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Whole-body cryostimulation in obesity. A scoping review

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ABSTRACT

Currently available treatments for the management of obesity struggle to provide clinically significant weight loss and reduction of the chronic low-grade inflammatory state in order to reduce obesity-related complications. This scoping review aims to provide an up-to-date picture of the therapeutic effects of Whole-Body Cryostimulation (WBC) in patients with obesity and evidence-based indications for its complementary use in the treatment of obesity. We searched the literature until the end of August 2021, retrieving 8 eligible studies out of 856, all evaluated for their methodological quality using the Downs and Black checklist. Overall, the limited data presented in this review article seem to support the efficacy of WBC as an adjuvant treatment in obesity. The cryogenic stimulus has important anti-inflammatory/antioxidant effects and its effectiveness is directly related to the individual percentage of fat mass and initial fitness capacity, mimicking an exercise-induced effect. Based on the limited results gathered, WBC emerges as a promising adjuvant therapy to reduce systemic inflammation, oxidative stress, abdominal obesity, and body mass. However, the data presented in this review article fail to reach definitive conclusions with regards to the efficacy of WBC in the treatment of obesity. Application of WBC protocols yields the potential to widen the therapeutic armor for the treatment of obesity and obesity-related disorders but larger, high-quality studies are still needed.

1. Introduction

At present, available treatment options for obesity management include behavioral changes, adapted physical activity, nutrition therapy, psychological support, web-related digital interventions, pharmacotherapy, and bariatric surgery (Byrne et al., 2006; Kuk et al., 2011; Wharton et al., 2020). Those complementary approaches, aimed to achieve and maintain clinically meaningful weight loss, can be used according to an escalation strategy based on the presence and severity of comorbidities (Byrne et al., 2006). Mostly, the recommendations in the literature are weight-loss centered. However, current non-surgical treatment options struggle to provide a clinically significant weight

loss in order to reduce obesity-associated medical complications (Wharton et al., 2020). Pharmacological therapies offer auxiliary treatments, but their effects on weight loss are, at present, moderate (Glandt and Raz, 2011), (Garvey et al., 2020), and, when the medication is stopped, usually after one year of treatment, more weight is regained (Gadde et al., 2018). Additionally, patients' compliance to prescriptions decreases over time and remains a relevant issue in terms of long-term weight control and health-related benefits (Anderson et al., 2001; Castellani et al., 2003; Glandt and Raz, 2011). Studies investigating the effectiveness of different weight loss strategies showed that more than 50% of the lost weight is regained within 2 years and almost completely regained by 5 years (Anderson et al., 1992, 2001). In the absence of a

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structured intervention, relapses of this chronic remitting disease are likely to occur (Franco et al., 2013; Wharton et al., 2020). Low-grade inflammation is a key feature of dysmetabolic conditions and, thereby, long-term approaches focused on both induction of weight loss and stimulation of the anti-inflammatory response should be adopted (Kuk et al., 2011; Wharton et al., 2020; Ziemann et al., 2013a). Regular exercise has been shown to increase energy expenditure and reduce chronic inflammation by decreasing mononuclear cell production of pro-inflammatory cytokines (Beavers et al., 2010), hypoxia, oxidative stress (Powers et al., 1999), serum leukocyte (Adamopoulos et al., 2001), and release of cell adhesion molecules (Koh and Park, 2018), stimulating the production of mediators by immune cells and tissue (i.e. skeletal muscle) with anti-inflammatory properties (Burini et al., 2020), myokine (Kirk et al., 2020), and adipose tissue lipolysis (De Glisezinski et al., 1998; You et al., 2004). The combination of a calorie restriction diet with exercise has been found effective in reducing serum concentrations of markers of chronic inflammation such as C-reactive protein (CRP), tumor necrosis factor- α (TNF α), and interleukin 6 (IL-6) in adults with overweight and obesity with active lifestyles (Liu et al., 2021). This also leads to a negative energy balance and triggers cascades of metabolic and neurohormonal adaptive mechanisms that limit systemic inflammation (Wharton et al., 2020; You et al., 2004). However, the induced weight loss is modest and the dropout rate from physical training programs is high, due to either musculoskeletal or motivational issues (Petridou et al., 2019; Redman et al., 2012). Therefore, it appears of paramount importance to find effective add-on intervention strategies that can raise the chances to reach the goals of established weight loss and improved inflammatory status.

Cryostimulation is a physical treatment providing widely acknowledged anti-inflammatory and lesser studied metabolic effects (White and Wells, 2013). It consists of a 2-to-3-minute exposure of a part or the whole-body to extremely cold (-110° to -140°) and dry air. There are actually two types of cryostimulation: partial-body cryostimulation (PBC) where the body, but not the head, is exposed to cold in a cryosauna, and the whole-body cryostimulation (WBC), where the whole body is exposed to cold air in a cryochamber (Bouzigon et al., 2016). In PBC, the cryogenic fluid is injected and vaporized around the body. In WBC, the cold production is based on vapor compression cycles with refrigerants and/or cryogenic fluids, mainly liquid nitrogen. WBC is widely used in sports medicine mainly to reduce effort-related pro-inflammatory responses, to relieve exercise-associated muscle soreness, and to enhance muscle post-exercise recovery (Furmanek et al., 2014). The sudden thermal stress induced by the exposure to cryogenic temperatures on the dermis, characterized by the presence of a 10-fold higher number of cold receptors in comparison to heat receptors, causes changes in the endocrine, circulatory, neuromuscular, and immunological systems. Such stress provides an allostatic load on the homeostatic systems of the body and, in particular, autonomic homeostatic responses of thermogenesis and vasoconstriction are elicited (White and Wells, 2013). Strong variations in skin temperature stimulate cold receptors and the thermoregulatory center in the hypothalamus (Castellani and Young, 2016; Research I. of M. C. on M.N et al., 1996). Cutaneous circulation represents the key point in thermoregulation. Vasoconstriction causes a displacement of blood from cutaneous vessels into deeper veins and from the periphery to the core increasing pre-load and central blood pressure and reducing heart rate, a decrease in cell permeability and leaking, and in the fluid diffusion in interstitial space that can occur after physical exercise (Research I. of M. C. on M.N et al., 1996; White and Wells, 2013). During vasoconstriction, activation of the sympathetic system accompanied by the release of noradrenaline occurs. The latter is known to modulate pain, together with other compounds, such as a release of endorphins and a slowed conduction velocity of sensory nerve fibers and, particularly, the slow conducting C fibers disabling the sensory receptors as well as their connections with the proprioceptors. Cryogenic temperatures cause changes in autonomic balance induced by peripheral and central blood volume changes.

Cold-induced vasodilation occurs, enabling a four-fold higher blood flow than normal resulting in the elimination of metabolic products. At distance from the cold stimulation, an increase in the parasympathetic cardiac control may also happen, as a compensatory mechanism downregulating the blood pressure (Louis et al., 2020; Zalewski et al., 2014), even during the night (Douzi et al., 2019). Changes in muscle, skin and core body temperature, with a maximum drop of core temperature after 50–60 min and the autonomic and thermal reactions to cryostimulation have been observed even up to 6 h after WBC exposure (Costello et al., 2012, 2015; Savic et al., 2013; Zalewski et al., 2014). Such changes may result in lower fatigue sensation and mood improvement with possible positive impact on depression and sleep quality (Rymaszewska et al., 2008). However, there is a range of individual responses to cold due to inter-individual differences, such as body size, BMI, fitness level, amount of subcutaneous fat, and gender (Castellani and Young, 2016; Gordon, 2001; Gordon et al., 2003). After repeated exposures to WBC the following effects have been measured: improvement of inflammatory and metabolic profile (White and Wells, 2013), enhancement of the antioxidant system (Pilch et al., 2021), improvement of insulin sensitivity (Hanssen et al., 2016), increase of brown adipose tissue (BAT) volume percentage (Hanssen et al., 2016), decreased percentage of adipose tissue (Więcek et al., 2020), enhanced secretion of endorphins (Leppälüoto et al., 2008), and slowed down nerve conduction velocity (Bouzigon et al., 2021). Given the proven anti-inflammatory, exercise-mimicking effects (Lombardi et al., 2017), it is conceivable that patients affected by dysmetabolic conditions characterized by chronic low-grade inflammation could benefit from this treatment. A limited number of papers have taken into consideration the effects of WBC on patients with obesity focusing on hematological markers, metabolic parameters, lipid, and endocrine profile, antioxidant enzyme activities, inflammatory and cellular stress response (Dulian et al., 2015; Lubkowska et al., 2015a; Pilch et al., 2020a, 2021; Więcek et al., 2020; Wyrostek et al., 2021; Ziemann et al., 2013a). From this initial evidence, WBC appears to yield beneficial effects also on body composition and adipose tissue. Therefore, WBC proposes itself as a promising additional option in the multidisciplinary treatment of obesity (Lubkowska et al., 2015a; Więcek et al., 2020). The goal of this scoping review is to provide an up-to-date picture of the evidence supporting the beneficial effects of WBC in patients with obesity and evidence-based indications on the possible adjuvant use of WBC in the treatment of obesity.

2. Methods

This scoping review follows a review protocol, which has not been registered in a public repository. A literature search was conducted using the electronic databases Pubmed and Scopus. The search strings were created by combining keywords referring to WBC (cryostimulation, cryotherapy, cryochamber, cryosauna, "cold immersion", "cold shock", "cold therapy", "cold exposure") with keywords referring to obesity or weight (obesity, obese, overweight, "weight loss"). There was no publication date restriction. Only articles written in English, Italian, French, and Spanish were considered. Additionally, articles that were already available to the authors of this review were added to the records pool. Finally, the cryotherapy review reference lists retrieved during the search were scanned for other potentially relevant articles. Articles were scanned according to the following inclusion criteria: 1) the study was presented in an original article; 2) the intervention assessed by the study was whole-body cryotherapy; 3) the study sample was composed of adult patients (i.e., with an age range of 20 and 67 years) with overweight or obesity. Overweight is defined by a BMI 25 to 29.9, class I obesity by a BMI 30.0 to 34.9, and class II obesity as having BMI 35 to 39.9 (Wharton et al., 2020). Cryotherapy was classified as exposing the whole body to extremely low temperatures that were -110° C to -170° C. Given the large differences in temperatures measured in cryosaunas and cryochambers and related physiological reactions after PBC

and WBC, 25 we decided to include only studies with WBC in this review. There was no restriction on either duration or frequency of exposure to the recovery treatment or its timing in relation to the exercise protocol. The article records retrieved during the search were exported to the Rayyan online software (Ouzzani et al., 2016) which was used for the title and abstract screening. This procedure was independently performed by two reviewers. Full texts of the remaining records were then accessed and the same reviewers independently decided on their inclusion. During both procedures, discrepancies were solved by consensus. The following data was extracted from the included articles using a standardized form: country where the study was performed, study design, target population (i.e., overweight patients, patients with obesity, both), comorbidities of the target population, female percentage of the sample, mean age of the sample, number of patients at the baseline, number of patients at the last follow-up, number of WBC sessions, duration of each WBC sessions, WBC temperature, other information about the WBC protocol, type of outcome, outcome assessment instrument, and a synthesis of the results. The methodological quality of the

included articles was assessed using the Downs and Black checklist (Downs and Black, 1998). Briefly, this checklist allows us to evaluate the reporting quality of the assessed study, external validity, presence of bias, presence of confounding, and power of the applied statistical analysis. The data were then charted to present the description of each study. The results of the studies were then summarized narratively to present evidence on the effects of cryotherapy in patients with overweight and obesity.

3. Results

The database search retrieved 879 records in total (856 nonduplicate papers were screened) and eight of yielded articles, with a total of 189 participants (29 with normal body weight and 160 with overweight and obesity), met the eligibility criteria and were included in this scoping review. Fig. 1 illustrates the flow diagram of the literature search while Table 1 presents the characteristics of these studies. Five articles used a non-controlled study design (Dulian et al., 2015; Lubkowska et al.,

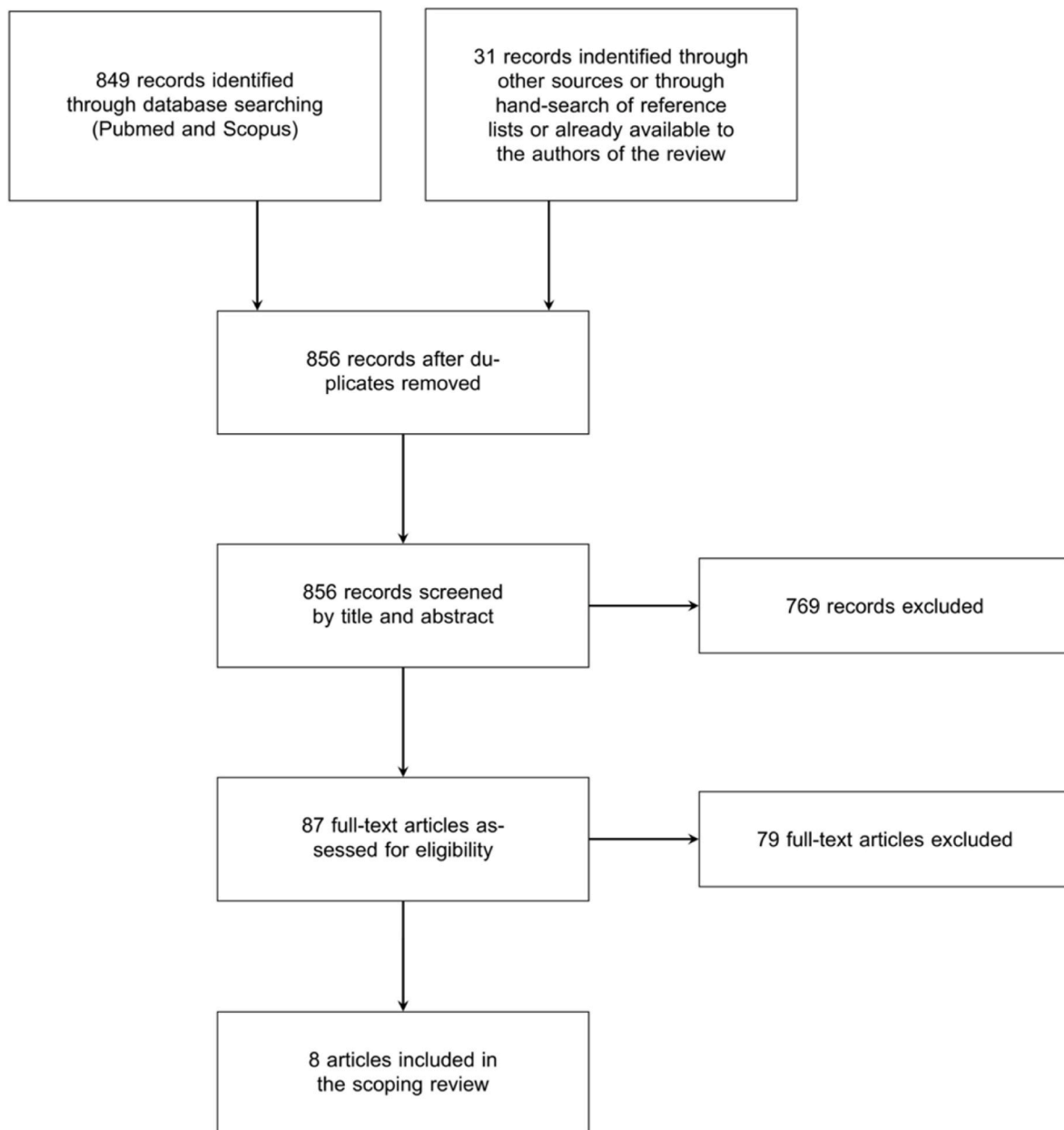


Fig. 1. Review process flow diagram.

Table 1
Summary of the included studies and results.

Study design	Author, Date, Country	Experimental population (n)	Subgroups (n)	BMI (kg m ⁻²)	Mean age ±SD (year)	Females (%)	WBC protocol	Measurements	Primary outcomes	Secondary outcomes	Results
Non-controlled Trial	Ziemann et al., 2013 Poland	OB ♂ (14)	HCF = 7 LCF = 7	HCF = 31.4 ± 2.0 IOb LCF = 34.0 ± 2.5 IOb-IIOb	40.0 ± 4.0	0	-110 °C 3min (30 s adaptation) 10 sess 5 days a week	Before sess 1 and 5; after sess 5 and 10	Inflammation	Body composition (BIA), hematological parameters (Adipokinesleptin, adiponectin, resistin, visfatin)	HCF ↑ IL-10, ↑ Visfatin, ↑ Resistin = TNFα, = IL-6, = Body composition, = Leptin, = Hematological parameters after 10th sess. LCF ↑ IL-10, ↓ Visfatin ↓ Resistin after 10th sess ↓ TNFα after 5th and 10th sess. = IL-6, = Body composition, = Leptin, = Hematological parameters after 10th sess.
	Dulian et al. (2015) Poland	OB ♂ (12)	HFL = 5 LFL = 7	HFL= 30.1 ± 4.0 IOb LFL= 35.7 ± 4.5 IOb-IIOb	38.0 ± 9.0	0	-110 °C 3min (30 s adaptation) 10 sess 5 days a week	Before sess.1 and 10; 30 min and 24 h after sess 1 and 10	Irisin concentration, inflammation	Hematological parameters	HFL = Irisin, = IL-6, ↓CRP after 10th sess LFL ↑ Irisin, ↓ CRP, =IL-6 after 10th sess All subjects ↑ Irisin, ↓ hepcidin after 10th sess
	Lubkowska et al., 2015 Poland	OB + Overweight ♂ (30)	OB + Overweight = 30 (30.39 ± 4.31, btw 26.3 and 41.1)	OB = 30.39 ± 4.31 (min= 26.2; max = 41.1) IOb- IIOb	40.0 ± 4.0	0	-120 °C 2-3 min (30 s adaptation) 20 sess + 20 sess (4 months after) 5 days a week	Before, immediately after and 1 month after a 6-month exercise programme; before first sess; after first 20 sess and second 20 sess	Body Composition (BIA)	Hematological/biological parameters (Lipid profile, Adipokine, antioxidant capacity)	Body composition = BW, =BMI, = WHR =components of body composition Blood sampling ↓RBC, ↓HGB, ↓Hct after the 1st series Lipid Profile ↓Total cholesterol, ↓[LDL], ↓TG, ↑[HDL] after the 1st and the 2nd series Adipokine Concentration ↑Visfatin, =Adiponectin, =Leptin, and =Resistin after 6 months Antioxidant Capacity

(continued on next page)

Table 1 (continued)

Study design	Author, Date, Country	Experimental population (n)	Subgroups (n)	BMI (kg m ⁻²)	Mean age ±SD (year)	Females (%)	WBC protocol	Measurements	Primary outcomes	Secondary outcomes	Results
	Więcek et al. (2020) Poland	OB + OW Menopausal ♀ (37)	MetS = 19 Healthy = 18	MetS = 30.09 ± 4.98 IOb Healthy = 25.50 ± 2.37 Both groups consisted of: NBM = 23.4 ± 2.29 OW = 27.48 ± 2.51 OB = 32.76 ± 6.05 IOb- IIOb	60.92 ± 3.82	100	−130 °C 3min (30 s adaptation) 20 sess 5 days a week	Before sess 1; after sess 10 and 20	Body composition (DEXA and skinfold)	IL-6, irisin, CRP	↓CAT activity, ↑SOD activity ↓GST, ↓R- GSSG activity after 2nd series MetS ↓Percentage of adipose tissue in total body mass, trunk and android area, ↓BM, ↓BMI, ↓Total body fat, ↓Leg fat, ↓trunk fat, ↓android fat after 20th sess ↓WC and ↓WHtR after 10th sess ↓WC, ↓AC, ↓ WHtR ↓Triceps thickness after 20th sess. ↑Irisin after 1st and 10th sess. ↑IL-6 after 10th and 20th sess. = CRP after 20th sess. Healthy ↑ Irisin after 1st and 10th sess = IL-6, = CRP, ↓ BM, ↓ BMI, ↓ Total body fat, ↓ Leg fat, ↓ WC, ↓ AC, ↓ HC, ↓ WHtR, ↓ Abdominal and Triceps thickness after 20th sess ↓ WC, ↓HC, ↓WHtR, ↓Abdominal thickness after 10th sess HBF ↓ RBC, ↓ MCV, ↓ Hct ↑MCHC after 10th and 20th sess NBF ↑RBC, ↑MCHC, ↓ Hct, ↓ MCV, ↓ MPV after 10th and 20th sess HBM ↓ WC, ↓ Body mass,
	Wyrostek et al. (2021) Poland	OB ♂ (24)	HBF = 14 (Body Fat = 29.35%) NBF = 10 (Body Fat = 11.40%)	not specified	HBF = 29.64 ± 4.13 NBF = 22.10 ± 2.33	0	−120 °C 2–3 min (30 s adaptation) 20 sess 5 days a week	Before sess 1; after sess 10 and 20	Hematological parameters		
Non- randomized		OB ♂ (21)	HBM = 12 NBM = 9	HBM = 36.23 ±	HBM =	0	−120 °C 2–3 min (30 s	Before sess 10 and 20; 1 h after sess 10 and 20	Body composition (BIA)	Leukocyte expression of HSPA1A, HSPB1 and CRP	↓ WC, ↓ Body mass,

(continued on next page)

Table 1 (continued)

Study design	Author, Date, Country	Experimental population (n)	Subgroups (n)	BMI (kg m ⁻²)	Mean age ±SD (year)	Females (%)	WBC protocol	Measurements	Primary outcomes	Secondary outcomes	Results
controlled Trial	Pilch et al., 2020, Poland			8.13; IIOb = 23.58 ± 2.00	29.08 ± 4.19 NBM = 22.00 ± 2.45			adaptation) 20 sess 5 days a week			↓ FM and ↓ PBF, = CRP mRNA after 20th sess NBM ↓ PBF, ↓ FM, ↓ Body mass, ↓ fat mass ↓PFB, ↓ WC after 20th sess. ↓ HSPB1 mRNA after 10th and 20th sess = CRP mRNA NW ↓ TOS/TOC = TAS/TAC, = OSI levels, ↓ SOD1 activity OB = TAS/TAC, = OSI levels, ↑ SOD1 activity, ↑ CAT activity N after 10th and 20th sess : =LEP, =TG(< IIOb) btw 10th and 20th sess: ↓ nonHDL-C, =HDL, =LDL, =HDL/LDL After 20th sess: =BAI, =VAI IOb and IIOb btw 10th and 20th sess: ↓ LEP, ↓ TNFα, ↓TC, ↓ nonHDL-C, =ADP, =HDL, =LDL, =HDL/LDL (> N) IOb btw 10th and 20th sess: ↓TG. After 20th sess: =BAI, ↓VAI nonHDL-C> N & IOb IIOb after 10th and 20th sess: =TG (> N) btw 10th and 20th sess: =HDL, =LDL, =HDL/LDL After 20th sess: =BAI, =VAI, HDL< N , LDL> N
	Pilch et al. (2021) Poland	OB + NW ♂ (24)	OB = 14 NW = 10	OB = 35.88 ± 0.53 IIOb NW = 23.56 ± 1.89	OB = 29.64 ± 4.13 NW = 22.10 ± 2.33	0	-120 °C 2-3 min (30 s adaptation) 20 sess 5 days a week	Up to 2 h Before sess 1; up to 2 h after sess 20	Prooxidant/antioxidant balance		
	Pilch et al. (2022) Poland	Non-active IOb + IIOb + healthy body weight ♂	N= 9 IOb= 9 IIOb= 9	N = 23.0 ± 1.5 IOb = 31.3 ± 1.5 IIOb = 42.7 ± 8.0				-120 °C 3 min (30 s adaptation) 20 sess. 1/ day, 5 days/ week	Up to 1 h before the first sess; Up to 1 h after 10 and 20 sess	Lipid profile and adipokine levels in IOb+ IIOb. Effect of BMI on the beneficial effects of WBC	Inflammation

↑ increase; ↓ decrease; = no changes.

Abbreviations (alphabetical order).

IOb: class one obesity; IIOb: class two obesity; AC: abdominal circumference; BIA: body impedance analysis; BM: body mass; BMI: body mass index; BW: body weight; CRP: C-reactive protein; CAT: catalase; FM: fat mass;

GSSG-R: glutathione reductase; GST: glutathione S-transferase; DEXA: Dual Energy X-Ray Absorptiometry; HBF: high body fat; HBM: high body fat; HC: hip circumference; HGF: high cardiorespiratory fitness; Hct: hematocrit; [HDL]: high density lipoprotein concentration; HFL: high fitness level; HGB: hemoglobin concentration; HSPA1A/HSPB1: heat shock proteins genes; IL: interleukin; LCF: low cardiorespiratory fitness; [LDL]: low density lipoprotein concentration; LFL: low fitness level; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; min: minute; MPV: mean platelet volume; N: healthy body weight; N: healthy body weight; n: sample size; NBF: normal body fat; NBM: normal body mass; NW: normal weight; OB: subjects with obesity; OSF: oxidative stress index; OB: subjects with obesity; OW: overweight; PBF: percent body fat; RBC: red blood cells; RQ: respiratory quotient; Sess.: session; TAS/TAC: total antioxidant status/total antioxidant capacity; sec: seconds; SOD1: superoxide dismutase 1; TOS/TOC: total pro-oxidative status/total pro-oxidative capacity; TG: triglycerides; TNF α : tumor necrosis factor; VCO2: carbon dioxide production; WBC: whole-body cryostimulation; WC: waist circumference; WHR: waist-to-hip ratio, WHtR: waist-to-height ratio.

2015a; Więcek et al., 2020; Wyrostek et al., 2021; Ziemann et al., 2013a) while the other three used a non-randomized controlled study design (Pilch et al., 2020a, 2021, 2022). All seven studies were conducted in Poland and 4 of them involved the same laboratory (Pilch et al., 2020a, 2021; Więcek et al., 2020; Wyrostek et al., 2021). Scoring the quality of the articles using the Downs and Black quality checklist (Downs and Black, 1998) was carried out independently by three researchers (MG, JMF, SB), who discussed their scoring disagreements and reached a consensus. The maximum score that articles could receive from this assessment tool was 27 points. The average score was 16.75 points. All studies scored above 15 points, reaching a maximum score of 18 on three occasions. The quality assessment of each of the included articles is presented in Table 2.

Four studies investigated the markers of inflammation TNF α , IL-6, Interleukin 10 (IL-10), CRP (Dulian et al., 2015; Pilch et al., 2020a; Więcek et al., 2020; Ziemann et al., 2013a) and analyzed body composition (Lubkowska et al., 2015a; Pilch et al., 2020a; Więcek et al., 2020; Ziemann et al., 2013a). One study also measured the changes of TNF α together with adipokines and lipid profile (Pilch et al., 2022). Four studies measured the hematological parameters (Dulian et al., 2015; Lubkowska et al., 2015a; Wyrostek et al., 2021; Ziemann et al., 2013a), two studies the antioxidant capacity (Lubkowska et al., 2015a; Pilch et al., 2021), and the irisin concentration (Dulian et al., 2015; Więcek et al., 2020). One article assessed leukocyte expression of HSPA1A/HSPB1 (Pilch et al., 2021) and measured ferritin, hepcidin, and iron metabolism (Dulian et al., 2015). Each study considered recruited participants with obesity and overweight, and three of them analyzed participants with normal body weight as controls (Pilch et al., 2020a, 2021, 2022). One study included menopausal women with obesity, with and without (control group) metabolic syndrome (Więcek et al., 2020). One study divided the participants into three-groups: those with class II obesity, those with class I obesity, and those with a healthy body weight (Pilch et al., 2022). Six articles compared the effect of WBC on two groups (Dulian et al., 2015; Pilch et al., 2020a, 2021; Więcek et al., 2020; Wyrostek et al., 2021; Ziemann et al., 2013a), and one article on three groups (Pilch et al., 2022). Three of them included subjects with normal body weight as the control group (Pilch et al., 2020a, 2021, 2022). One of them included both subjects with normal body weight and obesity/overweight as the control group (overall, 33 participants without obesity and 11 participants with obesity or overweight) (Więcek et al., 2020). One study included only one experimental group with 30 participants with obesity/overweight. In this study by Lubkowska et al., the subjects also participated in a 6-month training program with double exposure to WBC, 20 sessions each (Lubkowska et al., 2015a). One study included only female subjects (Więcek et al., 2020) while seven studies only involved men (Dulian et al., 2015; Lubkowska et al., 2015a; Pilch et al., 2020a, 2021, 2022; Wyrostek et al., 2021; Ziemann et al., 2013a). For the WBC session, the participants, minimally dressed (e.g., shorts, gloves, woolen sock, wooden clogs, a band or a cap protecting the auricles, surgical mask), had to remove any accessories (e.g., glasses, contact lenses, jewelry), dry their body (i.e., to avoid skin burns). In all eight studies using WBC, the participants spent a 20-to-30-sec adaptation period at -60°C in a vestibule connected directly to the main chamber. Subjects were instructed by trained personnel who supervised the entire procedure and were asked to breathe calmly and slowly during the procedure (Lubkowska et al., 2015a; Pilch et al., 2020a, 2022; Więcek et al., 2020; Wyrostek et al., 2021) and to keep on moving (Lubkowska et al., 2015a; Więcek et al., 2020; Wyrostek et al., 2021). Afterward, cryostimulation was applied at -110°C in two studies (Dulian et al., 2015; Ziemann et al., 2013a), -120°C in five studies (Lubkowska et al., 2015a; Pilch et al., 2020a, 2021, 2022; Wyrostek et al., 2021), -130°C in one study (Więcek et al., 2020). The cryostimulation treatments lasted not less than 2 min and for up to 3 min in every study. The number of exposures varied between 10 (Dulian et al., 2015; Ziemann et al., 2013a) and 40 sessions (Lubkowska et al., 2015a), in one case over two distinct periods. No adverse events

Table 2
Quality assessment of each of the included articles (Downs & Black quality analysis tool).

	Author	year	Reporting	External Validity									Internal Validity									Power	Score								
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18			19	20	21	22	23	24	25	26
Non controlled trial	Items		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	27	
	Ziemann et al	2013	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	17	17
	Dulian et al.	2015	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	18	18
Non randomized controlled trial	Lubkowska et al.	2015	1	1	1	1	1	0	1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	15	15	
	Więcek et al.	2020	1	1	1	1	1	0	1	1	0	1	0	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	17	17	
	Wyrostek et al.	2021	1	0	1	1	1	0	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	15	15	
	Pilch et al.	2020	1	1	1	1	1	1	1	1	0	1	0	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	17	17	
	Pilch et al.	2021	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	18	18	
	Pilch et al.	2022	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	1	1	17	17	

were reported in any of the included studies.

Blood pressure was usually measured only before (Lubkowska et al., 2015a; Pilch et al., 2020a, 2021, 2022; Więcek et al., 2020; Wyrostek et al., 2021) or before and after each treatment (Pilch et al., 2021; Wyrostek et al., 2021) to monitor possible rise in blood pressure, one of the contraindications of cryostimulation. In some cases, the subjects were allowed a light breakfast before the treatment (Dulian et al., 2015; Ziemann et al., 2013a).

4. Discussion

This paper reviews the most recent literature (between 2013 and 2022) on the effects of WBC in patients with obesity and aims to provide a comprehensive and updated summary of the most recent results in order to support its adjuvant therapeutic use. Given the small amount of good-quality published studies on this topic, it was not possible to conduct a systematic review. This exploratory review primarily discusses the effects of WBC treatment on a broad spectrum of hematological (i.e., inflammatory, metabolic, endocrinological, antioxidant) and physiological parameters (maximal oxygen uptake, respiratory quotient, body composition) in individuals with class I and class II obesity.

4.1. Hematological parameters

Hematological parameters outside the health-related reference interval are diagnostic for a variety of ailments including obesity (Purdy and Shatzel, 2021). Four of the selected articles described the effect of WBC on hematological parameters but the results are inconsistent due to variations in methodological factors, such as sample size, number of sessions, temperature exposure, class of obesity, and blood sample collection times. Ziemann et al. reported no significant variation 24 h after 10 sessions of WBC in white blood cells, red blood cells (RBC), and hematocrit (Hct). Most of the initially observed values and differences between the groups were maintained suggesting that cardiorespiratory fitness level, and, probably, class of obesity (not specifically described in the groups), were not influenced by WBC (Ziemann et al., 2013a). Wyrostek et al. described statistically significant differences (in terms of the reference interval) in red blood cell parameters [RBC, Hct, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and mean platelet volume (MPV)]. They reported a decrease in RBC, MCV, Hct and an increase in MCHC in the high-body fat group (HBF) and a decrease in Hct, MCV, MPV, and an increase in RBC and MCHC in the normal-body fat group (NBF) after 10 and 20 sessions. Repeated exposure to cryogenic temperatures did not affect the red blood cell distribution width-coefficient of variation (RDW-CV) while PLT differed only between study groups, but the effect of WBC was not significant since there was no temporal indication of an effect (Wyrostek et al., 2021). On the other hand, the study by Lubkowska et al. showed a decrease in RBC, Hb, Hct, leukocytes (this latter only temporarily) accompanied by an increase in MCH, MCHC, and RDW (Lubkowska et al., 2015a). However, this study involved a study cohort with obesity and overweight undergoing two sets of 20 daily WBC sessions for 6 months, combined with a physical training program that may have affected outcomes associated with cold stimulation. Dulian et al. only investigated the effect of WBC on iron metabolism. They found that the decrease of hepcidin, an iron regulatory hormone that can inhibit the transport of iron from cells through the ferroportin blockade, after 10 sessions of WBC was not followed by any change in iron and ferritin concentrations (Dulian et al., 2015). Thus, WBC seems to exert a general positive effect on these subjects regardless of their fitness level or their obesity class. In three studies, WBC showed no detrimental effects on immune cells. No significant changes in white blood cells parameters were noticed in subjects with obesity undergoing 10 (Wyrostek et al., 2021; Ziemann et al., 2013a) or 20 WBC sessions (Więcek et al., 2020), but only mild acute changes between experimental groups were

maintained. However, Lubkowska et al. observed a transient decrease in the number of white blood cells at the end of the experiment but this could be due to the combination of WBC and physical training and not to the heterogeneity of the study group since it is a general effect (Lubkowska et al., 2015a). Finally, one study observed decreased leukocyte expression of two heat shock protein-encoding genes: HSPA1A (significantly lower in the normal weight as compared to the group with class II obesity, after 20 sessions) and HSPB1 (significantly lower in the normal weight group) suggesting that this reduction may affect adipose tissue and could correlate with fat reduction (Pilch et al., 2020b).

In summary, a decrease of hemoglobinization, possibly associated with enhanced hemolysis, is a specific but temporary feature of the WBC treatment. Similar results have also been reported by studies not performed on cohorts with obesity/overweight (Banfi et al., 2008; Lombardi et al., 2013, 2017) indicating that they may simply reflect a temporary physiological adaptation. Hence, these findings should be considered when designing a treatment program. Furthermore, it is also important to consider that hematological changes could be influenced by the number of WBC sessions, as shown by Szygula et al. in a study conducted on physically active students (Szygula et al., 2014). A temporary decrease of Hb, Hct, and RBC after 10 sessions remained consistently low up to 20 sessions and then increased after the 30th session, possibly due to a recovery in erythropoiesis.

Overall, from the results of the articles cited above, it appears that 10 and 20 sessions of WBC are safe for patients with different classes of obesity and the possibility of increasing the number of treatments could be further explored.

4.2. Inflammatory response

Quantification of the inflammatory response has been widely used to determine the degree of inflammation in various conditions including obesity (Guillot et al., 2014; Ramos et al., 2003; You et al., 2004). The local and systemic anti-inflammatory effects of WBC have been described in previous studies (Banfi et al., 2009a; Stanek et al., 2020; Ziemann et al., 2012). Out of the eight studies that used WBC in obesity, four measured different inflammatory markers, including TNF α (Pilch et al., 2022; Ziemann et al., 2013a), IL-6 (Dulian et al., 2015; Więcek et al., 2020; Ziemann et al., 2013a), IL-10 (Ziemann et al., 2013a) and CRP (Dulian et al., 2015; Pilch et al., 2020a; Więcek et al., 2020), before and after WBC.

Ziemann et al. compared the results obtained in participants with low (LCF) and high cardiorespiratory fitness (HCF). The authors reported a significant decrease in TNF α concentration in subjects with obesity after ten 3-min WBC sessions at -110°C from their baseline values, which were elevated, most likely due to low-grade systemic inflammation. This result was correlated with cardiorespiratory fitness since the difference was more pronounced in LCF as compared to HCF (Ziemann et al., 2013a). Similarly, a significant progressive reduction in TNF α was reported between 10 and 20 WBC in class I obesity and class II obesity by Pilch et al. (2022) but was not accompanied by an increase in ADP levels, usually inhibited by TNF α in adipocytes (Furukawa et al., 2004). In patients with inflammatory rheumatic diseases (Lange et al., 2008) and in professional tennis players (Ziemann et al., 2012) the decrease in TNF α concentrations was comparable to that previously reported after low-intensity exercise (Petersen and Pedersen, 2005). Banfi et al. assessed the effect of WBC on serum mediators of inflammation in athletes who reported increased concentrations of anti-inflammatory cytokines and a decrease in the pro-inflammatory cytokines/chemokines, IL-2, and IL-8 (Banfi et al., 2009b) in peripheral blood as a consequence of local and systemic analgesic effects of WBC. IL-6 can act both as a pro-inflammatory cytokine and as an anti-inflammatory myokine depending on its production site, the stimulation pathway that enabled its release, and its basal concentration (Villar-Fincheira et al., 2021). Chronic inflammatory conditions are characterized by mildly elevated levels of IL-6 that play a role in

systemic inflammation, i.e. by stimulating other anti-inflammatory cytokines such as IL-10 and inhibiting the production of the pro-inflammatory cytokine TNF α (Petersen and Pedersen, 2005). Visceral adipose tissue mass, BMI and waist circumference are positively correlated with IL-6 concentration in individuals with obesity (Park et al., 2005) and has been shown to have a metabolic effect that stimulates lipolysis and fat oxidation (van Hall et al., 2003). By contrast, increased levels of IL-6 can originate from contracting muscle and act as an anti-inflammatory mediator (Lombardi et al., 2016). In menopausal women with obesity and metabolic syndrome, 10 and 20 sessions of WBC increased IL-6 concentrations (Więcek et al., 2020), as seen in professional tennis players exposed to 10 WBC sessions, twice a day for 5 days in combination with moderate-intense physical training (Ziemann et al., 2012), and two separate groups of clinically healthy untrained men in which the same WBC protocol significantly increased IL-6 above baseline (Lubkowska et al., 2010, 2011). Lubkowska et al. reported that in young healthy men, the concentration of IL-6 in the blood is above baseline after the 1st and the 10th exposure to WBC (Lubkowska et al., 2011). Nevertheless, in two different studies on men with obesity, 10 sessions of WBC did not significantly alter IL-6 concentrations (Dulian et al., 2015; Ziemann et al., 2013a), while its decrease after 10 sessions was reported only in LCF subjects with obesity and not in the HCF group with obesity (Ziemann et al., 2013a). It has already been shown that IL-10, an anti-inflammatory cytokine with multiple, pleiotropic effects in immunoregulation and inflammation, increases in rugby players after 5 sessions of WBC (Banfi et al., 2009b). In HCF and LCF subjects with obesity, 10 sessions of WBC increased IL-10 and the rise was sustained 24 h after the last session. Interestingly, baseline values of IL-10 were already significantly higher in the LCF group, suggesting that elevated IL-10 concentrations could be a component of the enhanced defensive response to low-grade systemic inflammation. In subjects with obesity, BMI was significantly associated with CRP, and baseline CRP concentrations were reported to be higher in subjects with obesity than in subjects without obesity (Park et al., 2005), confirming that obesity is characterized by a higher inflammatory state.

Therefore, it would be natural to predict that the anti-inflammatory effect of a cold stimulus, such as WBC, would decrease the level of CRP which usually rises rapidly in response to inflammation. However, the results are not always as expected. Dulian et al. (2015) confirmed the anti-inflammatory effect of WBC in people with obesity, reporting that the decline in CRP levels was similar in both the low fitness (LFL) and high fitness (HFL) level group with obesity regardless of the number of sessions (either 1 and 10). A similar decrease was also observed in well-trained athletes exposed to 5 sessions of WBC for up to 96 h after exercise (Pournot et al., 2011). However, WBC did not induce significant changes in men or menopausal women with obesity, regardless of their body mass (high or normal) or comorbidity with metabolic syndrome reproducing the results obtained by Śliwicka and colleagues who did not show significant changes in CRP levels after 10 WBC treatments in 20-year-old men without obesity, regardless of their fitness level (Śliwicka et al., 2020).

Globally, even if the findings are not always in line, WBC appears to yield an anti-inflammatory effect that is highly correlated with the fitness level in individuals with obesity.

4.3. Redox balance

Chronic inflammation and high production of reactive oxygen species (ROS) contribute to the increase in oxidative stress in obesity. With increased body fat and central obesity, the activity of antioxidant enzymes such as superoxide dismutase (SOD1), catalase (CAT), and glutathione peroxidase (GPx), is significantly diminished (Manna and Jain, 2015). In the study by Pilch et al., WBC exerted an antioxidant effect only in normal-weight subjects. Subjects with obesity had higher baseline levels of oxidative stress as compared to their lean counterparts and their total oxidative status and antioxidant capacity did not change

after 20 WBC sessions (Pilch et al., 2021).

Although previous studies on athletes and healthy subjects had shown the beneficial antioxidant effect of WBC already after a limited number of sessions (Lombardi et al., 2017), a dose-dependency was observed in healthy men, with 20 sessions being the optimal number of sessions (Lubkowska et al., 2008, 2012).

As for antioxidant enzymes, subjects with obesity showed a significant increase in SOD1 activity, whereas a significant decrease was observed in the lean group (Wyrostek et al., 2021). Interestingly, Lubkowska et al. reported an increased SOD activity in individuals with obesity after successive cryostimulation series that eventually decreased below the baseline values one month after a physical exercise program (Lubkowska et al., 2015a). Data regarding CAT activity were inconsistent in the two studies cited above. Baseline CAT activity, similar in lean subjects and individuals with obesity, significantly increased after 20 WBC sessions only in the group with obesity (Pilch et al., 2021). Conversely, Lubkowska et al. found that CAT activity significantly decreased after the second set of WBC combined with physical exercise, only to increase again 1 month after the intervention, without returning to baseline (Lubkowska et al., 2015a).

Fewer antioxidant activity is required to reduce the risk of oxidative damage during WBC, since cryostimulation already yields an antioxidant effect. In fact, the effect of WBC on subjects with obesity after 20 sessions on the reduction of oxidation and the production of free-radical is deduced from the reduced activity of glutathione peroxidase (GPx) (Lubkowska et al., 2015a) (although not always significant) (Pilch et al., 2021), GST and the unchanged activity of glutathione reductase (R-GSSG), the latter returning to baseline values after an initial decrease (Lubkowska et al., 2015a).

In summary, WBC generally appears to improve the effect on redox balance in a session-dependent manner, probably through the decrease in the total oxidant production which, consequently, induces antioxidant activity. However, no specific effects were observed in subjects with obesity.

4.4. Body composition

Measurement of body composition may vary according to the technique used and the population characteristics. In two articles, body composition was assessed to describe only the population sample in terms of the amount of fat and lean mass but, disappointingly, it was not studied after WBC (Pilch et al., 2020a; Więcek et al., 2020). In their earlier article, Pilch and colleagues reported the participants' body composition at baseline without describing the technique used for their quantification (Pilch et al., 2020a). After 10 WBC sessions, Więcek reported a significant reduction in waist, hips and abdominal circumference, waist-to-height ratio, triceps and abdominal skinfold thickness in one group of women with overweight and two groups of menopausal women with obesity: healthy and with metabolic syndrome (MetS). After 20 sessions of WBC, these effects intensified. A significant reduction in body mass, BMI, absolute total body fat, and leg fat was also achieved. Furthermore, the MetS group showed a significant reduction in the percentage of the total, trunk, and android fat (Więcek et al., 2020) but since the authors did not clearly differentiate according to BMI, it is not possible to compare the effect of WBC among the groups, especially between subjects with class I and class II obesity. Similar results were obtained by Pilch et al. in males with class I obesity with high body mass, and normal body mass controls. After 20 sessions of WBC, fat mass, the percentage of body fat, the circumference of the hips and waist, and the BMI significantly decreased (Pilch et al., 2020a). However, after 10 WBC sessions, Ziemann et al. found no changes in body composition in class I obese men (Ziemann et al., 2013b) while Lubkowska et al. reported no significant changes in body weight, waist-hip ratio, BMI, body fat mass, skeletal muscle, and subcutaneous fat mass after 40 WBC exposures associated with an intensive exercise program (Lubkowska et al., 2015b). However, the group included subjects with

an average BMI greater than 30, most probably consisting of both class I and II obesity since the minimum BMI was 26.2 kg m⁻² and the maximum was 41.1 kg m⁻². Finally, in agreement with their previous work (Pilch et al., 2020b) but in contrast to the results of the groups of Lubkowska (Lubkowska et al., 2015b) and Ziemann (Ziemann et al., 2013b), Pilch group's latest study (Pilch et al., 2022) found the greatest changes in subcutaneous fat tissue thickness that was significantly reduced in the class I obesity group.

In summary, although most studies suggest that WBC leads to a reduction in adipose tissue and circumferences in different regions of the body, the results regarding body composition are heterogeneous in the analyzed studies, partly due to the presence of confounding interventions such as dietary therapy and physical activity, and the absence of a control group. Higher subcutaneous fat in individuals with obesity could cause lower heat loss (Speakman, 2018) by slowing the increase in metabolic rate compared with individuals without obesity. This would explain the different effect of WBC on body composition with different BMIs.

4.5. Lipid profile, adipokines and energy metabolism

Obesity is characterized by increased levels of LDL and TG (Lubkowska et al., 2015a) and lower HDL (Larrad et al., 2016). Lipids are the preferred fuel source for thermogenesis and a change in the lipid profile after WBC was expected since exposure to cold activates adipose tissue, both white (WAT) and brown (BAT) (Cheng et al., 2021; Hanssen et al., 2016). Nevertheless, Pilch et al. reported no significant changes in the lipid profile but only a positive trend to recover metabolic balance in adipose tissue in the class I obesity group (Pilch et al., 2022) whereas Lubkowska et al. noted favorable changes in the lipid profile after a six-month intervention with WBC with a decrease in triglycerides and LDL cholesterol and a slight increase in HDL cholesterol (Lubkowska et al., 2015b). However, the heterogeneity of the study group (subjects with class I and class II obesity, and overweight) and the exercise program followed by the study subjects may have contributed to this profile. In fact, it is well documented that exercise lowers total and LDL and increases HDL cholesterol levels.

Moreover, the selected articles exhibited discordant and different results regarding adipokines levels after WBC (Dulian et al., 2015; Lubkowska et al., 2015a; Więcek et al., 2020; Ziemann et al., 2013a). Ziemann et al. described that 10 WBC sessions influenced the concentration of pro-inflammatory adipokines in relation to the subjects' cardiorespiratory fitness levels. Resistin and visfatin increased at the end of the treatments in LCF participants with both class I and class II obesity and, on the contrary, significantly decreased in HCF subjects with only class I obesity, while adiponectin and leptin were not affected (Ziemann et al., 2013a). Interestingly, irisin, an exercise-induced myokine known to stimulate WAT browning and promote thermogenesis (Boström et al., 2012; Lombardi et al., 2017), increased in all participants with class I and class II obesity 24 h after the first and 10th session of WBC (Dulian et al., 2015). The same authors reported that plasma irisin concentrations increased significantly by 20% only in the low fitness level subjects with class I and class II obesity with an LFL (non-active), while they slightly decreased in subjects with an HFL (active) with only class I obesity (Dulian et al., 2015). The observed increase in irisin was also noted in women with obesity and metabolic syndrome and in healthy ones after one WBC session and further increased after 10 exposures, to return to baseline after 20 sessions (Więcek et al., 2020). Lubkowska et al. found no change after WBC exposures in adiponectin, resistin, and leptin concentrations but only in visfatin levels after 6 months, compared to baseline (Lubkowska et al., 2015a). However, as mentioned before, the heterogeneity of the study group (subjects with class I and class II obesity, and overweight) and the fact that the participants engaged in physical activity during the 6-month program, as well as 2 sets of 20 sessions of WBC, may have influenced these results. A similar effect on adiponectin in response to WBC was also reported by Pilch

et al. who observed no changes between 10 and 20 sessions but observed that adiponectin levels in obese individuals, especially in those with visceral obesity, were lower than those in lean subjects (Pilch et al., 2022), in line with previous published results (Hotta et al., 2000; Meier and Gressner, 2004; Valassi et al., 2008; Vega and Grundy, 2013). Interestingly, they showed a significant decrease in leptin levels in class I and II obesity groups between 10 and 20 WBC sessions while in the healthy controls no effect was seen.

In summary, adiponectin does not seem to undergo significant changes after WBC. On the other hand, the decrease in leptin found by Pilch et al. suggests the possible positive influence of cold stimulation on the impairment of expression and functional activity of beta-3 adrenergic receptors in obesity (Collins et al., 1994) and its beneficial effect on metabolism, muscle shivering, and glucose uptake (Ahima and Lazar, 2008; Meier and Gressner, 2004). Of particular note is the absence of changes in leptin observed by Lubkowska et al. (2015b) because leptin, known to be reduced after physical activity and after body mass loss, should have had a synergistic effect with cold stimulation of WBC. As for visfatin, resistin and irisin, it seems that the initial level of fitness and the amount of fat mass determine the response to treatment, even if it still refers to a population with obesity. In a group of patients with class I and class II obesity, reduced fitness and increased adiposity, visfatin, resistin, and irisin increased significantly, while the counterparts with only class I obesity and higher fitness status responded in the opposite way.

5. Limitations

Our scoping review presents with some limitations. Firstly, the molecular mechanisms underlying the reported beneficial effects of WBC have not been investigated. Secondly, the lack of standardized protocols for the use of WBC in the treatment of obesity (temperature, number of sessions, time of exposure, and sample collection time varied among studies) may have accounted for discrepancies in the findings reported. Also, in this regard, confounding factors such as physical activity and diet, which have a key role in modulating antioxidant, anti-inflammatory, and body composition, were present in most articles. Thirdly, the absence of randomized controlled trials, blinding, or proper control groups within the searched papers dramatically reduced the eligibility of the articles. Finally, the absence of stratification of participants according to their BMI and class of obesity. A clear distinction was made only in the work of Pilch and collaborators (Pilch et al., 2020b, 2021, 2022), whereas in other studies, BMI values were averaged (at least for a subgroup of the study), not allowing to understand to which class of obesity the different participants belonged to.

In general, the modest bulk of literature, the low quality of the studies, the small sample sizes, and the variety of WBC protocols do not allow for proper comparison of outcome measurements among the studies. Therefore, future studies with larger sample sizes and more rigorous methodological study designs are needed to confirm the significance of the physiological changes and identify the effects of WBC at the molecular level. Many of the results obtained in the selected articles do not clearly address the questions of whether the number of WBC sessions should be considered as a function of BMI and whether increasing the number of WBC sessions parallel to an increase in BMI would yield positive results.

6. Conclusions

The seductive aspect of WBC relies on its dual anti-inflammatory/antioxidant and metabolic effect. WBC seems to yield the potential of becoming an adjuvant therapeutic approach to existing strategies, capable of reducing systemic inflammation, abdominal obesity, and body mass in individuals with obesity, particularly those with low fitness level. The efficacy of WBC appears to be directly related to individual body composition, fat mass percentage, and initial fitness capacity, mimicking exercise-induced effects. This seems of particular

interest in a population with a high dropout rate from exercise programs for various reasons and is advocated to unveil a new scenario in the treatment of obesity and obesity-related disorders. In addition to the effects reviewed in this paper, a recent meta-analysis highlights that sympathetic activity is markedly and significantly increased in subjects with obesity, even when subjects do not concomitantly display hypertension, diabetes mellitus, obstructive sleep apnea, and metabolic syndrome: conditions characterized per se by an adrenergic activation (Grassi et al., 2019). This adrenergic overdrive exhibits an early appearance and progression with increasing severity of these conditions. Therefore, WBC could provide additional benefits through its sympatho-inhibitory action.

6.1. Future perspective

Given the important limitations of the included studies, the data presented in this review article fail to reach definitive conclusions regarding the efficacy of WBC as add-on treatment in the management of obesity. Available data are still scanty and inconsistent, and the quality of the studies generally remains low. Further studies are needed regarding the number of WBC sessions, the temperature in the cryogenic chamber, the duration of exposure to cryogenic cold also in relation to individual body fat and physiological profile, and the duration of anti-inflammatory and metabolic effects elicited by a cycle of sessions. In addition, further research focusing on patients with varying degrees of body mass index and also undergoing treatments other than those used in current studies will be needed to shed light on factors that may influence individual responses to cryogenic exposure in order to define personalized gender-specific protocols and develop guidelines on its clinical use. Changes in response to WBC may differ between overweight and different classes of obesity because adipose tissue is an effective insulator and may act as a barrier to heat loss. Therefore, subjects with higher BMI may not show the effects seen in subjects with lower degrees of obesity because of their slower heat release and their greater metabolic rate which would explain the observed differences in the effects of WBC on class I and class II obesity patients. For these reasons, future studies with larger cohorts and control groups are needed to investigate the effects of more WBC sessions than those used in current studies, especially for subjects with class II obesity.

Authors' contributions

PC is the study's principal investigator. Study concept and design were contributed by PC, BD, GL, JMF, SB, MG, PP, and EMG. EMG, MG, PP, SB, and JMF searched specified data sources, selected articles, and extracted all necessary data. JMF, SB, PP, EMG, BD, GL, and MG analyzed the data. JMF and SB wrote the first draft of the manuscript. All authors revised and/or commented on drafts. All authors accepted the final version of the manuscript.

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Declaration of competing interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Data availability

No data was used for the research described in the article.

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