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Effect of Pulsed Electromagnetic Field on Lower Extremity Peripheral Arterial Disorder in Type 2 Diabetic Patient: A Randomized Study.

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Collection and/or assembly of data	√	√	√	
Data analysis and interpretation	√	√		√
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ABSTRACT

Background: Pulsed Electromagnetic Field (**PEMF**) has been shown to be effective treatment for many conditions as wound healing and pain relief. It is safe and non-invasive therapyandcould be employed as a complementary therapy in the treatment of peripheral arterial disorder (**PAD**).

Purpose. To investigatethe effect of **PEMF**on endothelial function of the lower extremity **PAD** in patient with Type 2 Diabetes Mellitus (**T2DM**).

Methods. Randomized controlled trial**.**30 male patients of**T2DM**With age ranged from 50-60 years old, with lower extremity **PAD**and intermittent claudicationwere recruited randomly according to power analysis test and divided into two equal groups;**Group** (**A**)received **PEMF**therapy at a frequency of 10 Hz, the treatment was administered for 20 min per session, 3 times per week for a period of 2 monthswith conventialphysical therapy**Group** (**B**) received High Intensity Interval training (**HIIT**) in the form of bicycle ergometer exercise for lower limb 3 times per week for 2 months withconventialphysical therapy. Pre- and post-treatment assessment using Numerical Pain Rating Scale (**NPRS**), ankle brachial index (**ABI**) and flow mediated dilatation percentage (**FMD** %) were done for all patients.

Results.Within groups the analysis using 2x2 mixed design **MANOVA**showed a statistically significant improvementfor all measured variables (**NPRS**, **ABI** and **FMD%**)in both group ($p<0.0001$).Between groups, the analysis revealedthere was no significant difference of the mean values ofthe **NPRS**"posttest" between both groups with($p=0.857$),there was significant difference of the mean values of **ABI**"posttest" between both groups with ($p=0.038$) and this significant increase in favor to group **A**, and there was clinical difference and high percent of improvement in**FMD%**in favor to group **B**.

Conclusion. PEMFtherapy has a significant effect on reducing pain and improving endothelial function in diabetic patients with **PAD.**

Keywords. Peripheral arterial disorder, pulsed electromagnetic field, endothelial function, ankle brachial index, flow mediated dilatation.

Introduction

Peripheral artery disorder is a chronically progressive occlusive lesion in the arteries that cause insufficient blood flow to the lower extremities, about 10.7% of individuals aged ≥40 years has **PAD[1]**.

Intermittent claudication is the most common symptoms of **PAD** involving the lower extremities which characterized by cramping, pain or tiredness in the leg or hip muscles while walking or climbing stairs and decreased walking ability. About 11.2%of patients with **PAD** develop critical limb ischemia, definedas chronic ischemic rest pain, ulcers, or gangrene **[2, 3]**.

There are many risk factors for **PAD**, smoking, hypertension, hyperlipidemia, diabetes mellitus, obesityand family history of vascular disease. Type 2 diabetes mellitus is one of the strongest risk factors to peripheral arterial disease, as it contributes to atherogenesis by inducing endothelial cell injury and dysfunction as much of the impact of chronic diabetes falls on the microcirculation. With long standing disease, there is progressive narrowing of vascular lumina, resulting in impaired perfusion, ischemia and dysfunction of the affected tissues **[4, 5]**.

Peripheral artery disorder has a poor outcome, it can lead to a high rate of amputation and death, also an increased risk of cardiovascular morbidity and mortality. **PAD** mainly affects the infra popliteal arteries and may induce more damage in small than in large vessels in patients with type 2 diabetes **[6]**.

There are several treatment options currently available for patients with **PAD**, which may be pharmacological, or revascularization (percutaneous transluminal angioplasty with or without stent placement) and exercise therapies **[7]**.

High intensity interval training was found to be an effective treatment for improving endothelial function in diabetics with peripheral arterial insufficiency as it increases the nitric oxide (**NO**)(vasodilator) and pain free walking time and maximal walking time **[8]**.

Pulsed electromagnetic field therapy has been shown to be effective in the treatment of many conditions. It is capable of initiating various healing processes including delayed fractures, wound healing and pain relief, and effective in improving the functional level and the capacity for independent living by increasing significantly the absolute claudication distance, peak walking time and ankle brachial pressure index as well as walking impairment questionnaire. Also, it increases circulating plasma NO level, and studies suggest that it has the potential to be utilized as a non-pharmacological and non-invasive technique **[9]**.

Ankle-brachial index is the screening test of choice for the diagnosis of patients with **PAD** as it is non-invasive, low cost, and easy to perform and precedes **[10]**.

Flow-mediated dilatation is a useful technique, to evaluate the endothelial function and vascular health in humans through ultrasound measurement of the artery diameter during reactive hyperemia and depend greatly on **NO[11]**, therefore this study was conducted to investigate the effect of **PEMF** on pain intensity level and endothelial function in lower extremity **PAD** disorder in **T2DM** patient.

Subjects and methods

Design

A randomized controlled trial was conducted to investigate the effect of **PEMF**on **NPRS**, **ABI** and**FMD%** in **T2DM**patients with **PAD**. Data were collected pre and post treatment fromJanuary 2019 and February 2021.this study was approved by the Research Ethics Committee of Cairo university [No. P.T.REC/012/002140]. It was prospectively registered in the clinical trials registry (PACTR201910673765658.) participant was voluntary. Each participant signed written informed consent prior to being enrolled in the study.

Participants

Studying Thirty male patients of **T2DM** of with lower extremity peripheral artery disease and intermittent claudication is considered an acceptable sample size based on the effect size retrieved from previous work in the medical literature. According to G-power analysis, the effect size for each group that consists of 12 patient is 0.90. all patients were selected from National Heart Institute, peripheral vascular outpatient clinic, Cairo, Egypt. They had been clinically and medically stable and were diagnosed by Doppler Ultrasound. Exclusion criteria included ankle brachial index ≥ 9, uncontrolled diabetes mellitus, Treatment with steroids or chemotherapy, cancer, previous surgical procedure in lower extremities, patients with severe symptomatic coronary artery disease, cerebrovascular disease and musculoskeletal disorder of lower limb preventing exercise training.

Randomization

The recruited patients were randomly assigned into two equal groups. A single blind randomization was carried out by assigning the odd numbers to **group (A)** (**PEMF**) and the even numbers were assigned to **group (B)** (**HIIT**). After randomization the study did record 4 patients dropped out. **Figure 1**.

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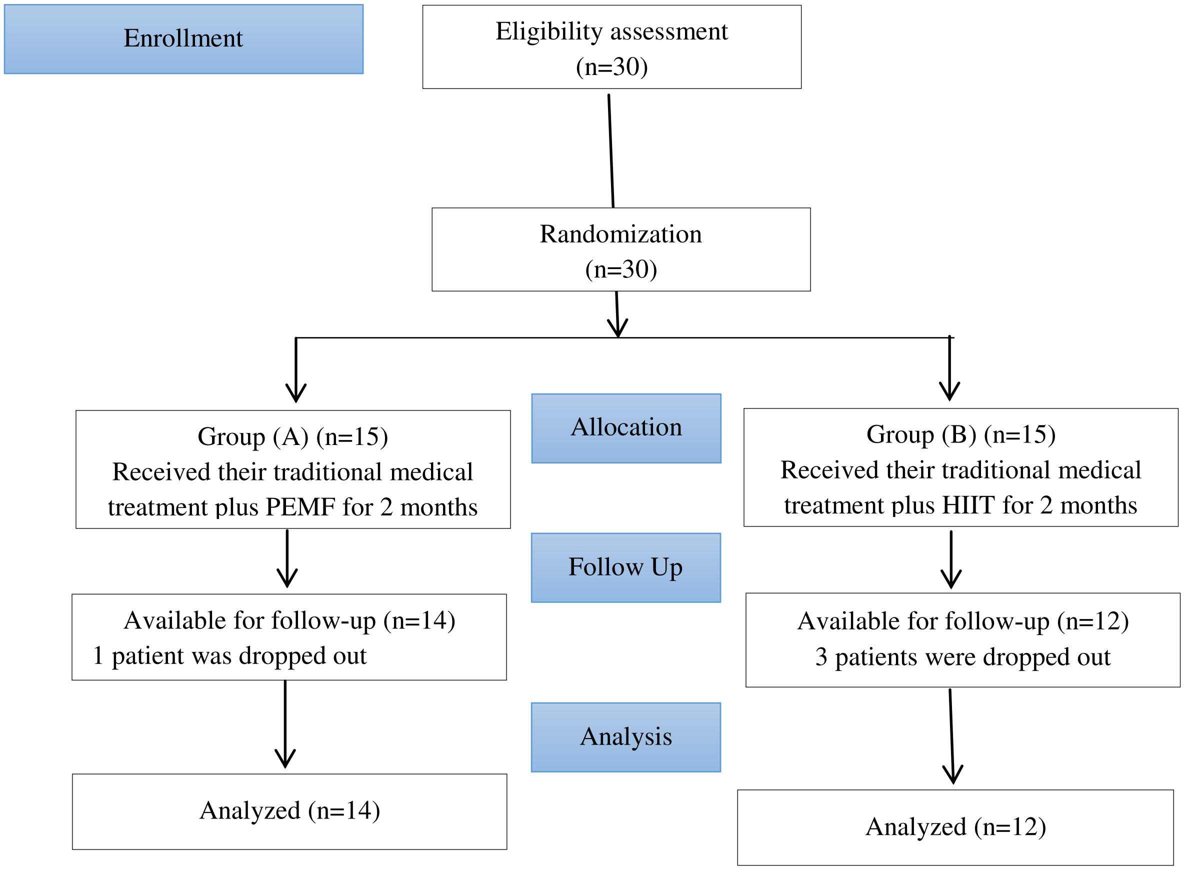

Figure 1: Flow chart of the study.

Interventions

Group (A)received **PEMF** for 24 sessions (3 sessions per week), whereas **Group (B)**received **HIIT** for 24 sessions(3 sessions per week), and both groups were on their medical treatment and received same conventicalphysical therapy.

The conventialphysical therapy

All participants in both **groups (A and B)** received exercises in form of heel raising exercise till his maximum repetition to reach onset of the claudication pain. and calf stretch by using long bath towel. **[9]**

Pulsed electromagnetic field therapy

Each participant in **group (A)**received a pulsed electromagnetic field at frequency of 10 Hz with low intensity was applied on the calf of the ischemic extremity while patient in supine relaxed position by Pulsed electromagnetic field therapy unit (JAMAVA S Magneto therapeutic apparatus) for 20 min.**[12]**.

High intensity interval training

Before the beginning of the therapy, patients were advised to wear a loose well-fitting comfortable clothes and suitable shoes for exercise. Also, they were instructed to avoid eating directly before the test. They had **HIIT**in the form of bicycle ergometer exercise for lower limb3 times/week for 30 min (at the beginning of the training) - 40min (at the end of 2 month training).The Patient was started cycling slowly without resistance at the beginning of the exercise for 5 minutes as a warming up then the active phase lasted for 20 min (at the beginning of the training) - 30min (at the end of 2 month training) and then decrease the speed and no resistance at the end of the exercise for 5 min as a cooling down.

Intensity and duration of the exercise was progressively increased throughout the 2 months program as patient tolerated and according to maximum heart rate (**MHR**).

Duration: 30-40 min (total session). starting with 1 min of high intensity training followed by 1.5 min of low intensity training repeated 8 (at the beginning of the training) - 12 cycle (at the end of the2 months).

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Intensity: high intensity (85%-95% **MHR**) and recovery (interval period) (60%-70% **MHR**) **[8]**.

Outcome measures

Numerical Pain Rating Scale

It was used to evaluate pain intensity pre- and post-treatment for both **groups (A and B)**. The **NPRS** is the most frequently used self-report measure of pain intensity in patient with acute pain due to its simple and easy to use. It is a segmented numeric version of the visual analogue scale (**VAS**) in which a respondent selected a whole number from 0 (No pain) to 10 (Maximal pain). It has a strong validity and reliability **[13].**

Ankle Brachial Pressure Index

It was usedas a screening test to help diagnose and grade the obstruction of **PAD** in the legs. It done for all patients from supine lying position by measuring the systolic pressures in the right and left brachial, dorsalis pedis and posterior tibial arteries. A by a hand-held Doppler probe (Nicolet Vascular Pocket Dop II; Nicolet Biomedical Inc, Golden, Colo). **ABPI** was obtained by dividing ankle systolic pressure over brachial systolic pressure according to the following equation

Ankle brachial pressure index =Ankle systolic pressure (mmHg) / Brachial systolic pressure (mm Hg) **[14]**.

Flow Mediated Dilatation percentage

It assessed the vascular endothelium function.Measurements were independently performed by same blinded investigator. Subjects were instructed to lie supine in a quiet, climate-controlled room (22–24°C), with their leg extended out laterally. Two adult size sphygmomanometer blood pressure cuffs were placed on the subject's the 1st left upper arm for blood pressure measurements and the 2nd cuff was placed on the studied leg approximately 20 cm over the medial malleolus. Then, the cuff was inflated to the pressure up to 100 mm Hg (at least 50 mm Hg) above systolic pressure for 5 minutes, after the 5 minutes the cuff was released causing hyperaemia. The diameter of posterior tibial artery was recorded before inflation and after 1min of deflation. Calculation of **FMD** was as a percentage of change of the peak diameter (in response to reactive hyperemia) in relation to the baseline diameter and is calculated using the following equation **[15]**.

FMD (%) = peak diameter - baseline diameter /baseline diameter. 100(%) **[16]**

Statisticalanalysis

Statistical analysis was conducted using **SPSS** for windows, version 23 (SPSS, Inc., Chicago, IL). Data were screened for normality assumption, homogeneity of variance, and presence of extreme scores. This exploration was done as a pre-requisite for parametric calculations of the analysis of difference. Descriptive analysis using histograms with the normal distribution curve showed that the data were normally distributed and not violates the parametric assumption for each of the measured dependent variables.Numerical pain rating scale, Ankle brachial index and Flow mediated dilatation percentage were normally distributed, as assessed by Shapiro-Wilk's test ($p > 0.05$). There was homogeneity of variances, as assessed by Levene's ($p > 0.05$) for the all variables. There was a linear relationship between the dependent variables, as assessed by scatterplot, and no evidence of multicollinearity, as assessed by Pearson correlation ($|r| < 0.9$). There were no univariate outliers in the data, as assessed by inspection of a boxplot and no multivariate outliers in the data, as assessed by Mahalanobis distance. Accordingly, 2x3 Mixed **MANOVA** test was used to compare the tested variables of interest at different measuring periods at three groups. With the initial alpha level set at 0.05.

Results

As indicated by the independent t-test, there were no significant differences (p>0.05) in the mean values of age, body weight, height and **BMI** between both tested groups **(Table 1)**.

The **NPRS**: **Within group's** comparison the mean ± SD values of **NPRS** score in the "pre" and "post" tests were 7.92±0.82 and 5.85±0.66 respectively in the **group (A).** Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant reduction of **NPRS** score at post treatment as compared to pre-treatment (P-value =0.0001). While, the mean ± SD values of **NPRS** scorein the "pre" and "post" tests were 8.00 ±0.73and5.91±0.99 respectively the **group (B).** Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant reduction of **NPRS** score at post treatment in compare to pre-treatment (P-value =0.0001). **Between groups**Multiple pairwise comparison tests (Post hoc tests) revealed that the mean values of the "pretreatment" test between both groups showed no significant differences with (P=0.82). As well as, there was no significant difference of the mean values of the "post treatment" test between both groups with (p=0.857) **(Table 2)**.

The **ABI**: within group's comparison the mean ± SD values of **ABI** in the "pre" and "post" tests were 241.2±13.31 and 194.73±7.62 respectively in the **group (A).** Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant increase of **ABI** post treatment as compared to pretreatment (P-value =0.0001). While, the mean ± SD values of **ABI** in the "pre" and "post" tests were 246.07 ±7.34 and 246.92±7.69 respectively in the **group (B).** Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant increase of **ABI** at post treatment as compared to pretreatment (P-value =0.0001). **Between groups**Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant difference of the mean values of the "post" test between both groups with (p=0.038) and this significant increase in favor to **group A(Table 2)**.

The **FMD**: within group's comparison the mean ± SD values of Flow mediated dilatation percentage in the "pre" and "post" tests were 241.2±13.31 and 194.73±7.62 respectively in the **group (A)**. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant increase of Flow mediated dilatation percentage at post treatment in compare to pretreatment (P-value =0.0001). While, the mean ± SD values of **FMD % in** the "pre" and "post" tests were 246.07 ±7.34 and 246.92±7.69 respectively the **group (B)**. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant increase of **FMD %** at post treatment in compare to pretreatment (P-value =0.0001).**Between groups** Multiple pairwise comparison tests (Post hoc tests) revealed that there was no significant difference of the mean values of the "post" test between both groups with (p=0.271). In spite of there was no statistically significant difference between **group A** and **group B**, there was clinical difference and high percent of improvement in favor to **group B**. (Table 2).

Table (1): Physical characteristics of participants in both groups (A&B).

Items	**Group A**	**Group B**	**Comparison**		**S**
	Mean ± SD	**Mean ± SD**	**t-value**	**P-value**	
Age (years)	57.71±2.16	57.25±2.45	0.513	0.613	**NS**
Body mass (Kg)	83.42±5.54	82.91±8.01	0.192	0.85	**NS**
Height (m)	1.72±0.059	1.71±0.065	0.16	0.874	NS
BMI (kg/m^2)	28.16±1.23	28.06±1.62	0.174	0.863	**NS**

SD: standard deviation, P: probability, S: significance, NS: non-significant.

Table (2): Mean ±SD and p values of NPRS,ABI and FMD percentage pre and post-test at both groups.

Numerical pain rating scale	**Pre-test Mean± SD**	**Post-test Mean± SD**	**MD**	**% Of change**	**p- value**
Group A	**7.92±0.82**	**5.85±0.66**	**2.07**	**26.13 %**	**0.0001***
Group B	**8.00 ±0.73**	**5.91±0.99**	**2.09**	**26.12 %**	**0.0001***
MD	**-0.08**	**-0.06**			
p- value	**0.82**	**0.857**			
Ankle brachial index					
Group A	**0.76±0.047**	**0.82±0.044**	**-0.06**	**7.89 %**	**0.0001***
Group B	**0.73 ±0.042**	**0.78±0.046**	**-0.05**	**6.84%**	**0.0001***
MD	**0.03**	**0.04**			
p- value	**0.081**	**0.038***			

Flow mediated dilatation percentage					
Group A	**9.67±1.37**	**10.6±1.56**	**-0.93**	**9.61 %**	**0.0001***
Group B	**9.50 ±1.62**	**11.25±1.38**	**-1.75**	**18.42%**	**0.0001***
MD	**0.17**	**-0.65**			
p- value	**0.784**	**0.271**			

*** Significant level is set at alpha level <0.05 SD: standard deviation**
MD: Mean difference p-value: probability value

Discussion

This study was conducted to investigate the effect of pulsed electromagnetic field on endothelial function and pain in diabetic patient with peripheral arterial disorder by assessing **NPRS**, **ABI** and **FMD** % before and after 2 months of treatment.

The finding showeda significant improvement in **(group A)** that received pulsed electromagnetic field as there was an improvement in**NPRS**, **ABI** and **FMD**%.

These significant improvement in **NPRS** and **ABI** were in consistent with those result observed and recorded by **Huo et al, (2010); Kwan et al, (2015);Santamatoet al, (2012); Sun et al, (2016) [17, 18, 19, 20].**

In line with the current study, a study done by **Mohamed MMet al, (2020) That** investigated and compared between the effect of interferential electrical stimulation and **PEMF** in management of intermittent claudication in **PAD**. The resultshowed improving inpain free and maximal walking distance and a significant improvement of **ABI**. **[9].**

Ayad M P, et al (2020)studied the effect of pulsed magnetic field therapy versus aerobic training on peripheral arteries in **T2DM**. By measuring thearterial blood flow and intimal thickness of the common femoral arteries before and after the intervention to evaluate endothelial function.The post-treatment results of this study showed increase in the arterial blood flow after the treatment for both Groups, and confirmed the effect of **PEMF** as therapeutic modality enhancing the arterial blood flow and reduce the intimal thickness in type 2 diabetic patients**[21].**

In addition, **Othman E, (2017) studied** patients with similar condition andreported reduction in pain and improvement of **ABI** after 2 months of pulsed electromagnetic field therapy for 20 min per session **[12].**

Similarly, the improvement occurredafter application of **PEMF** on **FMD** is in consistent with study that investigated the impact of **PEMF** therapy on endothelialvascular function and blood pressure in hypertensive humans and found improvement in **FMD** following 12 weeks of **PEMF** therapy**[22]**.

The improvement in **FMD** after **PEMF** Application may explained by several theories. Some studies demonstrated that **PEMF** elicited an increase of **NO**bioavailability and antioxidant level as the measurement of **FMD** is often thought to be an indirect assessment for **NO[23]**. other studies demonstrated that **PEMF** increased potent vasodilators including calcitonin gene-related peptide (**CGRP**) and adenosine **A2A**receptor which consequently led to an up regulation of **NO** availability **[24]**.

Another study showed that **PEMF** produced an increase in blood flow velocity of the superficial small vein; In addition, it assumed that magnetic fields might reduce blood viscosity. And the increase in peripheral circulation may accelerate removal of metabolic wastes away from tissues and reduce pain **[25]**

On the other hand, there was a significant improvement in **NPRS**, **ABI** and **FMD**% in **group (B)** that received **HIIT.** the improvement in this finding is in agreement with**Barclay G., (2012)**who reported that **HIIT** was shown to be superior to continuous, moderate aerobic exercise (**CME**) in improving endothelial function **[26]**.

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In addition,**HIIT** has a valuable effect on endothelial function in diabetics with peripheral arterial insufficiency as evidenced by significant increase in **NO** and pain free walking time and maximal walking time **[8]**.

Also, another study showed improved **ABI** after exercise training in individuals with uncomplicated **T2DM** with **ABI**<1.0, a level**[27].**

Many studies support the effectof **HIIT** as a treatment option for **PAD** as it improves a numberof important outcomes in patients with intermittent claudication includingwalking distances, **VO2Peak**, and quality of life **[28,29,30]**.

Study limitations

The study was limited by extraneous factors that may have interfered with the results of this study; these factors are related to variations in life style between patients as activity level, being working/non-working.

Conclusion

It was concluded that**PEMF**has an effect as a noninvasive treatment method for patient with **PAD**, as it reduced **NPRS score**, improved **ABI** and **FMD**%.

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Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

Authors state no conflict of interest.

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