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Ultrasonic transdermal insulin therapy: a strategy to improve wound healing and support physical performance in diabetic patients

Dalia G. El Sayed[1]*, Mohamed Salah El-Sayed[2,3], Radwa F. Hammam[4], Shimaa G. El Sayed[5], Amera S. Aly[6], Heba E. Mahmoud[7], Esraa H. Rostom[8]

[1] Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Modern University for Technology and Information, Egypt.

[2] Department of Physical Therapy, Faculty of Allied Medical Sciences, Al-Ahliyya Amman University, Jordan.

[3] Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Horus University-Egypt, New Damietta, Egypt.

[4] Basic Science Department, Faculty of Physical Therapy, Modern University for Technology and Information, Egypt.

[5] Department of Physical Therapy for Surgery and Women's Health, Faculty of Physical Therapy, Sinai University, Egypt.

[6] Department of Physical Therapy for Internal Medicine and Geriatrics, Faculty of Physical Therapy, Alsalam University, Egypt.

[7] Department of Physical therapy for Women's health, Faculty of Physical Therapy, Sinai University, Egypt.

[8] Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Egypt.

* Correspondence: Dalia G. El Sayed; dalia.galal@pt.mti.edu.eg

ABSTRACT

The aim of this study was to establish the impact of Transdermal Insulin Therapy in patients with chronic diabetic wound. This double blinded randomized control trial study involved 40 (12 female and 28 male) patients with stage II-III of chronic diabetic foot wound. The patients in the intervention group (I) were subjected, besides Transdermal Insulin Therapy, to Hyperpolarized light therapy and Standard wound cleaning and dressing. Hyperpolarized light therapy and Standard wound cleaning and dressing (standard treatment) were the treatment that were used in the control group (C). All patients were assessed before treatment initiation and then weekly for four consecutive weeks. Post-treatment revealed significant reductions in DIMST score IV (MD=-2.9, effect size=0.79) and DIMST score V (MD=-2.95, effect size=0.81) of the study group in comparison to the control group ($p<0.01$). Comparing within groups, in the intervention group there was a substantial reduction in score V in comparison with score I, II, III and IV ($p<0.001$), a substantial reduction in score IV in comparison

with score I, II and III ($p<0.001$), a substantial reduction in score III in comparison with score I and II ($p<0.001$) and a substantial reduction in score II in comparison with score I ($p<0.001$). The Transdermal Insulin Therapy by ultrasound has a significant effect on wound healing and supports the physical performance of chronic diabetic foot wound patients, and it should be considered in future treatment plans for diabetic wounds.

KEY WORDS

Transdermal Insulin; Ultrasonic; Wound Healing; Physical Performance; Diabetic Patients

1. INTRODUCTION

Prolonged wound healing is a characteristic feature of diabetes mellitus (DM). Chronic hyperglycemia linked to DM compromises blood circulation and injures the vascular system. Diabetic patients may experience neuropathy along with peripheral vascular dysfunction, complicating wound detection. Diabetic wounds are marked by severe inflammation, reduced angiogenesis, fibroblast proliferation, as well as impaired keratinocyte migration (Gorecka et al., 2019; Ebrahiminia et al., 2023).

Polarized light (PL) is a system that emits polarized, incoherent, low-energy, and polychromatic light, with waves oscillating in parallel alignment. Linear divergence via reflection (the multi-layer mirror system, Brewster mirror) is exceptionally efficient, achieving a polarization degree of 95% (M Allam et al., 2022). A Bioptron light source, with a wavelength range of 400–2000 nanometers and a power density of 40 milliwatts/cm², providing light energy of 2.4 joules/cm², was utilized for hyperpolarized light treatment (Aleksandar et al., 2008).

PL accelerates wound healing through various biological effects includes boosting cell membrane function, adenosine triphosphate accession in mitochondria as well boosting mitochondrial number, fibroblasts, collagen and thus tissue oxygenation and epithelialization (Mohamed et al., 2019).

Insulin is a crucial hormone for controlling blood sugar and cholesterol levels in the blood. (Edek et al., 2023) In addition to its systemic impact, numerous reports suggest that applying insulin topically causes localized effects. Many trials and case reports have been released reporting positive effects of topical insulin for many diseases such as dermatological compromises, ophthalmological diseases and others (Sridharan and Sivaramakrishnan, 2017; Alrubaye et al., 2025).

Therapeutic ultrasound is one of commonly used modalities for such dermatological problems because of the associated thermal effect which enhances vasculature, membrane permeability and

collagen fibers production which finally reflects on tissue healing (Yildirim et al., 2018). Therefore, dispersion of topical medications can be enhanced through the usage of US in phonophoresis process (Mahendra et al., 2022). According to the authors knowledge, this is the first study that investigates the impact of transdermal insulin therapy by ultrasound on wound healing and physical performance in chronic diabetic wound.

2. METHODS

2.1. Study Design

This study was a prospective double blinded randomized controlled trial study, with registration number (NCT06708975). All necessary information is reported in accordance with the study's conformance to all CONSORT criteria. A permission form was signed by all participants before they could be enrolled in the study.

This study was approved by the ethics committee at the Faculty of Physical Therapy, Cairo University (No. PT.REC/012/005342). This study's data was gathered at the MG clinic, which focuses on wound care and rehabilitation after surgery through physical therapy.

2.2. Participants

The present study was performed on 40 (12 female and 28 male) participants with grade II-III-degree diabetic foot wound. They were devoid of any clinical conditions such as limb infections, localized or proximate malignancy, and anti-coagulated patients. Their age ranges between 40 to 65 years. participants with mental and psychological conditions were excluded from the study. Physical examination was performed by an assessor who was blinded to patient allocation.

Data sampling was calculated by Using G*Power software program. The proper sample size was established using a pre-post comparison of the participants' responses, utilizing an effect size of 0.25, a power of 80%, as well as a significance level of 5%. The requisite sample size was 40 participants. The participants were allocated randomly into two groups: Intervention group I (20 participants), All participants received Transdermal Insulin Therapy, Hyperpolarized light therapy, Standard wound cleaning and dressing. and Control group C (20 participants): All participants received Hyperpolarized light therapy, Standard wound cleaning and dressing. The investigator who was blinded to both participant recruitment and care did the allocation also, participants were not aware of their assignment group.

2.3. Randomization and Concealed Allocation

The current study was a prospective randomized double-blinded study on 40 participants with stages II-III of chronic diabetic foot wound, all patients were random in using closed envelopes into two groups: The participants in the intervention group (20 participants of both sexes) were treated using Transdermal Insulin Therapy, standard wound cleaning and dressing as well as hyperpolarized light therapy. Participants in the control group (20 patients of both sexes) were treated with hyperpolarized light therapy and standard wound care cleaning dressing. A researcher who was blinded to both participant's' recruitment and care did the allocation also; patients were not aware of their assignment group.

Participants who met the inclusion criteria were randomly assigned to two groups. Following the initial examination, treatment commenced on the day after assessment, and patient scores were evaluated at one-week intervals for one month thereafter.

The subsequent ethical issues were under consideration: Prior to initiating treatment, the physiological advantages of this therapeutic approach were thoroughly elucidated to all patients. Baseline measures for each patient were recorded for comparative analysis before treatment commenced, and subsequent measurements were obtained at one-week intervals over the course of one month.

2.4. Outcome Measures

Time frame: All patients underwent evaluation prior to treatment during the initial assessment and subsequently on a weekly basis for four consecutive weeks post-treatment.

This study utilized the DMIST Scale as an assessment tool, which incorporates seven domains: depth, maceration, inflammation/infection, size, tissue type of the wound bed, kind of wound edge, as well as tunneling/undermining, to develop a novel diabetic foot evaluation scale. The abbreviation "DMIST" was created from the initials of the domains to refer to this scale. High validity was discovered to be provided by DMIST. It is anticipated that DMIST will add to the body of knowledge regarding diabetic foot care. Zero was the minimum score and 98 was the maximum score, with a greater number denoting a more severe injury and a zero signaling full recovery (Makoto et al., 2020).

2.5. Interventions

Transdermal Insulin Therapy

The participant was comfortably seated while the wound was cleansed with normal saline. An insulin solution, measured at 2 units per square centimeter, was then applied to the ulcer using a camel hairbrush. A sterile plastic bag filled with aquasonic gel was positioned over the wound and surrounding tissue to prevent any contamination of the equipment. Pulsed ultrasound, using an applicator measuring 1.9 cm^2, was administered over the gel pad with the ultrasound head moved in a circular pattern above the ulcer site. This pulsed ultrasound was applied to the plastic bag, focusing on the wound cavity, scab, and edges. The ultrasound therapy was executed with a pulsed duty cycle of 40% (4 milliseconds on, 6 milliseconds off) and a power density of 0.6 watts/cm^2 for six minutes (Radwan et al., 2022), three times weekly over four sequential weeks. After treatment, the wound was cleaned, and a sterile dressing was applied.

Hyperpolarized Light Therapy

This treatment was applied by using MedAll Bioptron Device that was made in Switzerland by Zepter Group with Serial Number (002-2019-04-2055), three times a week for one month, maintaining a 10 cm distance from the wound. All sessions were conducted over a duration of four sequential weeks.

Wound Care

The conventional wound care employs standard normal saline solution (NaCl) for cleansing, along with 2% hydrogen peroxide. At that juncture, a dry cloth (AAWM, 2011), was utilized, followed by Farm-active (Local Antibiotic Spray), a cotton fleece, and a cement strip. Daily wound care was administered, whether at the clinic or at home.

2.6. Intervention and Control Group

All 20 participants received transdermal insulin therapy using ultrasound, hyperpolarized light therapy, and standard wound care according to the following protocol:

Participants were instructed to assume a comfortable position during the cleansing and preparation of the wound. The therapist applied Transdermal Insulin (Mixtard) on wound surface area - each two units for one cm, pulsed mode, frequency: 3 MHZ, intensity: 0.5 W. Participants were instructed to assume a comfortable position during the administration of Hyperpolarized Light. The therapist utilized hyperpolarized light on the affected wound (Fluren) for 10 minutes at a distance of 10 cm, succeeded by a green lens for an additional 10 minutes, then a red lens for 5 minutes, and finally

a blue lens for another 5 minutes. Participants were instructed to remain relaxed for five minutes. We utilized saline solution for wound cleansing as well as Farm-active Topical Antibiotic Spray 150 ml as the antimicrobial agent, followed by the placement of a dressing using a Topical Eye Patch (El Sayed, 2021).

All 20 participants in the control group were given Hyperpolarized Light along with Traditional Wound Care in the same steps that were mentioned in the intervention group.

2.7. Statistical Analyses

Age was compared among groups using an unpaired t-test. The Chi-squared test was conducted to compare gender distribution among groups. The Shapiro-Wilk test was employed to assess the normal distribution of the data. Levene's test for homogeneity of variances was performed to assess the homogeneity of variances among groups. A mixed ANOVA was performed to compare within as well as between groups. Post-hoc analyses employing the Bonferroni correction were conducted for subsequent multiple comparisons. The significance criterion for all statistical tests was established at $p < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 28 for Windows (IBM SPSS, Chicago, IL, USA).

3. RESULTS

Table 1 shows the subject characteristics of study as well as control groups. There was no substantial difference among groups regarding age and sex distribution ($p > 0.05$).

Table 1. Descriptive statistics of participants' demographic characteristics in both groups

	Intervention group	**Control group**	***p* value**
	Mean ± SD	**Mean ± SD**	
Age (years)	49.65 ± 12.85	52.50 ± 13.04	0.77
Gender, n (%)			
Females	7 (35%)	5 (25%)	0.49
Males	13 (65%)	15 (75%)	

Note. *SD: Standard deviation; p-value: probability value*

Mixed ANOVA demonstrated a substantial interaction effect of treatment and time ($F = 19.48$, $p = 0.001$, Partial eta squared = 0.34). There was no substantial main effect of treatment ($F = 0.58$, $p = 0.45$, Partial eta squared = 0.02). There was a substantial main effect time ($F = 111.93$, $p = 0.001$, Partial eta squared = 0.75).

There was a substantial reduction in score IV (MD = -2.9, effect size = 0.79) and score V (MD = -2.95, effect size = 0.81) of study group in comparison with that of control group ($p < 0.01$). There was no substantial difference in score I, score II as well as score III among groups ($p > 0.05$) (Table 2).

Table 2. Mean DMIST Score I, II, III, IV and V of group A and B

	Score I	**Score II**	**Score III**	**Score IV**	**Score V**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	***p* value**
Study group	20.45 ± 5.01	17.85 ± 5.14	15.90 ± 4.32	13.35 ± 3.38	12.10 ± 3.43	0.001
Control group	18.85 ± 4.37	17.55 ± 4.43	16.80 ± 4.14	16.25 ± 3.96	15.05 ± 3.80	0.001
MD	1.60	0.3	-0.9	-2.9	-2.95	
95% CI	-1.41: 4.61	-2.77: 3.37	-3.61: 1.81	-5.26: -0.55	-5.27: -0.63	
Effect size	**0.34**	**0.06**	**0.21**	0.79	0.81	
***p* value**	***p = 0.29***	***p = 0.84***	***p = 0.51***	***p = 0.01***	***p = 0.01***	

Note. *MD: Mean difference; CI: Confidence interval; p value: Probability value*

In the intervention group there was a substantial reduction in score V in comparison with score I, II, III and IV ($p < 0.001$), a substantial reduction in score IV in comparison with score I, II and III ($p < 0.001$), a substantial reduction in score III in comparison with score I and II ($p < 0.001$) and a substantial reduction in score II in comparison with score I ($p < 0.001$). Figure 1 demonstrates the clinical improvement in chronic diabetic wound at the first visit and initial evaluation and after 4 weeks of treatment.

Figure 1. The clinical improvement in chronic diabetic wound

In the control group there was a substantial reduction in score V in comparison with score I, II, III and IV ($p < 0.01$), a substantial reduction in score II, score III and score IV in comparison with score I ($p < 0.01$); while there was no substantial difference among score II, score III as well as score IV ($p > 0.05$) (Table 3, Figure 2).

Table 3. Comparison of DMIST Score across time intervals

	Study group				Control group			
	MD	**95% CI**		***p* value**	**MD**	**95% CI**		***p* value**
		LB	**UB**			**LB**	**UB**	
Score I vs Score II	2.60	1.66	3.54	0.001	1.30	0.36	2.24	0.002
Score I vs Score III	4.55	3.25	5.85	0.001	2.05	0.75	3.35	0.001
Score I vs Score IV	7.10	5.35	8.85	0.001	2.60	0.85	4.35	0.001
Score I vs Score V	8.35	6.32	10.38	0.001	3.80	1.77	5.83	0.001
Score II vs Score III	1.95	1.12	2.78	0.001	0.75	-0.08	1.58	0.10
Score II vs Score IV	4.50	3.06	5.94	0.001	1.30	-0.14	2.74	0.11
Score II vs Score V	5.75	4.04	7.46	0.001	2.50	0.79	4.21	0.001
Score III vs Score IV	2.55	1.71	3.39	0.001	0.55	-0.29	1.39	0.57
Score III vs Score V	3.80	2.71	4.89	0.001	1.75	0.66	2.84	0.001
Score IV vs Score V	1.25	0.38	2.12	0.001	1.20	0.33	2.07	0.002

Note. *MD: Mean difference; CI: Confidence interval; LB: Lower bound; UB: Upper bound; p value*

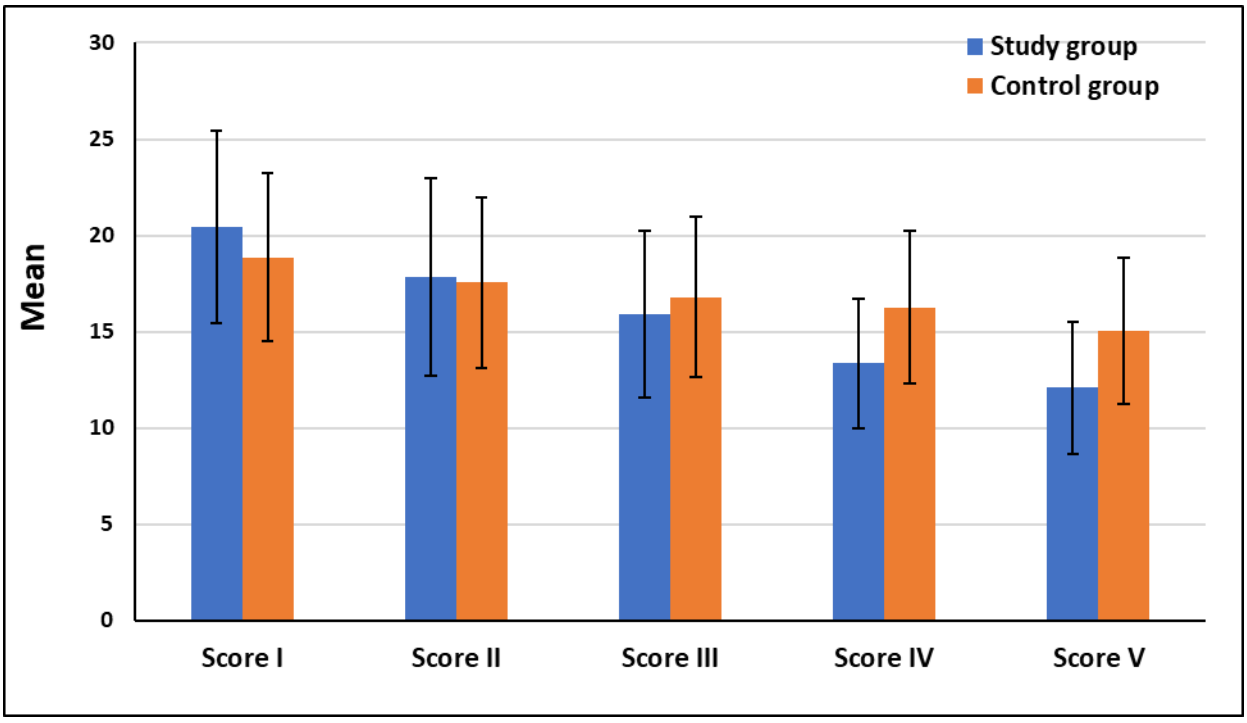

Figure 2. Mean DIMST Scale I, II, III, IV and V of I and C Groups

4. DISCUSSION

Diabetic wounds are the most challenging complications associated with diabetes, influenced by various risk factors. Treating these wounds is complex, requiring ongoing interdisciplinary cooperation, which results in both physical and emotional distress for patients and escalates healthcare costs. With the increasing number of individuals diagnosed with diabetes, it is essential to thoroughly understand the causes and treatment methods for diabetic wounds. This understanding can help reduce patient suffering and lower medical expenses (Huang et al., 2023).

Topical insulin facilitates wound healing by regulating oxidative and inflammatory responses. Insulin therapy reduces reactive oxygen species levels, which can adversely affect lipids, proteins, and DNA in burn injuries in rats (Dhall et al., 2015). Moreover, topical insulin enhances early neutrophil recruitment and exerts an anti-inflammatory effect in wounds by increasing M2 macrophage populations and IL-10 levels, facilitating the removal of necrotic tissue. In vitro, insulin enhances macrophage chemotaxis and phagocytosis, along with the secretion of inflammatory mediators, by regulating MCP-1 expression at wound sites (Chen et al., 2012).

Phonophoresis is the practice of administering topical medications locally using ultrasound. Ultrasound generates thermal, non-thermal, and chemical actions that propel drug molecules into tissues, resulting in increased penetration. The application of ultrasonic waves for the delivery of topical medication is regarded as painless, noninvasive, and associated with fewer adverse effects due to its localized administration at the site of discomfort (Dorji et al., 2022).

It is a randomized, double-blind, controlled trial conducted across multiple centers, analyzing the therapy's impact on wound closure and bacterial cultures, as well as its interaction with different levels of debridement and found that Kilohertz ultrasound therapy offers a promising treatment for diabetic foot ulcers, improving healing rates without increasing adverse events, making it a valuable addition to clinical wound care practices for diabetic patients (Ennis et al., 2005).

Combination therapy is becoming more popular these days for wound healing. Previous reports indicate that the integration of US as well as electric field stimulation techniques may exceed their limitations as well as significantly enhance the likelihood of chronic skin ulcer eradication. It has been proposed that the concurrent application of ultrasound and laser treatment modalities may yield more advantageous outcomes in the management of pressure ulcers (Matic et al., 2019).

Based on the information above, biochemical responses are accelerated by photo-biomodulation combined with low-level laser therapy. The absorption of laser photon energy by cells

can be transformed into chemical kinetic energy. Conversely, low-intensity ultrasound therapy exerts biomechanical as well as non-thermal effects on tissue. The micro-massage of cells induced by US radiation stimulates collagen production as well as enhances tissue tensile strength. Consequently, the concurrent application of laser photo-biomodulation and the biomechanical effects induced by US appear to enhance the wound healing process more effectively through biochemical as well as biophysical mechanisms. The fewer side effects and enhanced safety, together with specific controversies associated with each treatment, necessitated an examination of the combined efficacy of these two methods on diabetic wound healing, focusing on biomechanical aspects along with histopathology (Ganvir et al., 2016; Al-Qaisi et al., 2025).

Impaired wound healing is a significant issue in diabetic patients. Physical therapies such as ultrasound and laser are employed to address this. This study aimed to assess the combined impact of ultrasound and laser therapy on diabetic wound healing using a rat model. Each therapy independently seemed to promote wound healing by augmenting collagen and elastin levels, as well as enhancing biomechanical properties. However, the combination of laser and ultrasound therapies seemed to offer superior results compared to each method alone. Further research in this field is encouraged (Ebrahiminia et al., 2023).

Another study examined the effects of transdermal insulin delivery via low-intensity US on chronic lower limb venous ulcers. In this study, 60 participants with chronic lower limb venous ulcers were allocated into two groups: Group A, who were given insulin through low-intensity US along with standard medical care, and Group B, who were given topical insulin along with regular medical care. The findings indicated that transdermal insulin delivery is a safe, non-invasive, as well as beneficial approach for treating lower limb venous ulcers, suggesting it could be integrated into treatment protocols for these challenging conditions (Radwan et al., 2022).

In the current study the researchers performed a comparison between two groups, the intervention group (I) were subjected, besides Phonophoresis Insulin Therapy to Hyperpolarized light therapy and Standard wound cleaning and dressing. Hyperpolarized light therapy and Standard wound cleaning and dressing (standard treatment) were the treatment that utilized in the control group (C) and DIMST Scale was used in the assessment of outcome, the scale was named “DMIST” as an acronym from the initials of the domains, all patients were assessed prior to and following treatment in both groups, the researcher found significant improvement in intervention group via significant decrease in score V compared with score I, II, III and IV and significant decrease in score II, score III and score IV compared with score I whereas in Control group there was a substantial decrease in score V

compared with score I, II, III and IV , a significant decrease in score II, score III and score IV compared with score ; while there was no significant difference between score II, score III and score IV.

5. CONCLUSIONS

The Transdermal Insulin Therapy by ultrasound has a significant effect on wound healing and supports the physical performance of chronic diabetic foot wound patients, and it should be considered in future treatment plans for diabetic wounds.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the study's design, data collection, analysis, interpretation, and manuscript preparation. All authors reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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