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Effect of Hyperbaric Oxygen Therapy on Insulin Resistance in Post-Menopausal Women: A Randomized Assessor-Blinded Controlled Trial

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ABSTRACT

Background: In postmenopausal females, Insulin resistance is commonly encountered in clinical setting. Hyperbaric oxygen therapy has been proposed effective in lowering blood glucose level and improving function. Identification of clinical examination variables as predictors to blood glucose levels and dysfunction would offer therapists the chance to undertake clinical decisions and consequently improve treatment efficiency. **Objectives**: to examine the effect of hyperbaric oxygen therapy on insulin resistance in postmenopausal women. **Patients and methods**: This Predictive validity, diagnostic study included fourty postmenopausal participants with insulin resistance recruited from Kobry el Koba Military Complex with age 55-65 years, Their BMI was 30-34.9 kg/m. They were equally divided randomly into: group (A) who received Hyperbaric Oxygen therapy 5sessions per week for 30 consecutive sessions in addition to their oral hypoglycemic drugs. Group (B) who received their oral hypoglycemic drugs only. Participants in group(A) were assessed for fasting blood glucose level by glucometer, ACCU-Chek performa, before treatment and post the 1st 10 sessions and post the 2nd 10 sessions while both groups were assessed for HgA1C level by blood sample , Health related quality of life by Quality of life enjoyment and satisfaction questionnaire QLES-QSF pre- and post-treatment sessions. **Results**: Post-treatment, both groups showed a significant decrease in HbA1c levels and an increase in QLES-QSFB, Group A showed a significantly greater decrease in HbA1c levels and a significantly greater increase in QLES-QSFB compared to group B ($p<0.001$). In group A,after both 10 and 30 sessions, there was a significant decrease in fasting blood glucose (FBG)levels compared to pre-treatment levels ($p<0.001$).Additionally ,FBG levels significantly decreased after 30 sessions compared to after 10 sessions ($p<0.001$). **Conclusion:** Hyperbaric oxygen therapy was effective in managing insulin resistance in postmenopausal women.

Keywords: Hyperbaric oxygen therapy, Menopause, Insulin resistance, Glucometer

INTRODUCTION

Menopause is an aging process clinically diagnosed when a woman has not menstruated for twelve months, which usually occurs around the age of 45–55 years. Hormonal changes that begin at the menopausal transition and abrupt cessation of hormone production affect many biological systems **(1,2)**. Menopause has been associated with an increase in abdominal fat caused by the depletion of ovarian function **(3)**.These changes in body composition may cause disturbances in insulin sensitivity and in glucose metabolism in postmenopausal women **(4)**.

Menopause is a potential risk factor for developing insulin resistance independent ofage, likely due to the reduction in circulating estrogens **(5)**. In support of this hypothesis, it has been shown that surgically induced menopause increases the risk of developing insulin resistance and metabolic syndrome **(6).**Clinical studies show that post-menopausal women are more susceptible than premenopausal women to develop dyslipidemia, an increase in body weight (evaluated through

body mass index and waist circumference), and impaired glucose tolerance (as shown by their levels of hyperinsulinemia and increased fasting glucose levels) **(5,7)**.

Insulin resistance is characterized by the inability of circulating insulin to effectively regulate the uptake and/orutilization of glucose by insulin-sensitive tissues and organs. In normal conditions, an increase in blood glucose levels stimulates insulin production from pancreatic b-cells, as well as the inhibition of glucose production in the liver. However, insulin-resistant individuals do not respond to this signaling process, and paradoxically show an increase in both hepatic glucose production and insulin secretion, which can induce or aggravate hyperglycemia. **(8)**.

The factors that promote the emergence of insulin resistance include altered insulin signaling, hyperinsulinemia, hyperlipidemia, and obesity. These factors are also associated with chronic low-grade inflammation characteristic of type 2 diabetes mellitus (T2DM). Obesity is another factor that is strongly associated with the development of insulin resistance, and fat distribution plays a determinant role in the pathogenesis. Specifically, the accumulation of visceral abdominal fat is considered a risk factor for metabolic syndrome and cardiovascular diseases (CVDs) **(9,10)**. The prevalence of metabolic syndrome in postmenopausal women reportedly varies by country and race but is estimated to range from 32 to 58%. This is significantly higher than that in premenopausal women **(11)**.

Hyperbaric Oxygen Therapy (HBOT) is a therapy where patients breathe with 100% oxygen in high pressurized cabin with increased atmospheric pressure. HBO has been a recognized therapy in the management of decompression illness and air embolism. Increasingly, clinical studies are demonstrating a benefit for a variety of medical conditions including non-healing wounds particularly in people with diabetes **(12)**.Tissue damage as a result of radiotherapy and necrotizing tissue infections**.** The hyperoxia will provide vital oxygen to tissue with marginal perfusion **(13,14)**.

Previous studies showed that HBOT improves peripheral insulin sensitivity in type 2 diabetes mellitus and it also has a significant effect on oxidative stress alteration **(15)**. HBOT improves insulin sensitivity by reducing adipose tissue hypoxia and subsequently inflammation **(16)**. Other than that, it may also act by stimulating mitochondrial biogenesis through the increase of expression in peroxisome proliferator activated receptor-1 alpha (PGC1-α), a master regulator of mitochondrial biogenesis **(17)**.

Insulin sensitivity is increased during hyperbaric oxygen therapy in obese individuals with type 2 diabetes mellitus (T2DM) individuals, also found an improvement in insulin sensitivity and reduction in HbA1c in non-obese individuals without T2DM, suggesting this insulin-sensitizing effect was not confined to individuals with T2DM only **(16)**.

PATIENTS AND METHODS

The study was designed as a randomized controlled trial. Before the study began, the Faculty of Physical Therapy, Cairo University's Institutional Review Board approved the research conduction **(No: P.T.REC/012/004726)** and n a Clinical Trials.gov ID **(NCT06806345)**. The Helsinki Declaration Principles for Human Research were taken into account in this study. This study was conducted between 2023 and 2024.

This study was conducted at the department of physical therapy; Kobri El Koba Military Hospital from September 2023 till April 2024 to determine the effect of hyperbaric oxygen therapy on insulin resistance in postmenopausal women. Fourty patients participated in this study, their age ranged from 55-65 years, their BMI will be ranged from 30-34.9kg/m^2. All females were randomly divided into two equal groups:

Group (A) included 20 participants suffering from Postmenopausal insulin resistance who received Hyperbaric Oxygen therapy 5 sessions per week for 30 consecutive sessions in addition to their oral hypoglycemic drugs.

Group (B) included 20 participants suffering from postmenopausal insulin resistance who received their oral hypoglycemic drugs only. All participants in two groups (A and B) were assessed pre- and post- treatment through measuring of their Glycated haemoglobin (HgA1c), assessing the Physical Health, mood, work, household and leisure activities, family and social relationships, ability to function in daily life using Quality of life enjoyment satisfaction and questionnaire QLES-QSFB).Group A is assessed for their fasting blood glucose levels pretreatment, post 10 sessions and post 30 sessions (pre and post every session).

All patients underwent a suitable assessment to ensure inclusion criteria that contain all patients had controlled blood glucose levels all over the whole duration.

All Patients in group A had Cardiac Ejection Fraction (CEF)≥50%, blood pressure (BP)≤150/90 mmHg, Chest X-ray of all patients reported normal and all of them are clinically evaluated by a specialized ear ,nose, and thorax (ENT) physician to ensure fitting for the hyperbaric chamber. Study excluded patients with Chronic obstructive pulmonary disease, Cardiac pacemakers, epileptic fits, physically disable , any disorder that lead to ulcers other than diabetes such as a history of chronic peripheral arterial disease , cardiac Ejection Fraction < 50 %. All patients in all groups (A&B) were given a full explanation of the treatment protocol and a written informed consent form giving agreement to participation.

Randomization and blinding

All participants received detailed information regarding the study's objectives, procedures, advantages, their voluntary participation, confidentiality of data, and the option to withdraw at any point. They were then randomly divided into two equal groups (Group A and Group B) through a computer-generated randomization process. Following this allocation, there were no instances of participant dropout during the study **(Figure 1)**. Additionally, those evaluating outcomes and analyzing data remained unaware of group assignments to maintain objectivity.

The patients were randomly assigned into two groups of 20 patients for each, either control or treatment by using computerized randomization. A simple and straightforward procedure can be followed to randomize a group of subjects into two groups using https://www.randomizer.org/# randomize, a web-based tool designed for this purpose.

By opening a web browser and navigating to the Research Randomizer website, the total number of subjects to be randomized (40) was entered into the designated field. the desired allocation ratio for the two groups was set to 1:1. Upon clicking the "Generate Numbers" button, Research Randomizer will automatically generate a list of random numbers, each representing a subject. Each randomly generated number was paired with a corresponding group label, either "Group A" or "Group B," based on the allocation ratio, then the group assignment was for each subject, ensuring accurate allocation. Finally, Double-checking the group assignments is essential to ensure they align with the desired allocation ratio (Suresh, 2011)29. The current study is double blinded study as the randomizer of the study is blinded as well as the assessor of the outcomes.

Interventions

- Group A (study group): Patients received Hyperbaric Oxygen therapy 5sessions per week for 30 consecutive sessions in addition to their oral hypoglycemic drugs in Kobry el koba military complex at Hyperbaric oxygen therapy unit.
- Group B (control Group): Patients received their oral hypoglycemic medication only.

Hyperbaric oxygen therapy:

The patients in group (A) received Hyperbaric oxygen therapy with a gradual increase of oxygen pressure to be approximately 2.5 ATA through 15 min in a100% oxygen delivered for 60 min. Then, gradual decompression through 15 min for a total of 90min per each session for 30 sessions (5 sessions per week for 6weeks) with their oral hypoglycemic medications **(Figure 2)**.

Hyperbaric oxygen increases the oxygen delivery to blood and tissues by more than 10-fold, thus hyperbaric oxygen treatment may act to improve insulin sensitivity by reducing adipose tissue hypoxia and subsequently inflammation. It is increasingly recognized that obesity and Type 2 diabetes are characterized by adipose tissue dysfunction, including increased adipocyte size and local tissue hypoxia **(18)**. There are also alternative mechanisms of action, as hyperbaric oxygen treatment may act to improve insulin sensitivity by stimulating mitochondrial biogenesis. Increased expression of the master regulator of mitochondrial biogenesis, peroxisome proliferator activated receptor-1 alpha (PGC1a) This may be important, as individuals with Type 2 diabetes and those with a family history of Type 2 diabetes have reduced PGC1a expression and reduced mitochondrial function, which has been linked to increased lipid accumulation and reduced insulin action in muscle **(19-21).**

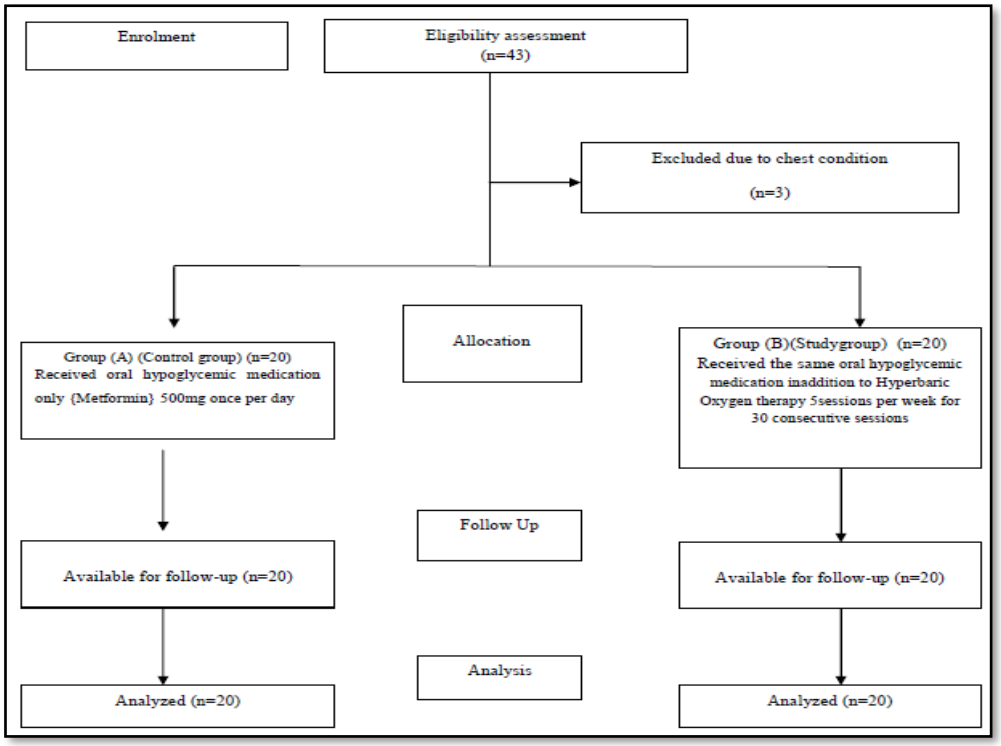

Figure 1: Flow chart of the study.

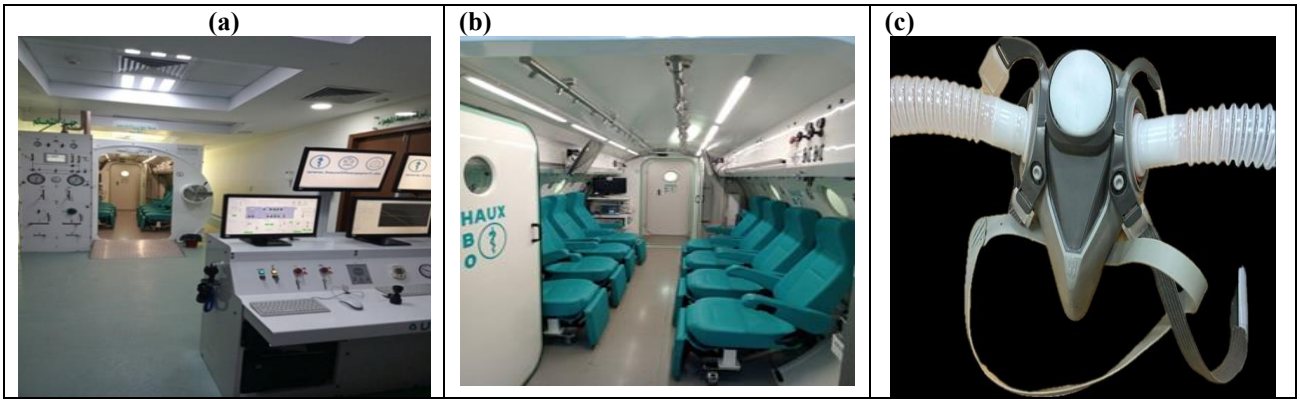

Figure (2): (a) The HBOT room with its controller: the omega Ω-shape chamber consists of the main and Antichamber (Haux, Starmed 2300, Germany); the HBOT Chamber; (C) Hyperbaric oxygen Mask.

Prior to the procedure, patients were instructed about the following:

Clothing inside the hyperbaric chamber, only 100% cotton clothing is accepted, without belts, jewelry or other accessories, and pockets must be completely emptied before entering the chamber. It is forbidden to wear shoes containing metal accessories, fur, shoes made entirely of plastic or shoes with air cushions. Hair must be secured with non-plastic clips, no hair clips, bobby pins, wigs and braids. Also, the hair must not contain wax, fixative, and permanent solution in the last 7 days or other hair care products. No make-up, perfume, creams, sprays, lotions or aftershave, ointments, oils. Nails must not be recently painted.

These recommendations are intended to optimize treatment effectiveness and minimize risks. Pure cotton clothing is recommended because it is safe and does not generate sparks or chemical reactions in the high oxygen and pressure conditions of the hyperbaric chamber. And avoiding petroleum-based products is very important, as they can be flammable in an oxygen-rich environment. Strict compliance with the above recommendations allows hyperbaric therapy sessions to be carried out in complete safety and with maximum effectiveness for patients **(22)**.

Hypoglycemic Drug:

All women in both groups (A& B) received oral hypoglycemic drug in the form of Metformin 500 mg once per day. Metformin reduces serum glucose level by several different mechanisms without increasing insulin secretion.it

increases the effects of insulin so it is termed "insulin sensitizer , metformin also suppresses the endogenous glucose production by the liver ,which is mainly due to a reduction in the rate of gluconeogenesis and asmall effect on glycogenolysis. Moreover, metformin activates the enzyme adenosine monophosphate kinase (AMPK) resulting in the inhibition of key enzymes involved in gluconeogenesis and glycogen synthesis in the liver while stimulating insulin signaling and glucose transport in muscles **(23)**.

Statistical analysis

All statistical analysis was conducted through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA). Unpaired t-test was conducted for comparison of subject characteristics between groups. Normal distribution of data was checked using the Shapiro-Wilk test. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups.Mixed MANOVA was conducted to investigate the effect of treatment on HbA1c and QLES-QSFB. ANOVA with repeated measures was conducted for comparison of FBG levels between pretreatment, post 10 sessions and post 30 sessions in group A.Post-hoc tests using the Bonferroni correction were carried out for subsequent multiple comparison. The level of significance for all statistical tests was set at $p < 0.05$.

RESULTS

The current study represented the subject characteristics of group A and B. There was no significant difference between groups in age, BMI and time since menopause ($p > 0.05$) (**Table 1)**.

Mixed MANOVA revealed a significant interaction effect of treatment and time ($F = 55.81$, $p = 0.001$). There was a significant main effect of treatment ($F = 6.77$, $p = 0.003$). There was a significant main effect time ($F = 292.29$, $p = 0.001$). There was a significant decrease in HbA1c and a significant increase in QLES-QSFB post treatment in both groups compared with that pretreatment ($p < 0.001$). The percent of change of HbA1c and QLES-QSFB of group A was 6.47 and 79.33% respectively and that in group B was 2.61 and 28.22% respectively. There was a significant decrease in HbA1c and a significant increase in QLES-QSFBof group A compared with that of group B post treatment ($p< 0.001$) **(Table 2)**.

There was a significant decrease in FBG post 10 sessions and post 30 sessions compared with pretreatment ($p < 0.001$). There was a significant decrease in FBG post 30 sessions compared with post 10 sessions ($p < 0.001$) **(Table 3)**.

Table 1. Comparison of subject characteristics between group A and B:

	Group A	**Group B**			
	Mean±SD	**Mean±SD**	**MD**	**t- value**	**p-value**
Age (years)	60.05 ± 2.65	59.20 ± 3.47	0.85	0.87	0.39
BMI (kg/m²)	32.00 ± 1.45	31.30 ± 1.63	0.7	1.44	0.16
Menopause Time (years)	8.30 ± 2.34	8.15 ± 2.03	0.15	0.22	0.83

SD, Standard deviation; MD, Mean difference;χ^2, Chi squared value; p value, Probability value

Table 2. HbA1c and QLES-QSFBpre and post treatment of group A and B:

	Pre treatment	**Post treatment**			
	Mean±SD	**Mean±SD**	**MD**	**%change**	**p value**
HbA1c (%)					
Group A	6.03 ± 0.29	5.64 ± 0.22	0.39	6.47	0.001
Group B	6.13 ± 0.31	5.97 ± 0.31	0.16	2.61	0.001
MD	-0.1	-0.33			
	p = 0.28	***p = 0.001***			
QLES-QSFB					
Group A	34.10 ± 8.12	61.15 ± 7.35	-27.05	79.33	0.001
Group B	36.85 ± 8.85	47.25 ± 10.08	-10.4	28.22	0.001
MD	-2.75	13.9			
	p = 0.31	***p = 0.001***			

SD, Standard deviation; MD, Mean difference;p value, Probability value.

Table 3. Pretreatment, post 10 sessions & 30 sessions mean values of FBG of group A:

FBG (mg/dl)				
Pre treatment	**Post 10 sessions**	**Post 30 sessions**	**F- value**	**p- value**
Mean±SD	**Mean±SD**	**Mean±SD**		
118.25 ± 7.48	110.05 ± 6.51	98.70 ± 6.39	103.91	0.001
117.93 ± 8.71	132.80 ± 12.81	-14.87	12.61	0.001
Multiple comparison (Bonferroni test)				
	MD	**% of change**	**p- value**	
Pre Vs post 10 sessions	8.20	6.93	0.001	
Pre Vs post 30 sessions	19.55	16.53	0.001	
Post 10 sessions Vs post 30 sessions	11.35	10.31	0.001	

SD, Standard deviation; MD, Mean difference;p value, Probability value

DISCUSSION

The purpose of the study was to evaluate the therapeutic effect of hyperbaric oxygen therapy on insulin resistance in postmenopausal women, The goal of treatment for insulin resistance in postmenopausal women are to prevent or delay complications and maintain quality of life. This requires control of glycemia, cardiovascular risk factor management, and regular follow-up. Life style modifications including physical activity, healthy diet, smoking cessation and maintains of healthy body weight are recommended as first line therapies from the time of diagnosis and as co-therapy for patients who also require glucose-lowering medications **(24)**.The decline in estrogen levels that occurs after menopause can cause insulin resistance. On the other hand, progesterone has a more nuanced relationship with insulin, but there is evidence that it can impact insulin sensitivity as well. Lastly, the decline in progesterone after menopause impacts blood sugar levels **(25)**.

Hyperbaric oxygen (HBO) therapy is a kind of treatment modality that 100% oxygen is pressurized higher than the barometric pressure at sea level in a hyperbaric chamber **(26)**.

Hyperbaric oxygen is used to treat anemia, carbon monoxide poisoning, and ischemia **(27)**. Hyperbaric oxygen therapy was found to improve glycemic control,increase insulin sensitivity in overweight or obese individuals with and without T2DM and improve atherogenic metabolic changes.suggested that it could be used as a therapeutic intervention for T2DM **(28)**.

Considering that insulin resistance is associated with hypoxia, oxidative stress, and inflammation, it can be hypothesized that HBO2 therapy decreases insulin resistance by increasing the anti-hypoxic,anti-inflammatory, and antioxidant defence systems **(29,30)**.

Hypoxia stimulate white adipocytes to produce of adipokines associated with inflammation, resulting in insulin resistance. The sensitivity of skeletal muscle to insulin is also reduced, as is the expression of glucose transporter type 4 (GLUT4) reducing glucose uptake and utilization and raising blood glucose levels **(31)**.

High levels of glycated hemoglobin (HbA1c) influence O2 transport to active muscles during maximal exercise **(32)**. Studies have shown that hyperbaric oxygen enhances glucose and lipid metabolism in skeletal muscle, delaying the onset of type 2 diabetes and obesity. Exposure to mild hyperbaric oxygen increased skeletal muscle oxidative capacity **(33)**.

Regarding group (A), our findings indicated significant reductions in glycated hemoglobin after treatment, reflecting the beneficial impact of Metformin on insulin resistance in postmenopausal women

Metformin is a widely prescribed insulin-sensitizing agent in current clinical use. Despite being most commonly associated with its ability to decrease plasma glucose levels**. Jahn et al. (34)** stated that the improved microvascular insulin sensitivity seen in their study may contribute to the improved metabolic actions of insulin after metformin. they emphasize that while the vascular and metabolic responses to insulin are improved, This is evident from the vasoconstrictive response to insulin still seen in the majority of the metformin-treated subjects and lower steady-state GIR after metformin treatment (3.9 ± 0.5 mg/min/kg between 120 and 150 min of the clamp) in the current study compared with that seen previously after 2 h of an identical insulin infusion in middle-aged, lean healthy adults (5.8 ± 0.4 mg/min/kg).

Regarding group (B), our findings revealed significant reduction in glycated hemoglobin after hyperbaric oxygen therapy and significant increase in QLES-QSFB. There was a significant decrease in FBG post 10 sessions and post 30 sessions compared with pretreatment ($p < 0.001$). There was a significant decrease in FBG post 30 sessions compared with post 10 sessions ($p < 0.001$). The between-group comparison revealed a significantly greater reduction in glycated

hemoglobin and a significant increase in QLES-QSFBof group B compared with that of group A post treatment ($p < 0.001$). These results aligned with **Albu et al. (35)** stated that peripheral insulin sensitivity is increased by approximately 40% during hyperbaric oxygen therapy providing a potential mechanism for the reductions in fasting glucose. This improvement is rapid, occurring within three treatments, and is sustained at least until the 30th treatment. The increase in insulin sensitivity was substantial, and similar in magnitude to the increase we have previously reported following 12% body weight loss at 1year in patients with Type 2 diabetes undergoing a diet and exercise programme.

Moreover, **Wilkinson et al. (16)** showed a significant increases of approximately 40% in peripheral insulin sensitivity following hyperbaric oxygen treatment,the improvement in peripheral insulin sensitivity only reached statistical significance in patients with Type 2 diabetes, four out of five individuals without diabetes also improved insulin sensitivity following hyperbaric oxygen treatment and had reductions in HbA1c, suggesting this insulin-sensitizing effect was not confined to individuals with Type 2 diabetes only. This reduction in HbA1c, in the absence of reduced fasting glucose, also supports improved insulin sensitivity

Also **Wilkinson et al.(28)** stated that peripheral insulin sensitivity is increased following HBOT in a relatively healthy urban population sample. Moreover, the increase in insulin sensitivity occurs in overweight and obese males without diabetes as well as those with type 2 diabetes. Importantly, the insulin sensitising effect was maintained after exit from the hyperbaric chamber for at least 30 minutes. They also observed small changes in inflammatory cytokines following HBOT that may have partly contributed to the observed increases in insulin sensitivity.

In contrast, **Demir et al.(36)** revealed that HBO2 therapy did not significantly affect the plasma glucose levels of patients without DM. Patients without DM have better glucose homeostasis to prevent drops in blood glucose, so it is unclear whether HBO2 therapy has a blood glucose-lowering effect. However, in patients with DM, there is a rapid decline in plasma glucose levels within the first 10 sessions of HBO2 therapy, which remained low until the final session.

Future research could focus on evaluating the long-term effects of HBO2 therapy and comparing its benefits with other treatment modalities, such as exercise or other pharmacological approaches. Investigating the impact of HBO2 therapy on metabolic pathways related to insulin sensitivity could provide valuable information on its underlying mechanisms. Additionally, exploring the clinical applicability of HBO2 therapy in managing insulin resistance, including its potential as an adjunctive therapy, could be beneficial.

This study's strengths lie in its randomized controlled trial design, which is the gold standard for evaluating intervention efficacy and minimizing bias. Additionally, the investigation of a novel non-pharmacological approach, hyperbaric oxygen therapy for treating insulin resistance and improve function and quality of life in postmenopausal women provide.

Blinding of outcome assessors and data analysts to group assignment helps minimize bias and enhances the reliability of the study results. However, this study had limitations, such as a shorter follow-up period and fewer patients than desired; the study was conducted within budget constraints, limiting our ability to perform extensive laboratory analysis. This limitation may have affected the scope and depth of the data collected. The initial study design considered only the minimum required laboratory tests and prioritised the collection of these types of data. As a result, valuable insights that could have been provided by additional laboratory tests such as haemograms, serum creatinine/eGFR, and liver function tests might have been missed. Although our study had a very short follow-up period and a very small sample size to observe significant changes in BMI, the reduction in BMI may have improved insulin resistance in both groups. The limitations of our study include the lack of follow-up on BMI.

CONCLUSIONS

Hyperbaric oxygen therapy significantly decreased insulin resistance in postmenopausal women. This suggests that HBO2 therapy could be a promising intervention for managing insulin resistance in this category of patients, but further research is needed to gain a comprehensive understanding of its potential.

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Author contribution: Authors contributed equally in the study.

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