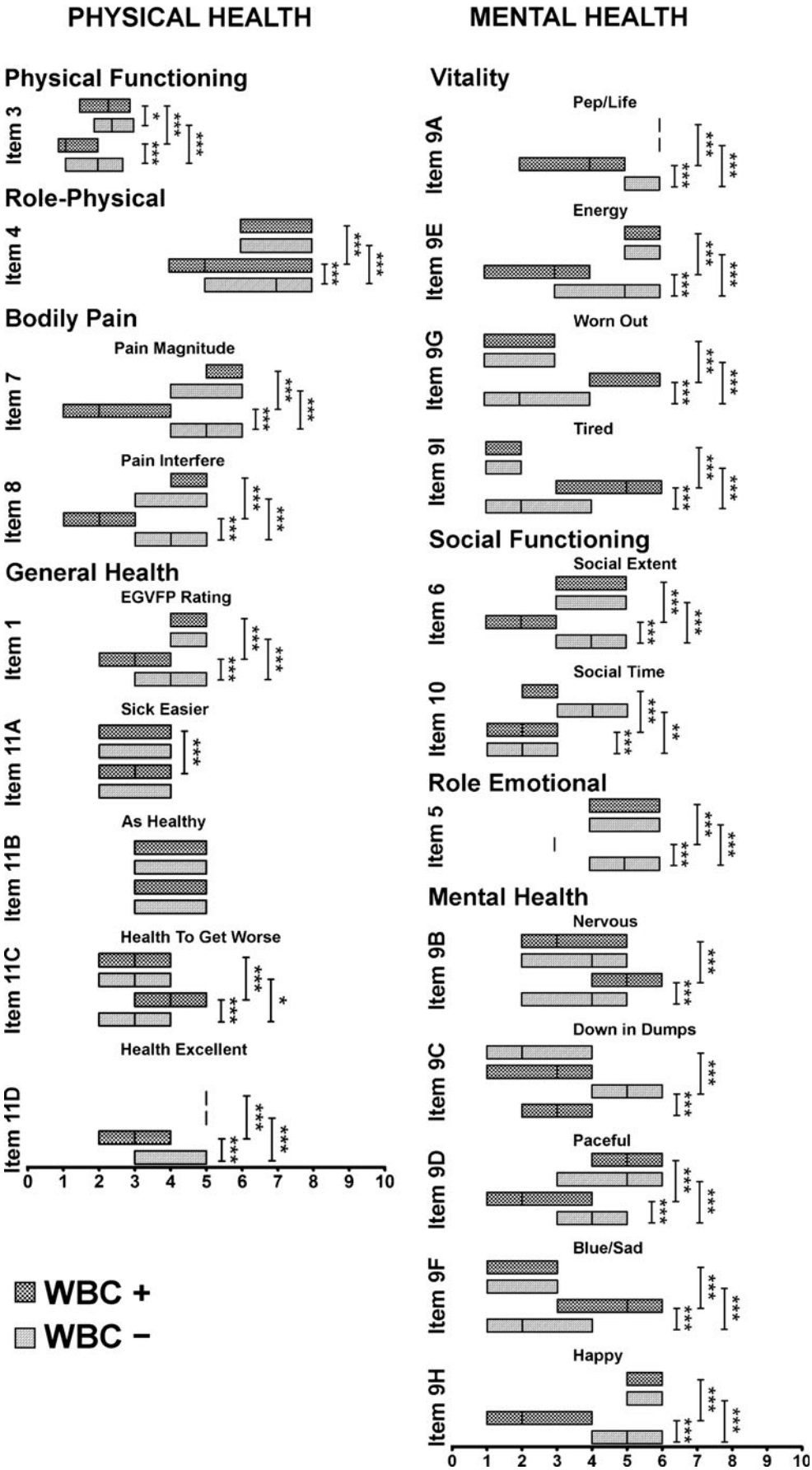

Fig. 2 Trends in the SF-36 items. The figure shows the SF-36 scores differences between the two groups pre- and post-observation and the score modification between the two observations. *Asterisks* indicate the level of statistical significance (*$p<0.05$; **$p<0.01$; ***$p<0.001$)

indexes and sub-indexes, that are widely recognized tools to assess the overall health status and the effect of the treatments. Possible mechanisms by which WBC reduces the pain sensation and fatigue, in FM patients, could reside in the improvement of the balance between pro- and anti-inflammatory mediators, having a recognized role in the modulation of pain, and in the reduction of nerve conduction velocity of nociceptive ways.

Disclosures None.

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