

ORIGINAL ARTICLE

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EFFECTS OF PULSED ELECTROMAGNETIC FIELD THERAPY VERSUS EXTRACORPOREAL SHOCK WAVE THERAPY ON PERIPHERAL CIRCULATION AND FUNCTIONAL BALANCE IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHY: RCT

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ABSTRACT

Background: Diabetic peripheral polyneuropathy (DPN) is an arousing problem that negatively affects body systems. Pulsed low frequency electromagnetic field (PLFEM) and Extracorporeal shock waves (ESW) are therapeutic modalities frequently used to treat varieties of pathological conditions. Objective of the study was to evaluate and compare effects of PLFEM and ESW on feet blood flow (maximum skin blood perfusion (SBP-max), minimum skin blood perfusion (SBP-min), and basal mean perfusion changes (BMCP)) (by Laser Doppler) and functional balance (by Berg balance scale "BBS") in patients with DPN.

Methods: Seventy patients with DPN were randomly assigned into PLFEM, ESW and control groups. PLFEM group received treatment twice weekly while ESW received treatment once weekly, for 12 weeks. Variables were evaluated pre-study (evaluation-1), post-study (evaluation-2) and 4-weeks post-treatment cessation (evaluation-3).

Results: At evaluation-2 and 3; SBP-max, SBP-min, BMCP and BBS showed significant increase in both PLFEM and ESW groups ($P < 0.05$) compared with non-significant changes in the control group ($P > 0.5$). At evaluation-2; SBP-max, SBP-min, BMCP and BBS mean values and percentages of change were [27.21±4.27(23.27 %), 10.51±2.32(50.004 %), 16.15±2.22(24.45 %), 43.18±2.95(33.01 %)], [24.74±3.33(10.62 %), 8.69±2.58(21.15 %), 14.48±2.35(11.66 %), 40.13±3.52(23.12 %)] and [22.12(-0.05 %), 7.196(-0.1 %), 13.06±2.38(-0.09), 32.76(-0.1 %)] for PLFEM, ESW and control groups respectively ($P < 0.05$).

Conclusion: While both PLFEM and ESW have significant long-term effects in improving lower extremity blood flow and functional balance in patients with DPN, but still PLFEM is more effective than ESW.

Keywords: Diabetic Neuropathy, Circulation, Balance, Electromagnetic, Shockwave.

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INTRODUCTION

Noninsulin-dependent diabetes (NIDD) is an arousing disorder that is commonly associated with variety of peripheral vascular consequences[1].Diabetic neuropathy (DN) is rapidly growing problem that can appear within 10 years of the diabetes onset,[2]and appears earlier in NIDD than in type 1 diabetes mellitus (T1DM)[3].Microvascular dysfunction, blood flow restriction and neural oxygen tension deterioration [4]are main elements in DN pathogenesis. Lower limb disorders secondary to peripheral vascular and sensory disturbances commonly seen in patients with the NIDD are among primary reasons for hospitalization [5].Diabetes-related Peripheral neuropathy (DPN) is an alarming complication of both T1DM and NIDD[6] that negatively affect the patient's ability to maintain normal mental and physical functions [7]. DPN is mainly discovered in patients with diabetes aged 40 years or more, [8] and is presented with varieties of manifestations[9] including impaired lower limbs sensory [10]and motor functions,[11]diminished proprioceptive sensitivity and balance, [12]improper walking patterns; all of which end in deteriorated physical performance and postural instability with subsequent increase in incidence of fall, [13] increased health-related annual cost, [14] and mortality [15]. Diabetes-related neural damage is mainly due to microvascular injury of small blood vessels supplying nerves[16]. It's a vicious circle; since microvascular disturbance is a major contributor to DPN, while DPN predisposes to further peripheral vascular insufficiency in patients with NIDD [17]. Vascular disorders in diabetic feet are common multifocal complications with accelerated progression, [18] that end in exaggerated motor disabilities [19]. Functional balance is an important prerequisite for proper task performance during static and dynamic situations that depends on complex interactions between the different sensory and motor systems components [20]. Functional balance defect is common in patients with DPN, either due to its direct effect on the neuromuscular system or altered postural strategies required to compensate for inadequate somatosensory inputs [21]. These disturbances hinder patients with PDN from safely performing daily living activities and predispose them for loss of balance during statics well as during complex dynamic tasks [22].

Treatment of NIDD should be directed towards correction of the underlying pathogenic mechanisms, treatment of associated symptoms, with targeting prevention and treatment of complications[23]. Current pharmacotherapy approaches primary objective is to reduce neuropathic pain [24]. Patients with DPN may find it difficult to start the treatment program with exercise training because of multiple comorbidities; so many physical modalities have been introduced to modulate pain, sensory loss, muscle weakness and many other symptoms in those patients [25]. Pulsed low frequency electromagnetic field (PLFEM) is an interesting therapeutic procedure [26], it achieved significant improvements when utilized in multiple peripheral vascular and musculoskeletal disorders treatment [27].

PLFEM can effectively enhance peripheral nerve function;modulate neuropathic pain and nerve impulse in patients with DPN [28]. Extracorporeal shock waves (ESWs) are acoustic waves with very high-pressure amplitude, fast pressure rise, very short pulse length and extremely short pulse rise time [29]. ESWs is non-invasive therapeutic modality with proven effectiveness in the treatment of various musculoskeletal disorders, [30] variety of dermatological disorders, burns, and diabetic foot wounds [31].

Variable physical modalities have been used to treat DPN, but many of them have not been compared with each other in effectiveness, [25]also long-term continued studies are warranted to assess the extent and long-term effectiveness of these therapeutic modalities[32].Both PLFEM and Extracorporeal shock waves therapy (ESWT) have increased clinical utilization in various acute and chronic disorders. Up to date and recent researches; long-term effects of PLFEMT and ESWT on peripheral blood perfusion and functional balance were neither evaluated nor compared in patients with DPN. This study, therefore aimed to evaluate and compare the efficacy of PLFEMT with that of ESWT in the treatment of DPN on a follow-up basis.

SUBJECTS AND METHODOLOGY

Participants

Seventy participants with NIDD and DPN were enrolled in this randomized controlled study. This number was chosen based on the power analysis procedure ($1-\beta = 0.95$, $\alpha = 0.05$, effect size = 0.4) and patient's allocation into PLFEM group (n= 22), ESWT (n=23) or Control Group (n= 25) was conducted via computer random generated numbers.

All participants (43 men and 27 women) matched the inclusion criteria, continue their regular medical and dietary regimens.Informed consents were obtained before the beginning of the study.There was no drop-out throughout the study course (Figure 1). The study adhered to the Helsinki Declaration of 1975, as revised in 2000 and was approved by the regional ethical committee.

The inclusion criteria were: Patients with NIDD of more than 10 years, age range 45 to 60 years, DPN more than 2 years duration, with fasting blood sugar values over 110 mg/dl, with glycated hemoglobin of more than 6.5 to less than 11 %, under oral route therapy, with well-controlled hyperglycemia over the last 3 months, with mild DPN (Valk polyneuropathy severity score between 2-9), with Snellen chart score value more than 16/20, sedentary life style, with documented balance disturbance (Berge balance scale "BBS" score less than 40).

Exclusion criteria were patients treated with insulin, with age of less than 45 or over 60, feet ulcerations, other severe complications that affect the study outcomes, patient participation and safety (including nephropathy, retinopathy, blood pressure abnormalities, serious musculoskeletal, vascular, or cardiac disorder), current smoking, patients who were under medications that affect balance or were familiar with the evaluation or treatment procedures. Ab-

sence of more than 2 treatment sessions was established as exclusion criteria.

Pre-study identical screening and evaluations were conducted for all participants. The principal assessed variables include blood flow parameters (max skin blood perfusion (SBP-max), minimal skin blood perfusion (SBP-min), and basal mean perfusion changes (BMCP) of the foot by Laser Doppler Flowmetry Periflux system and functional balance (FB) “through BBS”. Evaluations were performed pre-study, post 12-weeks and 4-weeks after treatment cessation (follow-up). Data were handled according to standardized procedures. Variables assessment was done between 9-11 am. Fasting blood glucose (FBG) in mg/dl and HbA1c %, weight in kg, height in m all were initially evaluated at the beginning of the study.

Evaluation of the skin blood flow

Assessment of foot skin blood flow was conducted according to the previously prescribed procedure, [33] using laser Doppler flowmetry (Periflux system 5001) in which laser doppler probe 407 was connected to laser doppler perfusion measurement (LDPM) unite, connected to the computer. While assuming supine lying position for at least 5 min (in which patient was asked to remain as motionless as possible; skin blood flow parameters (SBP-max, SBP-min and BMCP of the lower extremity) were evaluated for each patient from the pulp of the great toe using (laser doppler flowmetry Periflux system 5001 (PF 5010 - LDPM unit), Primed, Sweden) with sampling frequency 32 Hz. The probe tip touched the tissue without over-pressure to prevent the false results. Local heat application for 3-5 minutes before blood flow evaluation was produced about by thermostatic probe. This combination procedure accurately clarifies the tissues viability and microcirculation compromise.

Functional Balance evaluation (Berg Balance Scale)

Functional balance was evaluated via the BBS according to well-established procedure [34]. BBS was used to evaluate FB, composed of 14 functional items, with 5-point scale (from 0 to 4 for each item in which 0 indicated failure of completion of the task, and 4 means success in carrying out the task independently). The higher score indicated a better functional balance.

Treatments

After comfortably seated on a “17 inches height” seat; patient in the PLFEM group was treated by resting each foot on a PLFEM plate for 30 min, two sessions/ week, for 12 weeks.

Plates were connected to the PLFEM apparatus (Easy Qs device, ASA srl, Italy), with intensity of 50 % and frequency of 10 Hz.

The ESW was applied perpendicular to the skin via The Orthospec ESWT (Medispec LTD, Germantown, MD, USA). After proper cleaning of the treated area by alcohol while the patient assumed relaxed supine lying position; The ESW pattern of application was manipulated to cover

the width of the region from above the malleoli till tip of the big toes then to the plantar aspect. ESW was applied on the dorsal, plantar and lateral aspects of the ankle and foot. ESW was applied in form of 1000 impulse/session, one week apart for 12 sessions, 0.32 mJ/mm²).

The control group received only their prescribed oral hypoglycemic medications with no share in any of neither PLFEM nor ESW.

Statistical analysis

Statistical analyses were performed using SPSS software (version 16.0). Data was expressed as mean ± SD. Descriptive statistical analysis was performed for all variables at the evaluation 1, 2 and 3. Changes in mean values of skin blood flow parameters (SBP-max, SBP-min, and BMCP) of the lower extremity and FB (through BBS) within and between groups were analyzed. Repeated measures ANOVA with a Greenhouse-Geisser correction was used to determine if there were statistically significant differences in mean values of evaluated variables between the three evaluation points. Post hoc tests using the Bonferroni correction were done after that. The chi-square test of independence was used to test for equality of proportions between populations. The statistical significance was set to P<0.05.

RESULTS

Pre-study, there were non-significant differences in demographic characteristics between groups (p > 0.05), (Table I).

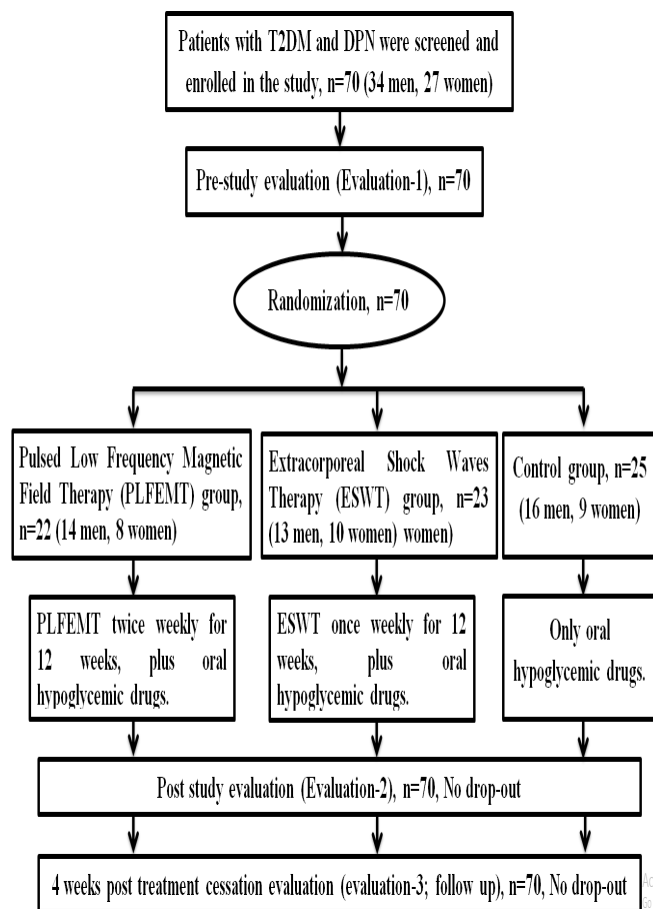


Figure 1. Patient's flowchart.

Pre-study results clarified that there were non-significant differences between the 3 groups neither in blood flow parameters (SBP-max, SBP-min, and BMCP) nor in FB scores. Data collected from all groups at the three evaluation points (pre-study “evaluation-1”, post-study “evaluation-2”, and 4 weeks post-treatment cessation “follow-up; evaluation-3”) were compared within and between groups (Tables 2, 3 & Figures 2, 3).

Blood flow parameters (SBP-max, SBP-min, BMCP):

Regarding SBP- max; There were significant increase in SBP-max mean values between the pre-study and post-study evaluations by (23.27 %) and (10.62 %) in the PLFEM and ESWT groups respectively (P<0.05), compared with non-significant decrease in SBP-max of the control group (-0.05 %-) between the same evaluation points (P= 0.08). In spite of rebound of the SBP-max at (evaluation-3; follow-up) in all groups; there’s still a significant increase in SBP-max mean values between the pre-study and the follow-up by (22.45 %) and (2.91 %) in the PLFEM and ESWT groups, respectively (P<0.05), compared with significant decrease in the control group (-0.14 %) between the same evaluation points (P=0.012) (Table 2). Adding to that; there were statistically significant differences in mean values and mean percent changes of SBP-max between groups at the post-study and the follow-up; but in favor of the PLFEM group (p< 0.05) (Table 2, 3 & Figure 2).

Table 1: The demographic characteristics of participants in all groups (Mean ± SD)

Variables	PLFEM group (N=22)	ESWT group (N=23)	Control group (N=25)	P value
Age (year)	53.5 ± 5.41	53.83 ± 4.4	53.68 ± 5.6	0.98**
Weight (kg)	80.05 ± 8.1	79.83 ± 6.65	81.04 ± 6.07	0.81**
Height (m)	1.65 ± 0.05	1.64 ± 0.04	1.64 ± 0.34	0.7**
BMI (Kg/m ²)	29.58 ± 4.04	29.71 ± 2.58	30.14± 2.17	0.8 **
FBG (mg/dl)	193.85 ± 9.42	195.41 ± 9.32	195.2 ± 15.39	0.89**
HbA1c (%)	8.1 ± 0.74	8.1 ± 0.46	8.04 ± 0.6	0.92**
Average T2DM duration (year)	11.82 ± 1.18	11.8 ± 0.65	11.88 ± 0.74	0.95**

PLFEM:Pulsed Electromagnetic Field Therapy,**ESWT:** Extracorporeal shock waves therapy, **FBG:** fasting blood glucose, **HbA1c:** Glycated hemoglobin, **T2DM:** Type 2 diabetes mellitus, **BMI:** body mass index

* Significant (P< 0.05) ** Non-significant.

Regarding SBP-min; There were significant increases in SBP-min mean values between the pre-study and post-study evaluations by (50.004 %) and (21.15 %) in the PLFEM and ESWT groups, respectively (P<0.05), compared with non-significant decrease in SBP-min of the control group by (-0.1 %-) between the same evaluation points (P= 0.16). In spite of rebound of the SBP-min at the follow-up in all groups; there’s still a significant increase in SBP-min mean values between the pre-study and the follow-up by (49 %) and (17.02 %) in the PLFEMT and ESWT groups, respectively (P<0.05), compared with significant decrease in the control group (-0.74- %) between the same evaluation points (P=7.94⁻⁵) (Table 2). Furthermore; There were statistically significant differences in mean values and mean percent changes of SBP-min between groups at the post-study and the follow-up; but in favor of the PLFEM group (p< 0.05) (Table 3, 4 & Figure 2).

Regarding BMCP; There were significant increase in BMCP mean values between the pre-study and post-study evaluations by (24.45 %) and (11.66 %) in the PLFEM and ESWT groups, respectively (P<0.05), compared with non-significant decrease in BMCP of the control group by (-0.09- %) between the same evaluation points (P= 0.08). In spite of rebound of the BMCP at the follow-up in all groups; there’s still a significant increase in BMCP mean values between the pre-study and the follow-up by (24.03 %) and (6.42 %) in the PLFEM and ESWT groups, respectively (P<0.05), compared with significant decrease in the control group by (-0.47- %) between the same evaluation points (P=2.65⁻⁵) (Table II). There were statistically significant differences in mean values and mean percent changes of BMCP between groups at the post-study and the follow-up; but in favor of the PLFEM group (p< 0.05) (Table 3, 4 & Figure 2).

Table 2: Within group's comparison of mean values of foot skin blood flow parameters and functional balance scores (F, P values).

Pre		PLFEMT group, (N=22)			ESWT group, (N=23)			Control group, (N= 25)		
		Post	Fol-low-up	Pre	Post	Fol-low-up	Pre	Post	Fol-low-up	
SBP-max	Mean ± SD	22.32 ± 4.57	27.21 ± 4.27	27.04 ± 4.25	22.43 ± 3.35	24.74 ± 3.33	23.07 ± 3.45	22.13 ± 3.05	22.12 ± 3.04	22.1 ± 3.04
	F, P values	569.86, 1.06 ⁻¹⁶ *			292.79, 3.38 ⁻¹⁴ *			3.27, 0.08**		
		303.46, 1.09 ⁻¹⁵ *			139.77, 7.33 ⁻¹³ *			5.41, 0.012*		
SBP-min	Mean ± SD	7.3 ± 2.39	10.51 ± 2.32	10.46 ± 2.32	7.26 ± 2.32	8.69 ± 2.58	8.4 ± 2.52	7.2 ± 2.54	7.2 ± 2.53	7.15 ± 2.51
	F, P values	472.13, 7.1 ⁻¹⁶ *			97.06, 1.58 ⁻⁹ *			2.087, 0.16**		
		231.90, 1.46 ⁻¹⁴ *			145.9, 4.82 ⁻¹³ *			14.64, 7.94 ⁻⁵ *		
BMCP	Mean ± SD	13.12 ± 2.45	16.15 ± 2.22	16.09 ± 2.21	13.04 ± 2.43	14.48 ± 2.35	13.84 ± 2.41	13.07 ± 2.38	13.06 ± 2.38	13.01 ± 2.38
	F, P values	286.41, 1.03 ⁻¹³ *			180.85, 4.33 ⁻¹² *			3.27, 0.08**		
		139.027, 1.85 ⁻¹² *			115.18, 4.79 ⁻¹² *			17.25, 2.65 ⁻⁵ *		
BBS	Mean ± SD	32.68 ± 3.76	43.18 ± 2.95	42.91 ± 2.78	32.87 ± 4.66	40.13 ± 3.52	38.61 ± 3.41	32.8 ± 4.42	32.76 ± 4.36	32.48 ± 4.29
	F, P values	856.06, 1.67 ⁻¹⁸ *			456.52, 3.33 ⁻¹⁶ *			1, 0.33**		
		459.1, 1.94 ⁻¹⁷ *			346.69, 8.26 ⁻¹⁷ *			5.41, 0.012*		

PLFEMT: Pulsed Electromagnetic Field Therapy, **ESWT:** Extracorporeal shock wave therapy, **SBP-max:** maximum skin blood perfusion, **SBP-min:** minimum skin blood perfusion, **BMCP:** basal mean changes of perfusion, **BBS:** Berge Balance Scale, * Significant (P < 0.05) ** Non-significant.

group) at the 3 evaluation points (Evaluation-1: Pre-study, Evaluation-2: Post study, and Evaluation-3: Follow-up; one month post-training cessation). Significant: P < 0.05 * Significant ** Non significant

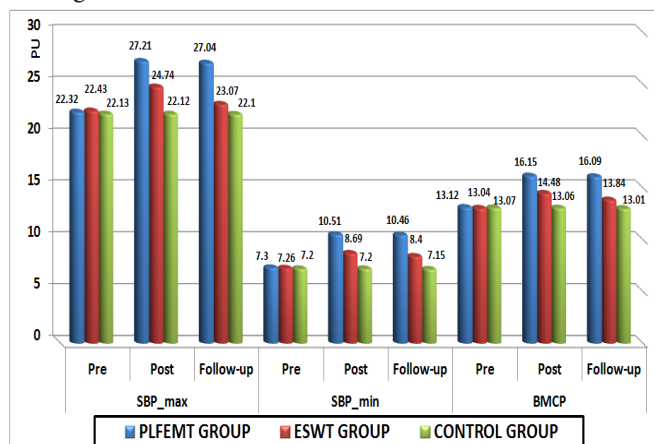


Figure 2: Between groups' comparisons (Means ± SD) of maximum skin blood perfusion (SBP-max), minimum skin blood perfusion (SBP-min), and basal mean changes of perfusion (BMCP) for the 3 groups (Pulsed low frequency magnetic Field therapy (PLFEMT) group, Extracorporeal shock wave therapy (ESWT) group, and Control

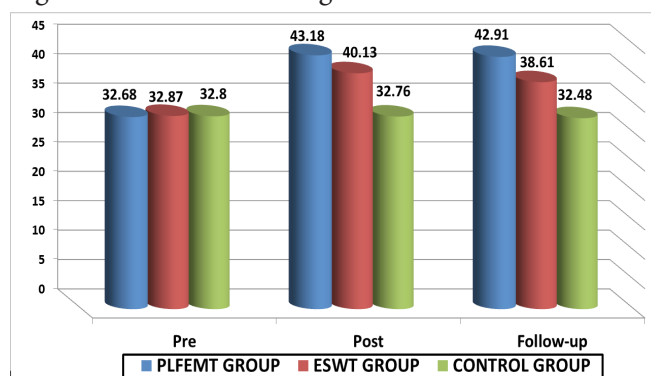


Figure 3: Between groups' comparisons (Means ± SD) of functional balance (Berg Balance Scale; BBS) for the 3 groups (Pulsed low frequency magnetic Field therapy (PLFEMT) group, Extracorporeal shock wave therapy (ESWT) group, and Control group) at the 3 evaluation points (Evaluation-1: Pre-study, Evaluation-2: Post study, and Evaluation-3: Follow-up; one month post-training cessation).

Table3: Between group's comparison of mean values of foot skin blood flow parameters and functional balance scores (F, P values).

Variables	Pre	Post	Follow-up	F, P values
SBP-max (PU)	0.04, 0.69**	12.03, 0.001*	12.14, 3.18 ⁻⁵ *	462.3, 1.51 ⁻³⁹ **
SBP-min (PU)	0.01, 0.99**	10.46, 1.11 ⁻⁴ *	10.79, 8.701 ⁻⁵ *	383.62, 4.57 ⁻³⁷ **
BMCP (PU)	0.01, 0.99**	10.37, 1.2 ⁻⁴ *	10.69, 9.33 ⁻⁵ *	251.76, 1.3 ⁻³¹ **
BBS	0.96, 0.91**	50.19, 4.79 ⁻¹⁴ *	50.54, 4.15 ⁻¹⁴ *	849.11, 8.11 ⁻⁴⁸ **

PLFEMT: Pulsed Electromagnetic Field Therapy, **ESWT:** Extracorporeal shock wave therapy, **SBP-max:** maximum skin blood perfusion, **SBP-min:** minimum skin blood perfusion, **BMCP:** basal mean changes of perfusion, **BBS:** Berge Balance Scale,

*Significant; P< 0.05, *Significant, **Non-significant, ^ψ Degree of freedom= 2, 67.

Table 4: Post-hoc multiple comparisons of mean values (between groups; P value).

	PEMT & SWT groups(P value)	PEMT & Control groups(P value)	SWT & Control groups(P value)
SBP-max (pre; eval-1)	0.92**	0.86**	0.78**
SBP-max (post; eval-2)	0.02*	6.43 ⁻⁶ *	0.01*
SBP-max (follow-up; eval-3)	4.35 ⁻⁴ *	1.32 ⁻⁵ *	0.35**
SBP_min (pre; eval-1)	0.95**	0.89**	0.94**
SBP_min (post; eval-2)	0.02 *	2.13 ⁻⁵ *	0.04*
SBP_min(follow-up;eval-3)	0.01*	1.80 ⁻⁵ *	0.08**
BMCP (pre; eval-1)	0.91**	0.94**	0.96**
BMCP (post; eval-2)	0.019*	2.29 ⁻⁵ *	0.04*
BMCP(follow-up; eval-3)	0.002*	2.72 ⁻⁵ *	0.23**
BBS (pre; eval-1)	0.884**	0.97**	0.96**
BBS (post; eval-2)	0.01*	2.55 ⁻¹⁴ *	2.17 ⁻⁹ *
BBS (follow-up; eval-3)	1.47 ⁻⁴ *	7.52 ⁻¹⁵ *	1.21 ⁻⁷ *

PLFEMT:Pulsed Electromagnetic Field Therapy,**ESWT:** Extracorporeal shock wave therapy,**SBP_max:** maximum skin blood perfusion, **SBP_min:** minimum skin blood perfusion, **BMCP:** basal mean changes of perfusion, **BBS:** Berge Balance Scale, * Significant; P< 0.05, * Significant, ** Non-significant

Functional Balance (Berge Balance Scale):

Regarding the FB; there were significant increase in BBS mean values between the pre-study and post-study evaluations by (33.01 %) and (23.12 %) in the PLFEM and ESWT groups, respectively (P<0.05), compared with non-significant decrease in BBS of the control group by (-0.1- %) be-

tween the same evaluation points (P= 0.33).

In spite of rebound of the BBS at the follow-up in all groups; there's still a significant increase in BBS mean values between the pre-study and the follow-up by (32.23 %) and (18.47 %) in the PLFEM and ESWT groups, respectively (P<0.05), compared with significant decrease in the control group by (-0.94- %) between the same evaluation points (P=0.012) (Table 2). Adding to that; there were statistically significant differences in mean values and mean percent changes of BBS between groups at post-study and the follow-up; but in favor of the PLFEM group (p< 0.05) (Table 3, 4 & Figure 3).

The results of this study clarified that; there were more pronounced increase on SBP-max, SBP-min, BMCP and BBS in the PLFEMT group than ESWT group after 3 months of either PLFEMT or ESWT treatment. Adding to that, 4 weeks post-training cessation; there were more significant sustained improvements on all evaluated variables in the PLFEM group than ESWT group.

DISCUSSION

The goal of this study was to explore and compare the effects of twelve-weeks PLFEM with that of the ESWT program on SBP-max, SBP-min, BMCP and BBS in patients with DPN. Results clarified the effectiveness of PLFEM and ESWT on peripheral blood perfusion and functional balance in patients with DPN. Results also revealed that PLFEM has more beneficial effects when compared with the ESWT in patients with DPN.

NIDD and DPN are associated with widespread and debilitating consequences, including increased risk and incidence of peripheral vascular disorders, [35] deteriorated somatosensory and motor functions, with progressive course of functional balance [36] and physical abilities [37] impairment. Treatment of DPN is a multi-disciplinary and long term approach that targets controlling the symptoms and improving the functional status [38]. PLFEM is a well-known therapeutic modality with documented therapeutic effectiveness in variable musculoskeletal and neurological disorders. PLFEM accelerates patient's recovery, shorten the rehabilitation time, [39]and enhances the effectiveness of many medications prescribed for patients with DPN [40]. Peripheral vascular and neural deficits brought about by impaired microvascular perfusion and neural tissues ischemia are the leading causative factors for DPN in patients with NIDD [41].Smith et al., 2004 reported that PLFEM can produce pronounced local arteriolar vasodilation in rat [42].The observed vascular and functional improvements in PLFEM group came in accordance with the previously postulated and proved mechanisms in which PLFEM can empower the neural cell metabolism, and hence supports the neural function, [43]reverse the peripheral neuropathy damage through reducing endoneural hypoxia, improving microcirculation, arousing cell proliferation and modulating neural regeneration in patients with DPN [28]. Furthermore; PLFEMT repetitive application on the soles of feet in patients with DPN produces neural regeneration

and reduces the accompanied neuropathic discomfort [44] through stimulation of opioid receptors and improving function of already deteriorated neurons [45]. PLFEMT can positively affect neuronal electrical activities through altering neuronal cell membrane potential and so ends in modulating nerve signals [33].

The main concept stands behind using PEMF in the treatment of DPN is the proved ability of the PLFEM to stimulate micro-vessel recruitment, [46] enhance perfusion, improve tissues and endoneural microcirculation [47] and hence counteracting the peripheral vascular and neural ischemia. [48] PLFEM can also enhance functional recovery of the peripheral nerves [49]. Functional improvements in response to PLFEM in patients with DPN came in line with recently published studies that reported that PLFEM can be safely and effectively used in patients with DPN and balance deficits [32], [50]. Adding to that; PEMF can positively modulate neuromuscular activities [26], [27]. FB recovery in response to PLFEM can be further attributed to the fact that frequency-modulated electromagnetic neural stimulation is able to increase touch perception and motor conduction velocity in peripheral nerves [51]. Application of PLFEM has the ability to enhance the reflex excitability of functionally attenuated spinal cord motor neurons, increase neural conductivity and improve the function of 1a afferent nerve [52].

Extracorporeal shock waves are safe and effective physical modality used to enhance angiogenesis in the different pathologies, with the interval between sessions varied from 2 days to two weeks [53], [54]. The ESW is an adjunctive therapeutic modality that serves to prevent complications and improve lower limb circulation in patients with NIDD and DPN [41]. The favorable impact of ESW on tissue blood perfusion in the current study came in accordance with many previously published studies reported that ESWT can effectively enhance tissues blood perfusion and healing process in patients with full thickness burn. The ESWT - dependant increase in perfusion is associated with stimulation of vessel endothelial growth factor (VEGF), control of the inflammatory cascade, and enhanced tissue regeneration [55]. Tassery and Allaire, 2003 reported that ESW can stimulate release of endorphins and creating small tunnels through which new blood vessels can grow, and so enhancing the blood flow [56].

Beside the complete biological effects of ESWs action is not yet fully identified; ESWs produce favorable biological responses at the cellular level. ESWs enhance the release of cellular angiogenic growth factors and hence support revascularization and cell proliferation [57], [39]. ESWs can effectively stimulate biological regeneration, enhance blood supply and improve tissues' metabolic processes [58], [29]. The increase in peripheral circulation in cases with NIDM and DPN can be further explained on the basis that ESWT enhances endothelial nitric oxide (NO) synthase production and activity which is important for vasodilation, angiogenesis and neurotransmission [59]. ESWT increases basal NO production, rate of neuronal NO synthase and

reduces the amount of exudates in lower extremities disorders [54]. Results of the current study were in line with that of Wang et al., 2003 who reported that the ESWT can effectively enhance the process of neovascularization at the bone-tendon injured site, [57] stimulate production and expression of angiogenesis-related markers, [31] protect against capillary endothelial damage, attenuate extracellular matrix proteolytic activity and hence maintain tissues vitality [60].

Although undertaken efforts to be unbiased; it was a hard task to mad the patients as well as therapists who were applying the PLFEMT or ESWs to be blind about the therapy type. To compensate for this point; randomization and evaluation procedures were performed blindly and delivered therapeutic program to each group was conducted by single therapist. Longer follow-up periods are warranted in the future studies to compensate for the relatively short-follow in this study.

CONCLUSIONS

According to the results of this study, both PLFEMT and ESWT are effective therapeutic modalities in increasing peripheral blood perfusion and functional balance in patients with PDN. PLFEMT is more effective than ESWs in increasing peripheral blood perfusion and functional balance in patients with PDN for an extended period of time.

List of abbreviations:

NIDD: Noninsulin-dependent diabetes, **T1DM:** Type 1 diabetes mellitus, **DPN:** Diabetic polyneuropathy, **PLFEM:** Pulsed low frequency electromagnetic field, **ESWs:** Extracorporeal shock waves, **SBP-max:** max skin blood perfusion, **SBP-Min:** minimal skin blood perfusion, **BMCP:** basal mean perfusion changes, **FB:** functional balance, **FBG:** Fasting blood glucose, **LDPM:** laser Doppler perfusion measurement, **BBS:** Berg Balance Scale, **NO:** nitric oxide.

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