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RESEARCH ARTICLE

Effect of extracorporeal shock wave therapy on skin blood perfusion in patients with diabetic foot: Randomized controlled trial.

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Abstract

Introduction: Diabetes mellitus (DM) is associated with serious microvascular complications, which have significant impact on patient's quality of life, morbidity, and mortality**. Aim:** The aim of this study was to investigate the effect of extracorporeal shock wave therapy (ESWT) on blood perfusion of diabetic foot in patients with type 2 diabetes mellitus (T2DM)**. Methods**: Thirty patients with T2DM, aged 40 to 55 years and were randomly assigned into group-A (study group) received ESWT (3000 shock, 1000/session, 3 sessions, 2 weeks a part, 0.32mJ/mm^2) in addition to oral hypoglycemic drugs or group-B (control group) received oral hypoglycemic drugs only. Maximum skin blood perfusion (SBP max), minimum skin blood perfusion (SBP min), and basal mean changes of perfusion (BMCP) of the legs were evaluated at the beginning and after four weeks for both groups**. Results**: SBP min, SBP max and BMCP were evaluated before and after the study. At the end of the study; SBP min and percentage of improvement (%) for the groups-A and B were 9.9±2.7 (44.93%) and 7.25±3.44 (0.93%) respectively. SBP max and (%) for the groups-A and B were 25.19 ± 4.14, (15.62%), 22.17 ± 2.52, (0.12%) respectively. BMCP and (%) for the groups-A and B were 15.37±2.64 (16.09%) and 12.73± 2.49 (0.29%) respectively (P<0.05). **Conclusion**: ESWT is effective in increasing blood perfusion and microcirculation in diabetic foot of patient with T2DMP.

INTRODUCTION

Diabetes mellitus (DM); a metabolic disorder characterized by defects in insulin secretion/ action or both; is accompanied with long-term dysfunction of various organs, especially blood vessels **(American Diabetes Association, 2005).** The rapid rise in the incidence of DM and its related complications is an alarming concern to health care professionals **(Wu et al., 2007).** Diabetes becomes one of the most common chronic non-communicable diseases, the global prevalence of DM in 2000 was estimated at 131 million and is expected to reach 366 million by 2030 (**Wild S et al., 2004).**

With its wide-spread prevalence; 90% to 95% of patients with DM have type 2 diabetes mellitus (T2DM). The incidence of T2DM is expected to continue rising because of the globally prevailing inactive life style. T2DM-related micro or macrovascular complications are frequently associated with disability and mortality **(Creager et al., 2003)** and impaired patient's quality of life **(Viberti, 2005).**

Lower limb diabetic ischemia is a serious complication that can lead significant pathologic consequences including ulceration, infection, destruction of deep tissues and amputation **(Khalifa et al., 2009).**These consequences, if ignored, take continuous serial and sequential pattern because patients with diabetes have diminished ability to establish collateral circulation **(Gayle et al., 1998).** Risk of peripheral arterial disease (PAD) is increased by age and duration of diabetes, with "the below knee vessels" are the most affected site **(American Diabetes Association, 2003a).**

Diabetic foot and lower limb disorders share large proportion of morbidity in patients with T2DM, the matter that arises the need for effective foot care interventions for those patients **(Reiberet al., 1995).**Prevention and early intervention is a cornerstone in management of T2DM related PAD because the process of improving the circulatory health of the extremity with bad and deteriorated status is costly and time consuming **(Rodrigues and Mitta, 2011).**

Rapid changes in diagnostic, treatments and vascular services procedures are associated with the emergence of new interventions that resulted in considerable variation in practice **(NICE 2012).** The non-invasive techniques play an important role in PAD evaluation and management when utilized in evaluation of vascular status health **(Rodrigues and Mitta, 2011).** Noninvasive blood flow evaluative measures are usually preferable, Laser Doppler Flowmetry (LDF) can be efficiently used to evaluate skin microcirculation and perfusion in patients with T2DM **(Núńez et al., 2004).**

Shock waves (SW) are sound waves generated by a vibration-creating source, characterized by a very high pressure amplitude (up to 1000 bar/100 MPa), very short pulse length in the range of 300 ns and extremely short pulse rise time of around 10 ns**(Jankovic, 2011),** transported through tissue via fluid and solid particles interaction **(Perez et al., 2003).** Extracorporeal shock waves Therapy (ESWT) have been used for the treatment of number of musculoskeletal disorders **(Furia, 2006)**, dermatological disorders, poorly healing burns and diabetic leg wounds. ESWT can successfully improve blood supply and tissues metabolic processes and hence stimulates biological regeneration processes and long-term healing **(Jankovic, 2011).**

Material and Methods

Subjects

Forty patients diagnosed with T2DM were evaluated for eligibility for this study, of them; thirty patients (17 male (57%) and 13 female (43%)) with T2DM were eligible for the study. Patients were recruited from the outpatient clinic of Kasr Al-Aini Hospital. All evaluative and treatment procedures were applied in the outpatient clinic of the Al-Aguza Physical Rehabilitation Center, Army Hospital, Egypt. All patients fulfilled the inclusion criteria of the study and had no exclusion criteria. This study was carried out according to the principles of the Declaration of Helsinki 1975, revised Hong Kong 1989 and was approved by the corresponding department council and ethics committee.

Inclusion criteria:

The inclusion criteria were as follows: Age from 40-55 years old, established T2DM for 10-15 years duration, Under tight medical control, treatment only with oral hypoglycemic agents (not taking insulin), and an inactive previous lifestyle for at least the previous 6 months.

Exclusion Criteria:

Age over 55 or less than 40 years, pregnant women, smoking, history of serious cerebrovascular or cardiovascular diseases that could affect patient safety and continuity of the study, existent of chronic respiratory or cardiopulmonary disorders and sever current lower extremity symptoms.

The study protocol was explained in details for every patient before the initial assessment. All patients were informed about the purpose, nature of the study and a written informed consent was obtained before participation in the study; giving agreement to participation and publication of the results of the study. Initial medical screening was performed for each patient by the physician; clinical history was documented for all participants with particular

attention to identify any long-term complications of diabetes. All participants were asked to continue their pharmacological regimen, regular diet, normal daily activities and lifestyle throughout the study.

Patients were randomly assigned into two groups through two stages by a person who did not share any other part of the study. First; eligible patients who fulfilled the inclusion criteria were initially recorded. Second; after medical counseling; patients were randomly assigned into either group-A; study group (n=15; received ESWT plus oral hypoglycemic medications or group-B; control group (n=15; received oral hypoglycemic medications only) through opening an opaque envelope prepared by an independent person with random number generation.

Evaluation:
Patients in both groups underwent an identical battery of tests; pre and post-study evaluations. All evaluative and treatment procedures were conducted at the same time of the day (between 9-11 am). Surrounding environment was controlled to be the same for all patients throughout the study. Evaluated variables include maximum skin blood perfusion (SBP max), minimum skin blood perfusion (SBP min), and basal mean changes of perfusion (BMCP) of the lower extremity, all variable were evaluated at the beginning and after four weeks for both groups. Weight in Kg and height in cm were also evaluated using a standard laboratory scale. Involvement and assessment of the patients was conducted after agreement of their physician.

Evaluation of the skin blood flow by Laser Doppler:
While assuming supine lying position for at least 5 min (IN WHICH patient was asked to remain as motionless as possible); skin blood flow was evaluated for each patient using (Laser Doppler FlowmetryPeriflux system 5001 (LDF), Perimed, Sweden). After proper cleaning of the pulp of the great toe, The Laser Doppler probe was positioned on the pulp of the right great toe that the tip touched the tissue without over pressure to prevent the false measurements. A combined laser Doppler and thermostatic probe was used for local heat provocation while blood perfusion was measured.

Interventions:
Each group adhered to the prescribed regimen throughout the study. After the physician permission; group-A; study group (n=15; received ESWT "3000 shock, 1000/session, 3 sessions, 2 weeks a part, 0.32mJ/mm^2" plus oral hypoglycemic medications, while group-B; control group (n=15; received oral hypoglycemic medications only). No adverse events were recorded throughout the study. ESWT treatment was applied after proper cleaning of the lower leg and foot by alcohol, while the patient assumed relaxed supine lying position.

The ESWT was applied perpendicular to the skin using The Orthospec ESWT (Medispec LTD, Germantown, MD, USA). The ESWT pattern of application was adjusted to cover the width of the area from above the malleoli till tip of the big toes then to the plantar aspect. ESWT was applied on the dorsal, plantar and lateral surface of the right ankle and foot. ESWT was applied in form of 3000 shocks (1000 shock/session, 2 week apart for 3 sessions).

The ESWT treatment was performed using an electrohydraulic, or "spark-gap", method of creating therapeutic shockwaves, according to previously mentioned procedure in which the used portable shockwave generator targeted the shockwaves to a 35-mm diameter therapy zone that enables shockwaves of sufficient energy to be delivered to the tissues in a single therapeutic session **(Malay et al., 2006).**

Statistical analysis
All data were examined using SPSS version 16.0. Data were collected and statistically analyzed using pre and post study T-test to test hypothesis and to control both within and between variabilities. All results were shown as means and standard deviations (SD), and a p-value less than 0.05 was considered as a statistically significant value.

Result

For this study, forty patients with T2DM were evaluated for eligibility for this study. Of these; thirty patients were eligible and included. In the baseline (pre-treatment) evaluation; results revealed that there were statistically non-significant differences between the two groups (study group; group-A and control group; group-B) before treatment (pre-test values) in the demographic characteristics including age, height, weight, BMI, FBG, HbA1c and average duration of T2DM among both groups, (table I); $P < 0.05$.

Table I: Demographic data of participants in both groups (pre- study).

Variables	Study group (group-A; n=15)	Control group (group-B; n=15)	T value	P value☼
Age (year)	50.4 ± 3.09	50.93 ± 3.39	0.45	0.66**
Height (m)	170.78 ± 6.6	171.13 ± 4.88	0.13	0.9**
Weight (kg)	78.33 ± 7.14	79.07 ± 9.28	0.24	0.81**
BMI (Kg/m^2)	36.23 ± 6.07	38.27 ± 8.47	0.76	0.46**
Fasting blood glucose (mmol/L)	173.6 ± 23.88	166.8 ± 22.57	0.801	0.43**

☼Level of significance at P<0.05.* = significant ** = non-significant

Within groups

Post-study results revealed that there were significant increase in mean values of maximum skin blood perfusion (SBP max), minimum skin blood perfusion (SBP min), and basal mean changes of perfusion (BMCP) of the lower extremity within group-A, compared with non-significant increase in the same measured variables within group-B (P < 0.05), **(Table II).**

Between groups:

Post-study results of between groups' comparisons revealed that there were significant differences in mean values of SBP min, SBP max and BMCP of the lower extremity (P < 0.05) **(Table II), (Figure 1).**

Table II. Within and between groups' comparisons of SBP min, SBP max and BMCP mean values (T & P values).

Variable	Group	Pre	Post	T & P values
SBP min	**Study group**	7.23 ± 2.71	9.9±2.66	10.84, 3.42^{-8} *
	Control group	7.21 ± 3.46	7.25±3.44	1.47, 1.64**
	T & P values	0.02, 0.99 **	2.36, 0.03 *	
SBP max	**Study group**	21.95±4.22	25.19±4.14	-9.9-, 1.05^{-7}*
	Control group	22.15±2.52	22.17±2.52	-1.08-, 0.301 **
	T & P values	-0.16-, 0.88 **	2.41, 0.02*	
BMCP	**Study group**	13.29±2.44	15.37±2.64	-11.7-, 1.29^{-8}*
	Control group	12.71±2.55	12.73± 2.49	-0.94-, 0.36 **
	T & P values	0.64, 0.53 **	2.82, 0.01 *	

Minimum skin blood perfusion (SBP min), Maximum skin blood perfusion (SBP max), and basal mean changes of perfusion (BMCP) of the lower extremity.

Level of significance at P<0.05.*= significant **= non-significant

Minimum skin blood perfusion (SBP min) evaluation:

The pre and post-study mean values of (SBP min) are reported in table **II**. By comparing the mean values of (SBP min) at pre and post-study evaluations for study and control groups; there was statistically significant increase in (SBP min) by about 44.9% for study group, and non-significant increase by about 0.93 % for control group **(Figure 1).**

Maximum skin blood perfusion (SBP max) evaluation:

The pre and post-study mean values of (SBP max) are reported in table **II**. By comparing the mean values of (SBP max) at pre and post-study evaluations for study and control groups; there was statistically significant increase in (SBP max) by about 15.62% for study group, and non-significant increase by about 0.12 % for control group **(Figure 1).**

Basal Mean Changes of Perfusion (BMCP) of the lower extremity evaluation:

The pre and post-study mean values of **(BMCP)** are reported in table **II**. By comparing the mean values of **(BMCP)** at pre and post-study evaluations for study and control groups; there was statistically significant increase in (SBP max) by about 16.09 % for study group, and non-significant increase by about 0.29 % for control group **(Figure 1).**

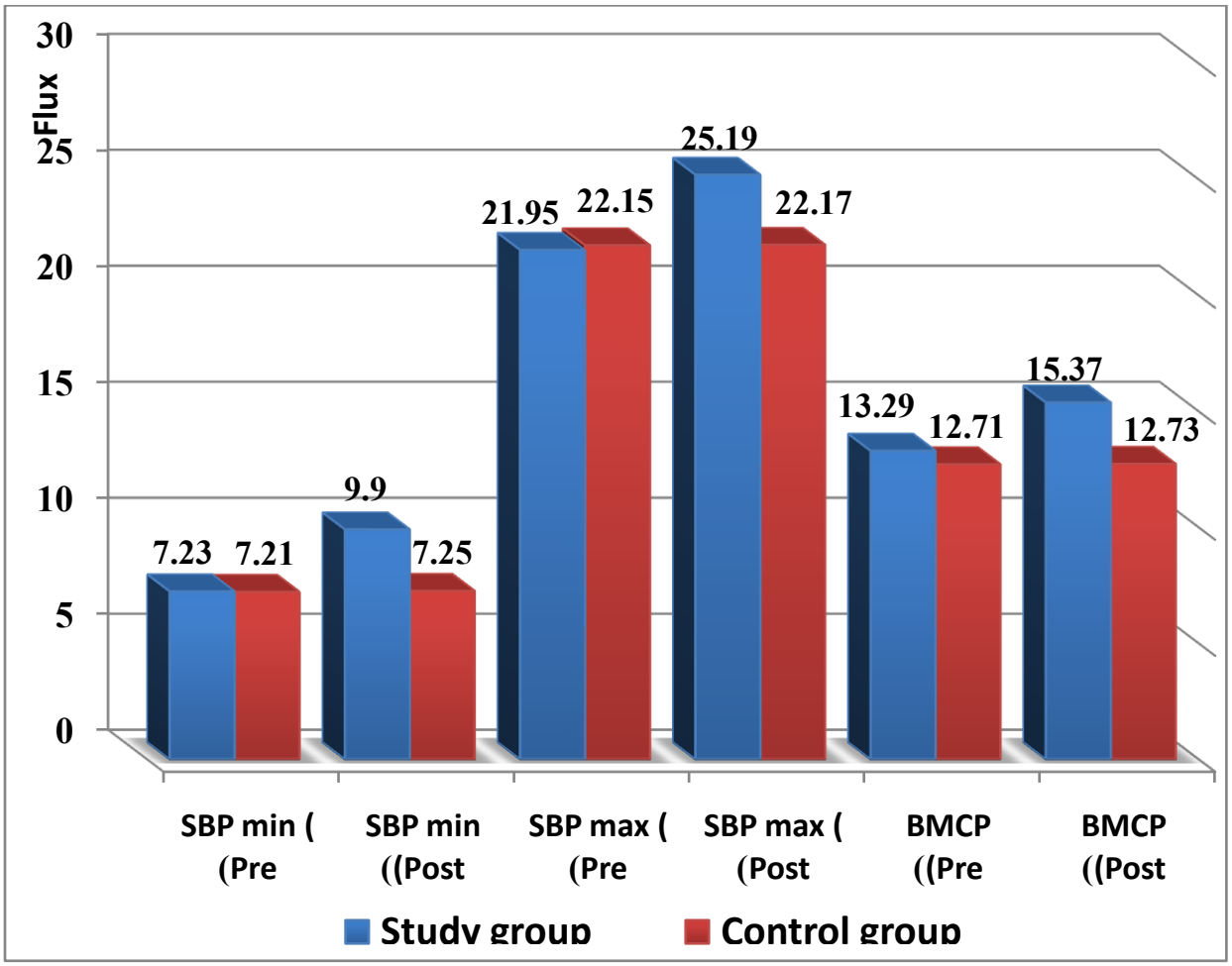

Figure (1): Mean valuesof Minimum skin blood perfusion (SBP min), Maximum skin blood perfusion (SBP max), and basal mean changes of perfusion (BMCP) of the lower extremity for both groups.

Discussion

Patients with T2DM have an increased incidence of atherosclerotic cardiovascular and peripheral vascular disorders **(American Diabetes Association, 2003b).** Diabetics are at great risk of morbidity and mortality from cardiovascular disease; the leading cause of death among diabetic people **(American Diabetes Association, 2010).** Therefore, efforts to prevent and/ or reduce diabetes- related complications by introduction of preventive or therapeutic measures into the treatment program must be a primary interest when caring for the diabetic patients **(Abdelaal et al., 2013).**

Foot problems are the most common reasons for hospitalization of patients with T2DM. Gangrene and amputation pose a major burden both to the patient and to the health care system. Impaired blood supply is considered among the most important risk factors for foot ulceration and gangrene **(Urbani et al., 2004)**.T2DM Accompanied vascular complications and abnormal endothelial function in patients with T2DM are considered among the main causes of morbidity and mortality. A high percentage of endothelial- damage markers are detected in diabetic subjects;

especially those with microvascular complications **(Regla et al., 2001).** With type 2 diabetes, the maintenance of skin blood flow is imperative to promote effective healing and prevent ulcerations in the skin **(Kilo et al., 2000).**

Recently, there has been an increase in the clinical application of shock wave therapy in various fields. The rational for the use of ESWT in patients with T2DM is based on stimulation of neovascularization and pain relief **(Maier et al., 2002)**, with minimal side effects that may include local bruising or short duration swelling and tenderness **(Lebrun, 2005).** This study was designed to explore the effect of ESWT on blood flow in patients with T2DM. A comparison was conducted between 2 groups of patients with T2DM (study and control groups). The results of this study revealed that ESWT significantly increases blood flow and perfusion in patients with T2DM.

In the present study, we found that application of ESWT lead to a significant increase in Minimum skin blood perfusion (SBP min), Maximum skin blood perfusion (SBP max) and Basal Mean Changes of Perfusion (BMCP) of the lower extremity as measured by laser Doppler flowmetry. Treatment with ESWT has been prescribed in many other cases, resulting in many favorable outcomes. ESWT fasten burn wound healing rate and perfusion in patients with deep partial full thickness burn. ESWT objectively increases perfusion to the ischemic tissue, stimulates growth factors, decreases inflammation and accelerate healing **(Arno et al., 2010).**

Results of our study were consistent with previous studies reported that optimal dosage of ESWT treatment positively affects flab ischemic zone increasing tissue perfusion, suppressing inflammatory response, increasing tissue perfection which leads to enhance tissue healing and improve function and vitality **(Kuo et al., 2007).** Another study stated that ESWT suppresses the early pro-inflammatory immune response, significantly blunts polymorphonuclear neutrophil and macrophage infiltration, attenuates acute pro-inflammatory cytokine expression and extracellular matrix proteolytic activity and hence protects against additional capillary endothelial and skin damage (**Davis et al., 2009).**

The beneficial effects of application of ESWT can be further explained on the basis of possible molecular mechanism of the anti-inflammatory action of ESWT treatment. ESWT can increase neuronal nitric oxide synthase (nNOS) activity and basal nitric oxide (NO) production. Furthermore; ESWT reverts the decrease of nNOS activity and NO production induced by a mixture of lipopolysaccharides (LPS), interferon-γ (IFN-γ) plus tumour necrosis factor a (TNF-a). Additionally; NO is important for vasodilation, angiogenesis and neurotransmission. ESWT can effectively enhance endothelial NOS (eNOS) activity in endothelial cells **(Ciampa et al., 2005)**. Application of ECSWT proved to be effective in reducing the amount of exudates, increasing percentage of granulation tissue compared with fibrino-necrotic tissue. ESWT therapy is a safe, feasible and cost-effective treatment for the lower extremities disorders and ulcers **(Saggini et al., 2008)**.

Results of the current study were consistence with results obtained from a study conducted by **Wang et al.,** to evaluate the effect of Low-energy ESWT on stimulating the blood flow and revascularization of injured tissue. Application of ESWT enhanced the process of neovascularization at the bone-tendon injured site **(Wang and Chen, 2002)**. ESWT can significantly improve blood supply and tissue regeneration through stimulating production and expression of angiogenesis-related markers including endothelial nitric oxide synthase (eNOS), vessel endothelial growth factor (VEGF) and proliferating cell nuclear antigen (PCNA) **(Wang et al., 2003).** Furthermore; application of ESWT can relieve joints symptoms through altering focal circulation and soft tissue regeneration **(Hsu et al., 2008)**.

Beneficial ESWT effects observed in our study can be explained on basis that ESWT application creates little tunnels through which new blood vessels can grow, and so stimulating an increased blood flow to the area. Additionally; ESWT application stimulates release of local endorphins and provides local anesthetic effect**(Tassery and Allaire, 2003).**

Conclusion

ESWT is safe and effective and adjunctive modality to other therapeutic procedures described for management of circulatory disturbances usually encountered in patients with T2DM. Results of this study have clinical significance to physical therapists dealing with patients with T2DM. The utilized ESWT program in this study can be easily and safely applied in clinical practice settings and serve as an adjunctive treatment protocol to prevent complications and improve lower limb circulation in patients with T2DM.

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