

Effect of Chitosan Phonophoresis on Chronic Diabetic Ulcer Healing

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ABSTRACT

Background: A frequent and serious complication of Diabetes Mellitus (DM) is diabetic skin ulcers, so multiple medical and adjunctive therapies are always being introduced to overcome it.

The aim of the work: This study aimed to explore the impact of chitosan phonophoresis on chronic diabetic ulcer healing.

Patients and methods: Seventy-two patients suffering from chronic diabetic ulcers participated in the study. They ranged in age between 55 and 70 years. They were gathered from the hospitals of Cairo University and divided into three equal groups at random: Group [A] included 24 patients who received chitosan gel with sham therapeutic ultrasound. Group [B] included 24 patients who received chitosan phonophoresis. Group [C] included 24 patients who received therapeutic ultrasound only. The participants in all groups received wound care along with the previously-mentioned interventions. The data regarding ulcer status, assessed by Bates-Jensen Wound Assessment Tool (BWAT); and ulcer surface area, measured by imitoMeasure application, were collected and analyzed at baseline, 2 weeks post-therapy, as well as four weeks post-therapy.

Results: All groups showed significant improvement in chronic diabetic ulcer healing in terms of ulcer status and ulcer surface area over the treatment period ($p=0.001$). Regarding ulcer status, at baseline and at 2 weeks post-therapy, no statistical significant differences were detected among the three groups ($p=0.070$ and $p=0.070$ respectively) and the same was noticed regarding ulcer surface area ($p=0.104$ and $p=0.072$ respectively). At 4 weeks post-therapy, Group B showed statistical superiority over Group A and C in improving ulcer status ($p=0.041$ and $p=0.001$ respectively) and ulcer surface area ($p=0.015$ and $p=0.001$ respectively).

Conclusion: Four weeks of chitosan phonophoresis application has a superior effect in improving chronic diabetic ulcer status and reducing its surface area over than chitosan or therapeutic ultrasound alone.

Key words: chronic diabetic ulcer, chitosan phonophoresis.

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INTRODUCTION

Diabetic skin ulcer is one of the severe complications of DM, which has a high incidence and may cause death or disability (1). The number of diabetic patients has increased markedly in recent years and as a result, the significance of diagnosing and treating diabetic skin ulcers and gangrene complications has grown (2).

Complications involving the foot are prevalent in patients with DM (3, 4). One of the main causes of avoidable morbidity in persons with DM is Diabetic Foot Ulcers (DFU). Foot ulcers may lead to a dysfunction, infection, hospitalization, amputation of the lower extremities, and even death. Individuals with DM have a 19% to 34% lifetime risk of foot ulcers, and this percentage is increasing with aging and medical complexity (5).

Some of the substances that may be used to treat diabetic foot involve alginates, carbon dressings, collagen, silver, highly oxygenated fatty acids, silicone, along with various

antiseptics. Skin regeneration using synthetic acellular biomaterials is a relatively new concept. One of these biomaterials is chitosan, a polysaccharide that is made up of amino sugars and obtained by partial deacetylation of chitin, which is the least likely to be toxic or cause an immune reaction (6, 7, 8, 9). Because of its broad-spectrum antimicrobial action, chitosan has found use in the treatment of infection and the promotion of tissue repair (8, 9, 10).

The therapeutic properties of ultrasound may be used in phonophoresis, a technique which is utilized to improve the delivery of topical drugs (11). This method is used to enhance the penetration of topical drugs into deep tissues by increasing their absorption into the skin (12).

Up to current study researchers' knowledge and search, no previous studies explored the impact of chitosan phonophoresis on chronic diabetic ulcer healing. Hence, the need of our study has been established to reveal the impact

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of chitosan phonophoresis on chronic diabetic ulcer healing in terms of ulcer status and surface area.

PATIENTS AND METHODS

Study Design: It was a prospective, randomized, and controlled study.

Sample Size Calculation: Sample size calculation was done using wound surface area, as reported in Sutto et al. (13), with 80% power at $\alpha = 0.05$ level, for 3 groups and effect size = 0.4, employing F-test within and between interaction effects. The minimum acceptable sample size was 64 subjects. After adding 8 participants or 13% of the total, who might drop out, the overall sample size was 72 subjects with 24 subjects in each group. G*Power (version 3.0.10) was utilized to determine the sample size.

Participants: Seventy-two subjects with medically-controlled type II DM, aged 55 to 70 years, with ≈ 3 months grade II [according to Wagner's classification of DFU (14)] diabetic foot non-infected ulcers, participated in the current study. They were gathered from the hospitals of Cairo University. Pregnant women and those with medically-uncontrolled DM, infected ulcers, vascular insufficiency, associated bone fractures, grade 3-5 diabetic foot ulcers, implanted devices, impaired sensation, a known allergy or hypersensitivity to chitosan, skin disease, malnutrition, malignancy, or any disease/disorder/receiving intervention that may interfere with the study's objective were not allowed to participate.

Ethical Approval: Before participating in this study, each subject was thoroughly advised of his/her rights before signing an informed consent form. The study gained ethical authorization from Cairo University's Faculty of Physical Therapy's Institutional Review Board prior to the study's implementation [P.T. REC/012/005250], in addition, it had been registered on the Pan African Clinical Trial Registry [PACTR202410857820290]. The current study's methodology complied with the Helsinki Guidelines for Human research.

Randomization: To guarantee that each group had an equivalent number of subjects, block randomization was used. Through the use of sealed opaque envelope procedures, participants were assigned at random to either Group A, B, or C. After being randomly assigned, no subjects were dropped out.

Assessment Tools & Procedures: Evaluations were done pre-therapy, 2, and 4 weeks post-therapy. The BWAT was used to assess ulcer status. It contains 13 items that assess ulcer size, depth, edges, undermining, type and amount of necrotic tissue, exudate type and amount, surrounding skin color, peripheral tissue edema and induration, granulation tissue, and epithelialization. For each, a score of 1 indicates the healthiest and 5 indicates the most unhealthy (15). The imitoMeasure application, a smartphone application that is utilized to measure surface area through taken photographs, was used to measure ulcer surface area (16).

Treatment Procedures:

Seventy-two patients were allocated equally in groups A, B, and C. Patients in Group A received chitosan gel with sham therapeutic ultrasound, patients in Group B received chitosan phonophoresis, and patients in Group C received

therapeutic ultrasound only. The subjects in all groups received wound care in addition to the previously-mentioned interventions.

For all groups, therapeutic ultrasound was used on a rate of 3 sessions per week. According to the study of Byl et al. (17), the following parameters of therapeutic ultrasound were selected: Pulsed mode, 20% duty cycle, 1 MHz for frequency, 0.5 W/cm^2 for intensity. The intensity was kept at zero for Group A. The time of application was calculated for each ulcer depending on the formula that was introduced by Watson & Young (18).

For Group A and B, chitosan gel was used. Escárcega-Galaz et al. found that a 2% concentration of chitosan gel was optimal. This was accomplished by adding two grams of chitosan to one hundred milliliters of one percent acetic acid and the mixture was stirred for twelve hours (9). Chitosan gel was prepared by Chitosan Egypt Company. After cleaning the ulcer with normal saline, chitosan gel was applied to the ulcer bed. As introduced by Klucinec et al., the next procedure was followed. A sterile hydrogel sheet was placed over the ultrasound transducer head to provide acoustic coupling and maintain aseptic contact during treatment (19). The ultrasound transducer head was moved perpendicularly and continuously in a slow and controlled circular motion with overlapping circles throughout the treatment area to ensure uniform delivery of ultrasound energy (20).

The same was done for Group C but without using chitosan gel. After finishing, the following wound care was introduced.

Wound care:

Wound care was performed during each treatment session by cleansing the wound using normal saline and sterile cotton. The wound was then covered with a sterile adhesive dressing at the end of the session. Patients were instructed to repeat the same wound care procedure daily at home to maintain wound cleanliness and promote optimal healing (21).

Surgical wound management:

Whenever necrotic tissue or adherent non-viable tissue was present, surgical debridement was performed by the surgeon using a scalpel blade or curette until healthy viable tissue was reached. The wound was subsequently irrigated with normal saline and disinfected using 7.5% povidone-iodine scrub solution and 20% hydrogen peroxide. Dressing selection was based on wound exudate; a spongy dressing was applied for wounds with significant exudate, whereas a standard sterile dressing was used for wounds with minimal or no exudate (21, 22).

Data analysis and statistical design:

The results were presented as mean $\pm$ standard deviation. Subjects' characteristics across the three groups were compared using the ANOVA, while gender distribution was determined using the chi-square test. To check the normal distribution of the data, the Shapiro-Wilk test was used. For the purpose of comparing within and between effects of the groups on the outcome measures, repeated measures MANOVA was used. The data was analyzed using the Statistical Package for the Social Sciences (version 20 for Windows; SPSS Inc., Chicago, Illinois, USA). Significance

was determined when the p-value was below or equivalent to 0.05.

RESULTS

The participants' flow is demonstrated in Figure (1) regarding CONSORT 2025 (23).

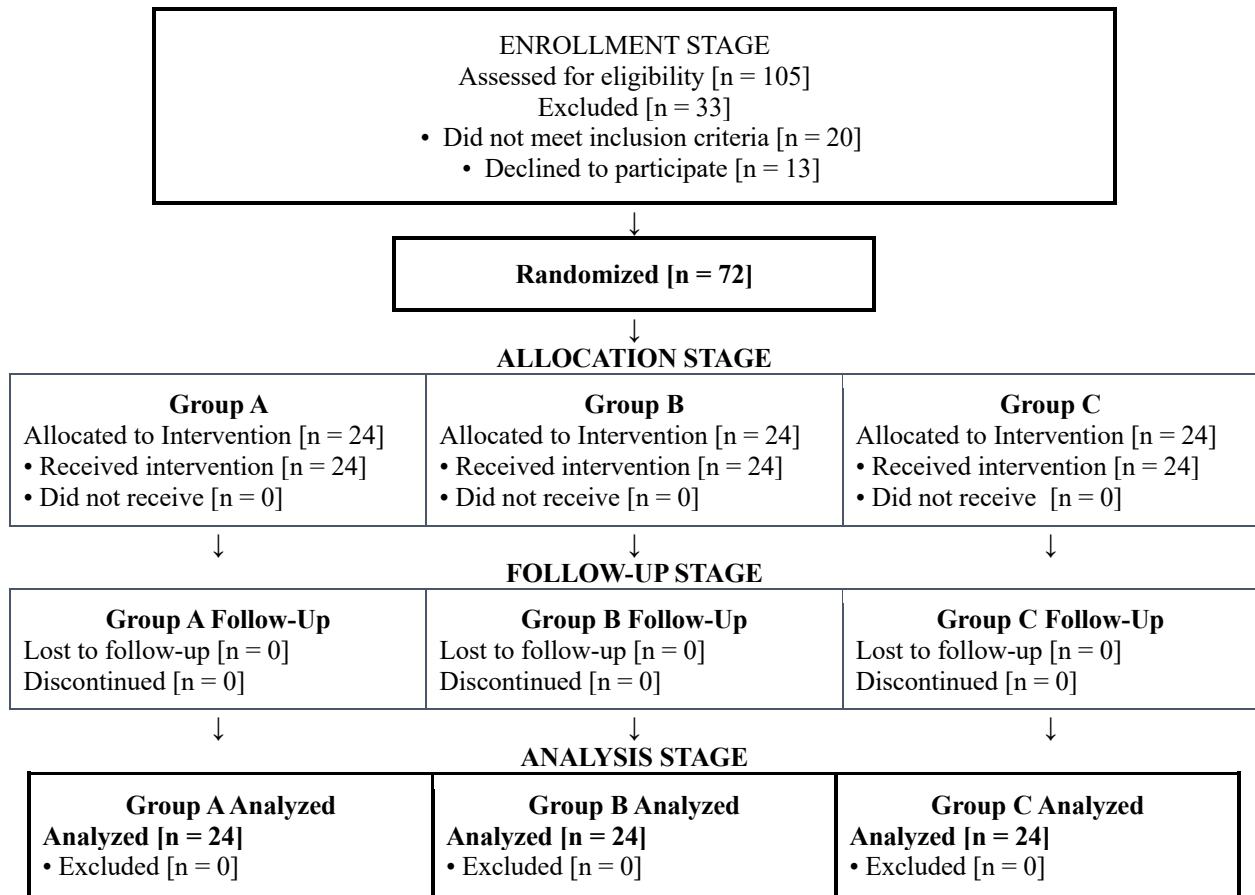


Figure (1): Participants flow in the study.

General characteristics of the subjects:

As revealed in table (1), means of the three groups' ages, weights, heights, and Body Mass Indexes (BMI) did not vary significantly ($p > 0.05$). There was also no statistical significant difference between the three groups in the sex distribution ($p = 0.485$).

Table 1. General characteristics of subjects of three groups.

Subject characteristic	Group A (n=24)	Group B (n=24)	Group C (n=24)	f-value	p-value
Age (years)	62 ± 5.64	61.54 ± 5.35	61.5 ± 5.25	0.063	0.939
Weight (kg)	69.92 ± 9.6	73 ± 8.55	75.5 ± 8.86	2.31	0.107
Height (cm)	160.71 ± 8.2	162.96 ± 7.72	164.29 ± 8.22	1.17	0.317
BMI (kg/m²)	26.77 ± 2.6	27.4 ± 2.59	27.88 ± 2.15	1.24	0.296
Sex distribution	Number (%)	Number (%)	Number (%)	Chi square =1.45	0.485
Males	10 (42%)	11 (46%)	14 (58%)		
Females	14 (58%)	13 (54%)	10 (42%)		

Data was expressed as mean ± standard deviation

Normality test:

We checked the data for outliers, homogeneity of variance, as well as the assumption of normality. All of the outcome measures were found to be normally distributed, according to the Shapiro-Wilk test.

Overall effect of treatment on the outcome measures:

The impact of therapy on the outcome measures was examined using repeated measures MANOVA. There was a statistical significant: interaction effect of (treatment *

time); effect of time; and effect of treatment, all with a p-value of less than 0.001.

Ulcer status:

Within group comparisons:

As observed in table (2), a statistical significant differences was detected in mean values of ulcer status in Groups A, B and C between the three measures ($p = 0.001$). Post hoc test revealed that, there a was statistical significant decrease following 2 weeks than baseline, following 4 weeks than baseline, and following 4 weeks than following 2 weeks in the three groups ($p=0.001$).

Comparison between groups:

No significant difference was detected in the mean values of ulcer status at baseline and following 2 weeks among the

3 groups ($p = 0.070$ and 0.070) respectively. However, a statistical significant difference was seen among the 3 groups after 4 weeks ($p = 0.001$). Post hoc tests, through pairwise multiple comparisons after 4 weeks, indicated that, there was a statistical significant difference between Groups A and B ($P = 0.041$) favoring group B, between Groups A and C ($p=0.030$) favoring group A, and between Groups B and C ($p=0.001$) favoring group B (Table 2).

Table (2): Comparison of mean values of ulcer status between the baseline, after 2 weeks and after 4 weeks between and within groups.

ulcer status	Group A	Group B	Group C	P value	η ²
Baseline	38.16 ± 3.94	39.46 ± 5.58	41.58 ± 5.88	0.070	0.071
After 2 weeks	29.24 ± 3.65	30.12 ± 5.13	32.46 ± 5.94	0.070	0.103
After 4weeks	20.2 ± 3.23	17.03 ± 2.78	23.52 ± 6.39	0.001*	0.227
(P-value)	0.001*	0.001*	0.001*		
Between group comparisons					
After 4 weeks	Group A versus B		Group A versus C		Group B versus C
MD (95% CI)	3.17 (0.1, 6.25)		-3.32 (-6.39, -0.24)		-6.49 (-9.57, -3.42)
p-value	0.041*		0.030*		0.001*
Between measures comparisons in each group					
	Baseline versus after 2 weeks		Baseline versus after 4 weeks		After 2 weeks versus after 4 weeks
	MD (p-value)		MD (95% CI), (p-value)		MD (95% CI), (p-value)
Group A	8.92 (0.001*)		17.96 (0.001*)		9.04 (0.001*)
Group B	9.34 (0.001*)		22.43 (0.001*)		13.09 (0.001*)
Group C	9.12 (0.001*)		18.06 (0.001*)		8.94 (0.001*)

Data is represented as mean $\pm$ SD, *: significant, η^2 : partial eta square, MD: Mean Difference, CI: Confidence Interval

Ulcer surface area:

Within group comparisons:

As observed in table (3), a statistical significant difference was detected in mean values of ulcer surface area in Groups A, B and C between the three measures ($p = 0.001$). Post hoc test revealed that, there was a statistical significant decrease following 2 weeks than baseline, following 4 weeks than baseline, and following 4 weeks than following 2 weeks in the three groups ($p=0.001$).

Comparison between groups:

No significant difference was observed in the mean values of ulcer surface area at baseline and following 2 weeks between the 3 groups ($p = 0.104$ and 0.072) respectively. However, a statistical significant difference was seen among the 3 groups after 4 weeks ($p = 0.001$). Post hoc tests, through pairwise multiple comparisons after 4 weeks, revealed that, there was a statistical significant difference between Groups A and B ($p=0.015$) favoring group B, between Groups A and C ($P = 0.001$) favoring group A, and between Groups B and C ($p=0.001$) favoring group B (Table 3).

Table (3): Comparison of mean values of ulcer surface area between the baseline, after 2 weeks and after 4 weeks between and within groups.

Ulcer surface area	Group A	Group B	Group C	P value	η^2
Baseline	9.63 $\pm$ 1.88	10.51 $\pm$ 1.34	10.28 $\pm$ 1.14	0.104	0.061
After 2 weeks	6.66 $\pm$ 1.46	7.37 $\pm$ 1.83	7.7 $\pm$ 1.49	0.072	0.070
After 4weeks	2.08 $\pm$ 0.73	1.34 $\pm$ 0.17	3.54 $\pm$ 1.36	0.001*	0.519
(P-value)	0.001*	0.001*	0.001*		
Between group comparisons					
After 4 weeks	Group A versus B		Group A versus C		Group B versus C
MD (95% CI)	0.74 (0.11, 1.36)		-1.46 (-2.09, -0.84)		-2.2 (-2.82, -1.58)
p-value	0.015*		0.001*		0.001*
Between measures comparisons in each group					
	Baseline versus after 2 weeks		Baseline versus after 4 weeks		After 2 weeks versus after 4 weeks
	MD (p-value)		MD (95% CI), (p-value)		MD (95% CI), (p-value)
Group A	2.97 (0.001*)		7.55 (0.001*)		4.58 (0.001*)
Group B	3.14 (0.001*)		9.16 (0.001*)		6.02 (0.001*)

Group C	2.58 (0.001*)	6.74 (0.001*)	4.16 (0.001*)
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Data is represented as mean $\pm$ SD, *: significant, η^2 : partial eta square, MD: Mean Difference, CI: Confidence Interval

DISCUSSION

Diabetic ulcers represent chronic wounds with impaired healing capacity that occur in individuals with DM. Prolonged hyperglycemia contributes to delayed wound repair by disrupting normal healing mechanisms and reducing resistance to infection (3).

The DFU is a devastating and severe complication of uncontrolled and chronic DM. At least 15% of those with DM will experience DFU at some point of their life. Reducing morbidity, decreasing amputations, and preventing death from DFU may be achieved via the use of both conventional local and invasive therapy in addition to innovative techniques (24).

This study was carried out to examine the impact of chitosan phonophoresis on chronic diabetic ulcer healing in terms of ulcer status, assessed by BWAT; and ulcer surface area, measured by imitoMeasure application.

The results of this conducted study revealed that therapeutic ultrasound alone; chitosan alone; and chitosan phonophoresis, each of them improved chronic diabetic ulcer healing over the treatment period. However, after 2 weeks of therapy, no considerable differences could be noticed between their effects; after 4 weeks of therapy, chitosan phonophoresis showed superiority over each of them and chitosan alone showed more effectiveness than therapeutic ultrasound alone.

Therapeutic ultrasound is known to improve wound healing by the ability of its energy to increase cell membrane permeability and improve local microcirculation. Additionally, the mechanical effects of ultrasound, including acoustic streaming and cavitation, may stimulate fibroblast activity, collagen formation, in addition to angiogenesis that are essential phases of tissue repair (25).

The unique properties of chitosan, such as its antibacterial activity, biodegradability, attraction to biomolecules, along with biocompatibility, provide an understanding of why it is so helpful in enhancing wound healing. This natural polymer exhibits excellent healing capabilities by reducing inflammation, preventing infections, and accelerating the development of new skin cells (7).

The higher efficacy of chitosan alone over therapeutic ultrasound alone in improving chronic diabetic ulcer healing in this study can be attributed to the following factors; First, therapeutic ultrasound seems to be more promising in acute rather than chronic wound healing as chronic wounds are generally more resistant to therapeutic modalities due to their nature of prolonged inflammation, impaired cellular response, and delayed tissue regeneration. Second, therapeutic ultrasound is known to be more effective in chronic wound healing when applied as low-intensity, low-frequency ultrasound, typically in the range of approximately 20–40 kHz. Unlike a high-frequency therapeutic ultrasound (1–3 MHz), which is less commonly associated with enhanced cellular activity required for chronic wound repair (26, 27). So the previously mentioned well-documented biological properties of chitosan may provide a more suitable environment for chronic wound

healing compared with the therapeutic ultrasound used in this study.

In the current study, chitosan phonophoresis showed an efficacy in improving chronic diabetic ulcer healing and with a superiority over chitosan or therapeutic ultrasound when applied individually. This could be attributed to the advantage of phonophoresis in enhancing the transdermal delivery of pharmacological agents through the skin (25). Additionally, this could be interpreted by the synergistic interaction between chitosan and ultrasound, where each contributes through distinct but complementary mechanisms. Chitosan provides a bioactive scaffold with antimicrobial, anti-inflammatory, and regenerative properties that enhance cellular proliferation and tissue repair (7). Ultrasound contributes by promoting tissue activity, improving local circulation, and increasing skin permeability, thereby facilitating enhanced delivery of therapeutic agents. So when combined in phonophoresis, these effects are amplified, resulting in a potential adjunct modality in managing chronic wounds by accelerating the inflammatory resolution phase, improving drug penetration, enhancing local bioavailability, and facilitating tissue regeneration (25).

The superiority of chitosan phonophoresis has been supported by other studies, however applied on different conditions like studies of Azab et al. (28) on knee osteoarthritis, ElGendy et al. (29) on cubital tunnel syndrome, ElGendy et al. (30) on lateral epicondylitis, and ElGendy et al. (31) on carpal tunnel syndrome.

The present study revealed that the superiority of chitosan phonophoresis is observed after 4 but not 2 weeks of therapy indicating a time-dependent nature of the technique. This phenomenon has been also reported by other studies, however using other active substances in phonophoresis with other chronic conditions. Abed et al. (32) reported that metformin phonophoresis showed more pronounced effects in chronic knee osteoarthritis after longer treatment periods. Also, Kim and Kaminski (33) found that studies supported the use of phonophoresis for the management of chronic injuries for around three weeks of treatment. Additionally, Kozanoglu et al. (34) concluded that ibuprofen phonophoresis had no superiority on the measured outcomes in knee osteoarthritis when applied only for 2 weeks.

As in the present study, phonophoresis has been supported for its superiority in improving chronic ulcer healing, however used with other pharmacological agents like in the study of Elmlegly et al (35) which supported the superiority of hyaluronic acid phonophoresis in venous ulcers healing and the study of Elmetwally et al. (36) which concluded that platelet-rich plasma gel phonophoresis was more effective in treating chronic DFU.

Limitations: It is important to clarify that the current study might be limited by the lack of longer follow-up after treatment so further studies are recommended to examine the long-term impacts of chitosan phonophoresis on chronic diabetic ulcer healing.

CONCLUSION

Four weeks of chitosan phonophoresis application has a superior effect in improving chronic diabetic ulcer status and reducing its surface area over than chitosan or therapeutic ultrasound alone.

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