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Research article

Intermittent hypoxia-hyperoxia therapy in medical rehabilitation: Effects on body composition in patients with metabolic syndrome

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Abstract: Metabolic syndrome (MS) comprises a set of metabolic irregularities that elevate the risk of cardiovascular conditions and diabetes. The essential characteristic components are: high blood pressure and high triglyceride levels, low HDL cholesterol levels, hyperglycemia and obesity (particularly central adiposity). MS represents a major public health challenge and current intervention methods have limitations in effectiveness and long-term adherence. Intermittent hypoxia-hyperoxia therapy (IHHT) is an innovative method that involves controlled and alternating exposure to hypoxia and hyperoxia. This technique mimics the effects of altitude training and stimulates the body's adaptive mechanisms, contributing to improved mitochondrial function, increased oxidative capacity and the regulation of metabolic processes. According to the literature, IHHT is an innovative method that causes significant changes in the parameters studied in patients with MS. Body composition plays an important role in maintaining health. It is affected by multiple factors: environmental conditions, genetics and lifestyle choices. Body composition assessment is essential for evaluating nutritional status, identifying risks associated with conditions such as MS and monitoring progress during dietary and lifestyle interventions. A randomized controlled trial was carried out with 40 participants diagnosed with MS, who were split into two groups. The intervention group, consisting of 20 participants, underwent intermittent hypoxia-hyperoxia therapy (IHHT), while the control group, also with 20 participants, received a placebo therapy. The study aimed to evaluate whether IHHT could positively affect body composition. The study found no significant differences between the groups regarding the analyzed parameters. However, both groups showed progress, highlighting the relevance of medical rehabilitation, even without a notable impact of IHHT. The study results suggest that medical rehabilitation can benefit body composition in patients with MS, even without the additional contribution of IHHT. The study highlights that improvements in body composition can be influenced by factors such as discipline and active participation of patients in rehabilitation programs, emphasizing the importance of constant involvement in the medical rehabilitation process as a key factor for achieving desired outcomes. However, the lack of clear results in improving body composition could be attributed to factors such as the relatively short duration of the intervention, the small size of the study groups, or the influence of the placebo effect on patients' perceptions.

Keywords: intermittent hypoxia hyperoxia therapy, metabolic syndrome, body composition

1. Introduction

Metabolic syndrome (MS) comprises a set of metabolic irregularities that elevate the risk of cardiovascular conditions and diabetes. MS represents a major public health challenge and current intervention methods have limitations in effectiveness and long-term adherence [1].

The essential characteristic components are: high blood pressure and high triglyceride levels, low high-density lipoproteins (HDL) cholesterol levels, hyperglycemia and obesity (particularly central adiposity) [1]. Visceral adiposity is a key trigger for most pathways involved in metabolic syndrome, thus highlighting the importance of excessive caloric consumption as a primary contributing factor. Among all proposed mechanisms, insulin resistance, neurohormonal activation and chronic inflammation appear to be the main contributors to the initiation, progression and transition of MS to cardiovascular diseases [2].

One of the most significant public health burdens worldwide is MS, although pharmacotherapy has made many advances. MS can have its origins early in life, due to dietary imbalances, maternal pathologies, maternal exposure to chemicals and also the use of medications [3,4].

Intermittent hypoxic training (IHT) involves alternating episodes of hypoxia with those of lesser severity, such as normoxia, hyperoxia, or hypercapnia [5]. IHT is a noninvasive, easy-to-apply method used in sports medicine. This serves as an effective strategy for enhancing athletic performance during exercise in athletes. Beyond enhancing physical performance, it has also been used in healthy subjects, having potential beneficial effects for improving multiple physiological functions [6,7]. Intermittent hypoxia-hyperoxia therapy (IHHT) is an innovative method that involves controlled and alternating exposure to hypoxia and hyperoxia. This technique mimics the effects of altitude training and stimulates the body's adaptive mechanisms, contributing to improved mitochondrial function, increased oxidative capacity and the regulation of metabolic processes. According to the literature, IHHT is an innovative method that causes significant changes in the parameters studied in patients with MS [8].

Body composition plays an important role in maintaining health. It is affected by multiple factors: environmental conditions, genetics and lifestyle choices. Body composition assessment is essential for evaluating nutritional status, identifying risks associated with conditions such as MS and monitoring progress during dietary and lifestyle interventions [9].

Body mass index (BMI), commonly used to assess general obesity, does not accurately reflect overall body fat. BMI does not differentiate between various body components, such as fat and muscle mass. A deficiency in muscle mass and an excess of body fat are both linked to metabolic diseases [10,11].

Excess body fat, a characteristic of obesity, represents a major health risk. The World Health Organization, the International Diabetes Federation, the National Cholesterol Education Program-Adult Treatment Panel III and the American Association of Clinical Endocrinologists have proposed abdominal adiposity as the main parameter for determining metabolic syndrome [12].

Considering that the scientific literature already includes studies investigating the effects of IHHT on patients with MS, we hypothesized that this therapy could influence body composition parameters in these patients. While most research has focused on aspects such as improving the lipid profile or reducing systemic inflammation [8], there is the possibility that exposure to IHHT may have a significant impact on body composition. Given the complexity of MS and the close relationship between obesity, insulin resistance and metabolic dysfunctions [2], an intervention that could improve these aspects would be of great interest to the clinical management of patients with this condition. Therefore, we considered that studying the effects of IHHT on body composition could provide new insights into the potential of this therapy, thus offering the opportunity to uncover mechanisms that could contribute to more effective and personalized treatments for patients with MS.

2. Materials and Methods

A randomized controlled trial was carried out with 40 participants diagnosed with MS, who were split into two groups. The intervention group, consisting of 20 participants, underwent IHHT, while the control group, also with 20 participants, received a placebo therapy.

The study was approved by the Balneal and Rehabilitation Sanatorium of Techirghiol (SBRT) for its conduct and all patients signed informed consent.

This study aimed to evaluate whether IHHT could benefit body composition, assessed using a weighing scale, in patients diagnosed with MS. The research seeks to determine potential positive effects, thus contributing to the development of more effective interventions for managing MS.

The inclusion criteria in the study were the following: a confirmed diagnosis of MS; patients hospitalized for complex rehabilitation treatment in SBRT; the patient's consent; patients eligible for IHHT.

The exclusion criteria in the study were the following: the uncertainty of the MS diagnosis; rehabilitation treatment conducted in an ambulatory; the patient's disagreement to enroll in the study; patient with contraindications for IHHT.

40 patients were randomly allocated to the IHHT group or to the sham group (they received simulated therapy). Each group included 20 patients. The patients were advised to maintain their regular diet, physical activity, prescribed medications and daily routines throughout the study.

The randomization process was carried out using drawing lots with the help of tickets.

In this study, only the patients were blinded, while the researchers were not subjected to the same blinding conditions. This approach was chosen because "blind" studies are considered methodologically more rigorous, reducing the potential for bias from participants and ensuring an objective assessment of the results. Thus, by implementing this procedure, we managed to create an experimental framework that minimizes subjective influences and strengthens the validity of the study conclusions.

The patients included in this study were admitted to a specialized medical rehabilitation unit, SBRT. During their hospitalization, they benefit from a standardized diet that includes three meals a day (breakfast, lunch and dinner). All participants receive the same type of food, ensuring dietary uniformity throughout the study period. This controlled diet allows for careful monitoring of nutritional factors, eliminating variations that could influence the study's results.

The protocol used in this study involves exposing participants to hypoxia and hyperoxia. In the hypoxia phase, participants are exposed to an oxygen concentration of 9-16% for 5-7 minutes, followed by a hyperoxia period with an oxygen concentration of approximately 35% for 2-5 minutes, according to the recommendations in the specialized literature. Before starting the actual therapy, patients performed hypoxic tests 1 and 2 to be classified into a typology (I, II, III) and to determine the optimal oxygen level. Subsequently, using the data collected, the device automatically calculated and scheduled personalized treatment sessions for each patient.

In addition to IHHT therapy (real or simulated), patients in both groups received a complex rehabilitation treatment. This included therapy using salt water and sapropelic mud from Lake Techirghiol, kinetotherapy, electrotherapy and massage therapy.

Upon admission, patients underwent a comprehensive assessment that included identifying comorbidities, family and personal medical history, and reviewing medication for related conditions and behavioral factors. Body weight and body composition were assessed using the Tanita RD-953 scale.

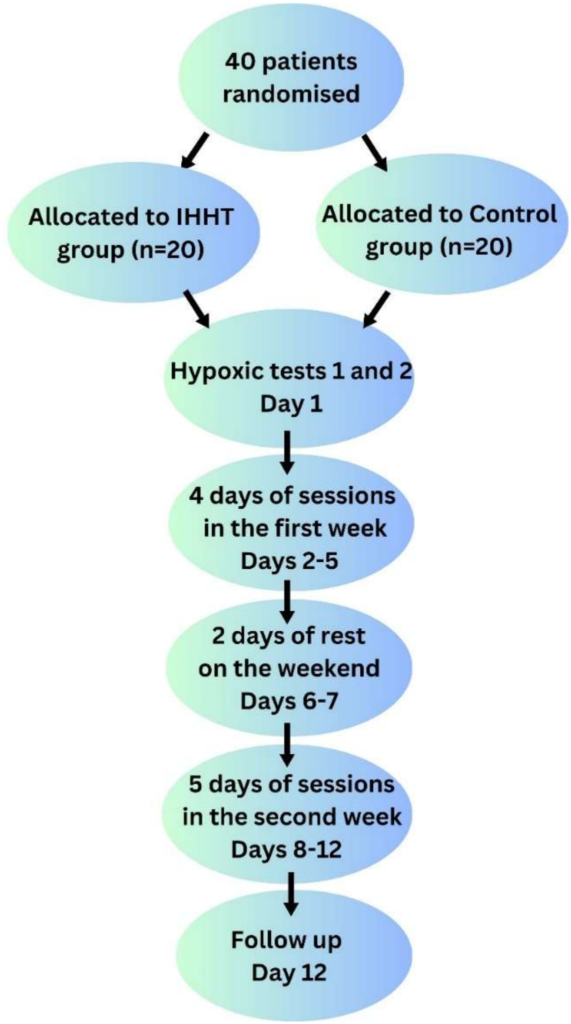

Figure 1 – Study design flowchart

3. Results

The statistical analysis was performed using IBM SPSS statistics software version 25.

Table I presents the demographic characteristics of both the interventional and control groups, highlighting the absence of significant differences between the groups across the evaluated variables. However, differences were observed regarding dietary habits. From the perspective of dietary habits, four main categories of nutritional behaviors were analyzed. Among these, minimal differences were noted in two specific categories: a balanced diet and predominantly protein intake. These variations suggest differences in dietary preferences between the two groups, highlighting demographic or behavioral particularities that may influence the nutritional profile of the participants.

Table I – Demographic data

		Interventional group		Control group		Total	
Sex	Female	12	60.00%	9	45.00%	21	52.5%
	Male	8	40.80%	11	55.00%	19	47.5%
Age	40-50	2	10%	1	5%	3	7.5%
	50-60	5	25%	4	20%	9	22.5%
	60-70	9	45%	11	55%	20	50%
	70-80	4	20%	4	20%	8	20%
Nutritional status	Obesity grade I	12	60%	15	75%	27	67.5%
	Obesity grade II	6	30%	5	25%	11	27.5%
	Obesity grade III	2	10%	0	0%	2	5%
Dietary habits	Balanced diet	11	55%	3	15%	14	35%
	Cheeses pre-dominate	3	15%	2	10%	5	12.5%
	Carbohydrates predominate	3	15%	3	15%	6	15%
	Proteins pre-dominate	3	15%	12	60%	15	37.5%
Lifestyle	Active person	16	80%	15	75%	31	77.5%
	Sedentary per-son	4	20%	5	25%	9	22.5%
Physical ac-tivity	Many times a week	4	20%	0	0.00%	4	10%
	Sometimes	8	40%	5	25%	13	32.5%
	Never	8	40%	15	75%	23	57.5%
Alcohol	Yes	3	15%	2	10%	5	12.5%
	No	3	15%	3	15%	6	15%
	Ocassional	14	70%	15	75%	29	72.5%
Smoking	Yes	2	10%	4	20%	6	15%
	No	10	50%	8	40%	18	45%
	Former smoker	8	40%	8	40%	16	40%
Environment	Urban	12	60%	14	70%	26	65%
	Rural	8	40%	6	30%	14	35%
Sleep quality	Restful	6	30%	8	40%	14	35%
	Restless	14	70%	12	60%	26	65%

Table II highlights how IHHT affected the various parameters analyzed in both groups. The analysis of the results shows that the evaluated parameters did not present significant differences between the two groups that received IHHT and the one that underwent placebo treatment. These findings suggest that the intervention did not have a different impact than the placebo treatment, indicating a lack of significant efficacy of the therapy compared to its simulation.

Table II – Descriptive statistics for the parameters analyzed at admission and discharge in the interventional and control groups

	Group	N	Mean	Median	SD	Min	Max	Percentiles P25	Percentiles P75
Age (years)	Interventional	20	63.25	67.00	8.52	48.00	75.00	56.25	68.75
	Control	20	63.30	65.50	7.38	48.00	74.00	58.50	67.75
Body fat at admission (%)	Interventional	20	36.41	36.70	10.57	16.50	53.60	29.10	44.50
	Control	20	36.45	34.75	6.95	24.30	45.80	29.90	44.00
Body fat at discharge (%)	Interventional	20	36.15	36.50	9.50	16.90	53.80	29.28	43.78
	Control	20	35.65	33.75	7.06	23.60	47.60	29.75	43.38
Visceral fat at admission	Interventional	20	14.25	13.75	3.74	8.00	21.50	11.63	17.38
	Control	20	15.48	14.25	3.60	10.00	22.00	12.75	18.25
Visceral fat at discharge	Interventional	20	14.48	14.00	3.59	9.50	22.00	11.63	17.63
	Control	20	15.25	14.25	3.73	9.50	22.00	12.63	18.13
Bone mass at admission (Kg)	Interventional	20	3.07	2.85	0.57	2.30	4.10	2.63	3.60
	Control	20	3.06	3.05	0.55	2.20	3.90	2.55	3.58
Bone mass at discharge (Kg)	Interventional	20	3.08	2.80	0.59	2.30	4.10	2.60	3.70
	Control	20	3.08	3.10	0.54	2.20	3.90	2.55	3.55

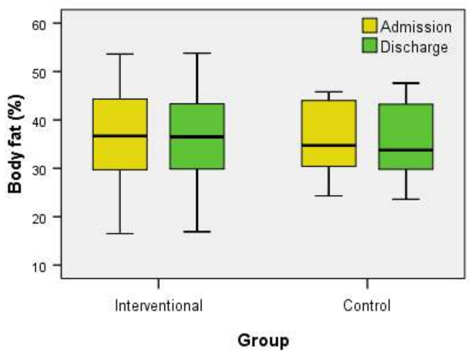

Figure 2 – Box plot comparison of body fat at admission and discharge between interventional and control groups

Mann-Whitney U Test revealed no significant differences in the body fat at admission (%) between the interventional group (Median = 36.70, n = 20, Mean rank = 20.70) and the control group (Median = 34.75, n = 20, Mean rank = 20.30), U = 196.00, z = -0.108, p = 0.914 > α = 0.05 and also no significant differences in the body fat at discharge (%) between interventional group (Median = 36.50, n = 20, Mean rank = 21.13) and control group (Median = 33.75, n = 20, Mean rank = 19.88), U = 187.50, z = -0.338, p = 0.735 > α = 0.05.

A Wilcoxon signed-rank test showed that for the interventional group (Z = -0.728, p = 0.467) the treatment did not elicit a statistically significant change in the body fat (%) between admission and discharge but for the control group (Z = -2.429, p = 0.015) the treatment elicits a statistically significant change in the body fat (%) between admission and discharge.

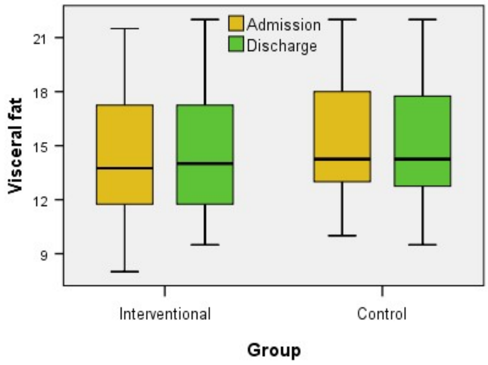

Figure 3 – Box plot comparison of visceral fat at admission and discharge between interventional and control groups

Mann-Whitney U Test revealed no significant differences in the visceral fat at admission between the interventional group (Median = 13.75, n = 20, Mean rank = 18.63) and control group (Median = 14.25, n = 20, Mean rank = 22.38), U = 162.50, z = -1.016, p = 0.309 > α = 0.05 and also no significant differences in the visceral fat at discharge between interventional group (Median = 14.00, n = 20, Mean rank = 19.18) and control group (Median = 14.25, n = 20, Mean rank = 21.83), U = 173.50, z = -0.718, p = 0.473 > α = 0.05.

A Wilcoxon signed-rank test showed that for the interventional group (Z = -0.169, p = 0.866) the treatment did not elicit a statistically significant change in the visceral fat between admission and discharge and for the control group (Z = -2.309, p = 0.021) the treatment elicits a statistically significant change in the visceral fat between admission and discharge.

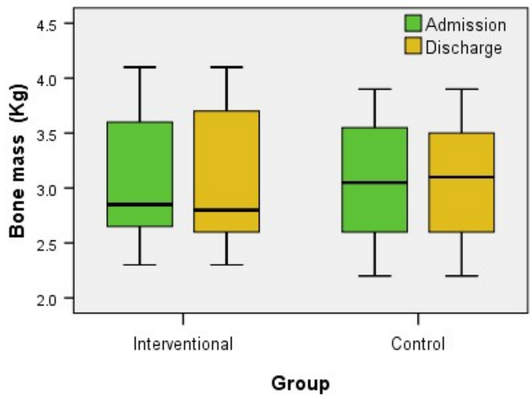

Figure 4 – Box plot comparison of bone mass at admission and discharge between interventional and control groups

Mann-Whitney U Test revealed no significant differences in the bone mass at admission (kg) between interventional group (Median = 2.85, n = 20, Mean rank = 20.63) and control group (Median = 3.05, n = 20, Mean rank = 20.38), U = 197.50, z = -0.068, p = 0.946 > α = 0.05 and also no significant differences in the bone mass at discharge (kg) between interventional group (Median = 2.80, n = 20, Mean rank = 20.53) and control group (Median = 3.10, n = 20, Mean rank = 20.48), U = 199.50, z = -0.014, p = 0.989 > α = 0.05.

A Wilcoxon signed-rank test showed that for the interventional group (Z = -0.418, p = 0.676) the treatment did not elicit a statistically significant change in the bone mass (kg) between admission and discharge and for the control group (Z = -

0.877, p = 0.380) the treatment did not elicit a statistically significant change in the bone mass (kg) between admission and discharge.

4. Discussion

Body composition analysis entails describing and measuring the various components of the human body [13]. In clinical nutrition, it is important to distinguish between fat mass and fat-free mass, including skeletal muscle mass. Additionally, understanding the distribution of fat is vital, as visceral and subcutaneous adipose tissues differ in structure and endocrine function, impacting cardiometabolic health and cancer risk in distinct ways [14-16]. Furthermore, alterations in specific body components, such as a reduction in skeletal muscle mass and a decrease in bone mineral density, can affect a patient's physical abilities, performance, and overall prognosis [17].

Central obesity plays a crucial role in the development of MS. The excessive accumulation of visceral fat is particularly harmful, leading to adipose tissue dysfunction [18]. It has been shown that visceral adiposity is a key trigger for most pathways involved in MS, highlighting the importance of a high caloric intake as a major causal factor [19].

Existing research in the scientific literature supports the safety and effectiveness of IHHT, which highlights its successful use in the treatment of various pathologies [20].

This study represents a novel and original investigation, being the first of its kind in the literature to analyze the impact of IHHT on body composition in patients with MS. To date, no other publications have addressed this specific subject, making this study a valuable contribution to understanding the potential of IHHT in managing MS. Furthermore, existing literature includes studies that support the efficacy of IHHT in patients with MS and obesity [8,21,22].

Bestavashvili et al published a study in 2021 that examined the effects of IHHT on the lipid profile and inflammation in patients with MS. The 65 patients with MS were randomly assigned to either the IHHT group or the control group. The study demonstrated that IHHT can be safely used in patients with MS. Following the treatment, a decrease in lipid metabolism and inflammatory markers was observed in the IHHT group, thus supporting the effectiveness of the treatment in reducing systemic inflammation and improving the lipid profile in patients with MS [8].

In 2023, a study investigated the effects of IHHT exposure on cardiometabolic risk factors and trimethylamine N-oxide (TMAO) levels in patients with MS. The results showed a trend of reduced TMAO levels in the blood in the IHHE group, accompanied by significant improvements in cardiometabolic and hepatic parameters compared to the control group. These results suggest that IHHE could be a safe and effective method for improving cardiometabolic health, possibly through the regulation of the gut microbiome and hepatic metabolism [21].

A recent study conducted by Uzun et al also demonstrated the beneficial effects of IHHT therapy in obese patients, improving physical performance, renal and hepatic function, as well as respiratory function, with the potential to offer significant benefits in the management and treatment of obese and/or metabolic syndrome patients [22].

Before initiating the study, patients were randomly assigned to either the intervention or control group to ensure an even distribution of factors that could influence the outcomes. A comparison of baseline characteristics between the two groups revealed no significant differences in terms of age, gender, nutritional status, lifestyle, alcohol consumption, smoking habits, environmental factors, or sleep quality. This aspect is crucial for minimizing the risk of bias and accurately interpreting the study results. Ensuring that patients in both groups have similar characteristics provides greater confidence that any observed differences in outcomes are caused by the treatment applied rather than by other confounding factors. Highlighting the initial uniformity of patient characteristics in both groups is important, as it enhances the validity and reliability of the study's conclusions.

The age distribution of participants in the two groups was evaluated and the results showed a significant similarity between them. The absence of major age variations between the groups supports the interpretation of the results as being associated with the applied intervention.

The study findings revealed no statistically significant differences between the two groups in terms of gender distribution. The uniformity of this factor ensures that the effects observed in the study are not influenced by the gender of the participants, which strengthens the validity of the results and their applicability to both men and women.

The uniformity in the distribution of nutritional status shows that the patient's nutritional status at baseline did not exhibit significant differences between the two study groups. Significant differences in nutritional status could influence how patients respond to treatments, and any observed results could be attributed more to these nutritional discrepancies than to the effect of the intervention being studied.

In the assessment of dietary habits, four main categories of nutritional behavior were analyzed. The minor differences observed in the two categories, namely a balanced diet and predominant protein consumption, indicate variations in dietary preferences between the two groups. These differences may be influenced by factors such as nutritional education, socio-economic status or even cultural traditions that impact the participants' eating habits. Eating habits are closely linked to metabolic health. Understanding the relationship between eating habits and health outcomes is essential for preventing metabolic diseases. Eating habits refer to the long-term practices that an individual maintains in daily life. Eating behavior is a fundamental activity in everyday life, involving both internal and external activities [23]. Adopting a balanced diet rich in fruits, vegetables, nuts, low-fat dairy and legumes can be recommended for the prevention and management of MS [24]. A study on 9,261 adults aged between 35 and 70 years analyzed eating habits such as meal frequency, consumption of fried foods, adding salt to prepared meals, and consumption of grilled foods using a standard questionnaire. Subjects who ate grilled food more than three times per month had a 1.18 times higher likelihood of developing MS compared to those who consumed it less than once per month [25]. A.J. and collaborators analyzed three epidemiological studies. Fruits and vegetables were linked to a lower prevalence of MS, while a diet rich in meat was often associated with MS components, especially impaired glucose tolerance. High dairy consumption was typically related to a reduced risk of MS components, though there was some inconsistency in the literature regarding the risk of obesity. This analysis concluded that no single dietary component can be entirely responsible for the association between diet and MS [26].

The percentages of sedentary and active individuals in both groups are similar. Instead, some differences were noted regarding the frequency of physical activity in the studied groups. Promoting physical activity is essential for patients with MS. Programs that encourage regular exercises, such as walking groups, fitness classes, and workplace wellness initiatives are essential [27]. Physical exercise increases calorie consumption, aiding in weight loss and reducing the overall risk of cardiovascular diseases. Approximately 30-60 minutes of moderate-intensity exercise and conscious efforts to modify a sedentary lifestyle can be beneficial for managing MS [2].

The two groups showed a similar distribution regarding the urban or rural environment of the patients, with no statistically significant differences. This demographic balance is important to ensure the objectivity of the study. This representation allows for an accurate evaluation of the treatment's efficacy and safety in different environmental contexts. Studies suggest that green spaces and urban infrastructure can contribute to the onset of MS [28]. Urbanization exerts a significant impact on the environment, generating air pollution, urban heat islands and other effects that are known to negatively influence metabolic health [29]. Residential areas in developing countries significantly influence lifestyle by altering energy consumption and energy expenditure. Urbanization is associated with reduced physical activity, a major cause of MS. A study conducted in three geographic areas (urban, semi-urban, and rural) in the coastal region of Cameroon, which included 879 participants (urban: 372, semi-urban: 195, and rural: 312), concluded that MS was more prevalent among urban residents, being associated with a low level of physical activity [30]. A study conducted by T.T. aimed to assess the prevalence differences of MS between rural and urban populations. The study also identified risk factors associated with MS and examined how these contribute to the rural-urban disparity. The study's conclusions showed that the rural environment was associated with a higher prevalence of MS. This aspect can be attributed to demographic composition differences and behavioral factors related to obesity between urban and rural residents [31].

Sleep quality did not show statistically significant differences between the two groups. The optimal duration of sleep needed to maintain health and well-being ranges from 7 to 9 hours per day for adults, and older adults, it is between 7 and 8 hours [32,33]. Insufficient sleep has been connected with an increased risk of obesity, disturbances in glucose and insulin regulation and the onset of MS [34]. After examining common risk factors for MS, it was determined that both insufficient and excessive sleep can raise the likelihood of developing MS. Poor sleep or overly long sleep durations have been connected to a higher risk of obesity and hypertension, while short sleep may contribute to elevated blood sugar levels [35,36].

Both groups show a similar distribution in the percentages of smokers, non-smokers and former smokers, indicating an adequate balance between them. Smoking is a known risk factor for MS, as it negatively impacts blood pressure, abdominal obesity, blood glucose levels and lipid profiles. Some of these smoking-induced effects may be reversed upon quitting, potentially lowering the risk of metabolic disorders. However, after cessation, the risk of MS might temporarily rise, possibly due to weight gain [37]. Research has demonstrated that smoking affects various measurements that determine obesity, such as body mass index, waist circumference and waist-to-hip ratio [38,39]. Fortunately, the negative consequences of smoking on glucose regulation can be reversed upon quitting [40]. Despite the dangers associated with smoking, it is seen as a way to control body weight. Compared to non-smokers, smokers have been shown to have a lower BMI. A study found that smoking more than 20 cigarettes a day independently increases the risk of having a high BMI, regardless of sex, suggesting that smoking a larger number of cigarettes may lead to weight gain [41-45]. A meta-analysis that included over 50 studies examining the long-term effects of smoking reported that, compared to non-smokers, smokers had higher serum triglyceride concentrations, higher LDL, and lower HDL levels. A dose-dependent relationship was demonstrated for each of these variables when comparing non-smokers with light, moderate, and heavy smokers [46-48].

Additionally, the patients did not exhibit significant differences in alcohol consumption. Epidemiological studies indicate a connection between alcohol consumption and the risk of developing and advancing MS [49,50]. The relationship between alcohol consumption and various aspects of MS complicates a clear understanding of the connection, making it a debated issue [51,52]. M.S. Freiberg and colleagues conducted a study to explore the link between alcohol use and the prevalence of MS and its components within the U.S. population.

Alcohol consumption was strongly linked to the prevalence of the following components of MS: low serum HDL cholesterol, elevated serum triglycerides, large waist circumference, and hyperinsulinemia ($P < 0.05$ for all) [50]. A study conducted in 2022 evaluated the effect of alcohol consumption on MS and obesity in Korean subjects. A total of 26,991,429 individuals aged 20 years or older were included. The study suggests that the risk of MS and obesity may be higher in Korean men, women, and older adults who consume more than 14 g/day of alcohol compared to non-drinkers. Among individuals with obesity, abdominal obesity, or those who need to manage blood pressure, glucose, or triglycerides, consuming more than 7 g/day of alcohol may increase the risk of MS [54,55]. Alcohol and MS often coexist as cofactors in liver disease. Studies suggest a harmful effect of MS on advanced alcohol-related liver disease. A study was conducted on 3,014 randomly selected subjects. Liver fibrosis was assessed by measuring liver stiffness. Among alcohol-consuming subjects, liver stiffness was associated with male sex, AST, ALT, years of alcohol consumption and MS. The study concluded that MS increases the risk of liver fibrosis in alcohol-consuming individuals [56].

Intermittent hypoxia–hyperoxia therapy offers significant benefits in alleviating symptoms and enhancing functionality in patients with various cardiovascular, respiratory, musculoskeletal, neurological and metabolic conditions, as well as in geriatric patients with multiple comorbidities. Many of these patients may have contraindications to multimodal therapies, including physiotherapy, due to the presence of multiple organ failures, such as kidney, liver or heart failure [57].

In our study, we did not obtain statistically significant results for the measured variables in the interventional group. However, it is important to note that, despite the absence of statistical significance, certain trends were observed in some patients, suggesting potential benefits of the applied intervention. Although these trends did not reach the threshold for statistical significance, they may represent a direction worth exploring in future research.

One aspect that should be considered is the effect size analysis. The interpretation of the results should not be done only in terms of statistical significance but also about the effect size and the observed trends. The effect size is an essential indicator of a study's relevance and can help assess whether the observed differences, even if not statistically significant, are large enough to justify the implementation of the intervention in medical practice. Our results suggest that if there is a real effect of IHHT, it is likely small and requires studies with greater statistical power to be detected. The effect size analysis could guide the design of future studies by adjusting the protocol or the characteristics of included patients. Determining an optimal sample size for future studies helps avoid both erroneous conclusions and the risk of overestimating or underestimating the therapy's effectiveness.

Regarding notable changes in body composition, we observed a few cases in which patients showed remarkable changes in the analyzed parameters. However, these changes were not sufficient to achieve statistical significance at the level of the entire group. It is important to note that these cases do not represent the overall trend of the group and may be influenced by individual factors such as personal response to treatment, genetic variations or personal behaviors. Despite this, these individual cases may provide valuable insights into the potential effects of the intervention and should be explored in more detail in future studies.

The results observed in the placebo group, which showed improvements in reducing body fat and visceral fat, represent an unexpected finding. These improvements may be explained by the psychological effects of participating in a controlled study and by patients' expectations regarding the treatment. This type of placebo effect is a well-known phenomenon in clinical research and can significantly influence outcomes. Another possibility is that the placebo treatment had a positive indirect effect on participants' behavior, stimulating them to engage more actively in the medical rehabilitation process [58]. This is an interesting direction to explore in future research, considering the impact that psychological factors and patient expectations may have on physiological outcomes.

The results obtained in our study, in which IHHT did not significantly impact body composition in patients with MS, are significant from multiple perspectives. First, our finding adds valuable information to the field since no previous research has directly investigated this topic. This finding requires a critical analysis to determine whether the lack of effect is due to methodological factors, such as the duration of the intervention or sample characteristics or whether IHHT is not an effective strategy in this specific context.

The absence of a significant effect does not necessarily equate to the absence of a real effect. In clinical studies, results can be influenced by sample size, intervention duration, individual participant characteristics and variability in treatment response. If the effect of IHHT on body composition is moderate or dependent on certain factors, the study may not have had sufficient statistical power to detect significant changes.

Thus, the negative result of this study does not definitively invalidate the potential of IHHT in managing body composition in patients with MS but rather suggests the need for future studies to more clearly assess the impact of this therapy.

An important question that must be addressed in analyzing the results of our study is whether the duration of IHHT was sufficient to induce significant changes in the body composition of patients with MS. The duration of the intervention is a crucial factor in any therapeutic strategy. Although we followed a protocol based on existing literature, it is possible that a longer treatment period could have led to more pronounced effects on body composition. This aspect could represent a valuable direction for future research, investigating the impact of an extended duration on the effectiveness of IHHT.

The placebo effect can influence the results of clinical trials, particularly in terms of behavioral and perceptual parameters. The placebo effect is a well-known phenomenon in clinical research, where study participants experience benefits or health improvements due to their perception that they are receiving an active treatment, even if the treatment contains no active ingredients or has no significant physiological effects [59]. In our study, where we used a placebo group to compare the effects of IHHT, it is possible that patients in the placebo group reported improvements in body composition due to psychological factors rather than the physiological effects of the actual treatment. Furthermore, the placebo effect can stimulate physiological changes through psychosomatic mechanisms, in which patients' positive expectations lead to the release of endorphins and other biochemical substances that may influence metabolism and overall health [59].

IHHT parameters, such as session frequency and duration, are essential variables and in our study, we followed a protocol based on the specialized literature. To determine the optimal IHHT parameters for each patient, it is important to conduct preliminary assessments through hypoxic tests. These tests help identify reference values that are both safe and effective for each individual, allowing for the development of a personalized profile.

Most available studies on IHHT have investigated the effects of this therapy on parameters such as cardiovascular function, physical performance and inflammatory markers. Some research has shown benefits related to insulin sensitivity, lipid profile or exercise capacity [8,57]; however, these studies have not specifically evaluated changes in body composition. Because the study focuses strictly on the effects of the therapy on body composition, our results cannot be directly compared with studies that have examined other physiological effects of IHHT.

Patient adherence to the intervention and psychological factors can significantly influence the outcomes of a study. Medical rehabilitation is a complex process in which the success of an intervention depends not only on the effectiveness of the applied treatment but also on individual factors such as patient adherence to the protocol and psychological influences associated with participation in a treatment program [36].

In the context of our study, it is essential to analyze the extent to which these factors influenced the observed results and whether they could at least partially explain the lack of significant effects of IHHT on body composition. One important aspect of our study was the high level of patient compliance with the treatment protocol. Participants rigorously followed the IHHT sessions without interruptions, indicating a strong acceptance of the therapy.

Additionally, most patients reported a positive experience, stating that they felt comfortable during the sessions and perceived the therapy as well tolerated. A key factor contributing to this compliance was the trusting and supportive relationship developed between patients and the therapist assisting each session. Through regular interactions and personalized support, the therapist not only ensured the proper administration of the treatment but also managed to create a motivating environment where patients felt safe and encouraged to continue the therapy. This close connection between patient and therapist can positively impact how participants perceive the treatment and their willingness to stay engaged in the rehabilitation process.

To enhance the effectiveness of IHHT in the context of body composition in patients with MS, several modifications to the protocol could be considered. Extending the duration of the intervention might allow for a deeper physiological adaptation, given that some metabolic effects require a longer time to manifest. A possible reason for the lack of significant effects in our study could be the relatively short intervention period. Thus, prolonging the treatment could facilitate more consistent metabolic changes.

Another important direction is integrating IHHT with other interventions, such as physical exercise and dietary modifications. Physical activity is a key factor in regulating metabolism and body composition and combining IHHT with a structured exercise program could enhance its beneficial effects. Additionally, a personalized nutritional strategy could promote more evident metabolic changes by optimizing energy substrate utilization and promoting a more favorable body composition [60].

However, interpreting results in this case could be challenging. If IHHT were combined with other strategies, such as exercise or nutritional interventions, a significant methodological limitation would arise: the difficulty in determining the extent to which each component of the intervention contributed to the final effects.

Although integrating IHHT with other therapeutic methods could amplify its positive impact on body composition, such a combination would make it harder to identify the specific contribution of IHHT to the observed results. To validate IHHT as an effective therapeutic method, its effects must be studied independently through rigorous experimental designs before exploring potential synergies with other interventions.

We do not believe that IHHT should be dismissed as a potential intervention for improving body composition in MS, especially considering existing evidence that this therapy has influenced other physiological parameters in patients with this condition [8,21]. This suggests that IHHT may impact physiological mechanisms that, in the long term, could indirectly contribute to changes in body composition.

In addition, the possibility that IHHT may have an effect dependent on the duration of the intervention or other individual factors justifies the need for additional studies. These studies should include: a longer intervention duration to allow for metabolic adaptations that could lead to body composition changes, larger patient samples to increase statistical power and identify potential subgroups of patients who may respond more favorably to IHHT and long-term patient follow-up to understand its lasting impact and possible late effects of the therapy.

The results of our study have several important practical implications for the development and optimization of rehabilitation programs for patients with MS. Although IHHT did not produce significant changes in body composition, it remains a promising intervention and understanding how it can be integrated into rehabilitation strategies is essential.

One positive aspect observed in this study was the high compliance of patients with the treatment, suggesting that IHHT may help increase patient motivation to follow a rehabilitation program, having a good acceptance rate and being easier to tolerate than other forms of intensive physical exercise. This study provides valuable insights for rehabilitation programs, indicating that IHHT can be used as a promising adjunctive strategy, but it requires optimization to achieve a clear impact on body composition.

We agree that medical rehabilitation can bring notable improvements in managing MS. In this context, the goal of our study was to assess whether IHHT could offer an additional benefit compared to conventional treatments. Our results suggest that medical rehabilitation, even without IHHT, can produce beneficial effects, which highlights the importance of integrated approaches and personalized treatment strategies.

Medical rehabilitation is an essential factor in managing MS and can lead to significant improvements even without the application of additional therapies, such as IHHT. Medical rehabilitation programs, which include physical exercises, lifestyle modifications and nutritional interventions, are recognized for their positive impact on metabolic health [61]. These programs help reduce the risks associated with MS, such as obesity, hypertension, dyslipidemia and insulin resistance, thus contributing to the improvement of body composition, cardiovascular function and overall health [61.

The absence of significant differences between the IHHT and placebo groups suggests that the protocol used in this study was not sufficiently optimized to produce clear effects on body composition in patients with MS. These results highlight the need to adjust the protocol, such as the study duration, to more accurately assess the effectiveness of IHHT in future research. IHHT interventions may require a longer duration to show significant effects and our study may have had an insufficient duration to capture such changes.

It is important to mention that the effects of IHHT may become more evident over time and the influence of lifestyle factors, such as diet and physical exercise, plays a crucial role in the management of MS [60]. In our study, we aimed to isolate the direct impact of IHHT on body composition, but it is clear that the success of the treatment also depends largely on other interventions, including lifestyle modifications. A combination of these factors may lead to more favorable outcomes.

Regardless of the effectiveness of IHHT, behavioral changes and the adoption of a healthy lifestyle are fundamental in controlling MS. A balanced diet, regular physical exercise, stress management and adequate sleep play a significant role in improving the overall health of patients and alleviating the symptoms of MS [60].

Given the complexity of these factors, it is difficult to quantify the effectiveness of each one in isolation and future studies should take this interaction into account.

A more detailed and longer design is necessary, integrating both IHHT and lifestyle changes, to better understand the impact of each component on the patient with MS.

5. Conclusions

IHHT may show promise in improving the body composition of patients with MS, but a long-term study is necessary. Although no significant improvements were observed in the body composition of patients, the therapy could have positive effects that were not evident over a short period. The duration of treatment could be a determining factor and a longer study could provide a clearer picture of the therapy's effectiveness. Despite no significant improvements being recorded in the group that received the therapy compared to the placebo group, the effects may become visible in a larger cohort of participants or under different conditions. Placebo effects are an important component in clinical studies and can significantly influence the results. In this case, the absence of significant differences between the studied groups suggests that patients may be influenced by their expectations and psychological interventions.

Medical rehabilitation programs can lead to improvements in the body composition of patients with MS, even in the absence of IHHT. The study highlights the importance of active and continuous participation in rehabilitation programs to support real progress in managing MS and associated risk factors. These results suggest that proper medical rehabilitation can serve as an important pillar in the treatment of patients with MS, even without additional interventions.

These conclusions support the need for further research and may explore potential limitations as to why no significant improvements were observed in the intervention group in this study.

As mentioned earlier, to date, there have been no studies directly investigating the effects of IHHT on body composition in patients with MS. Most previous research has focused on other parameters, without specifically addressing changes in body composition. In this context, our study makes an important contribution, but the results did not show significant effects of IHHT on body composition, which highlights the need for further research to evaluate the impact of this therapy in more detail.

However, these results do not completely invalidate the potential beneficial effects of IHHT, but suggest that there may be variable factors influencing the response to therapy. Future studies may better clarify the ideal conditions for applying IHHT.

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