



# Impact of Different Therapeutic Modalities on Healing of Diabetic Foot Ulcers

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## ABSTRACT

Diabetic patients are particularly burdened by foot ulcer as about 2.5% of patients with diabetes will develop a foot ulcer each year leads to lower extremity amputation by 15-40 times in diabetics greater than the rate in patients without diabetes mellitus. The aim of this study was to determine which therapeutic method out from hyperbaric oxygen therapy (HBO); laser and ultrasound, in addition to medical treatment obtain the best improvement in healing rate of foot ulcers in diabetic patients. Forty- five non-insulin dependent diabetic patients of both sexes complicated with foot ulcer grade II. Their age ranged from 35 to 50 years. were included into 3 equal groups ; Group (A) received laser therapy, group (B) received HBO and group (C) received the pulsed ultrasound therapy in addition to medical treatment. Measurements of ulcer surface area and volume for all patients in the three groups were done before treatment and after two months at the treatment program. There was a statistically significant difference between mean levels of the investigated parameters in laser therapy group and HBO group and HBO group & pulsed ultrasound therapy group after treatment. Where there was no significant difference between laser therapy group & pulsed ultrasound therapy group ( $p>0.05$ ). It is recommended to use HBO in addition to medical treatment to accelerate healing rate of foot ulcers in diabetic patients.

**Key words:** Hyperbaric oxygen (HBO) therapy, laser, ultrasound, diabetic foot ulcer.

## Diyabetik Ayak Ülser Tedavisinde Farklı Tedavi Şekillerinin Etkisi

### ÖZET

Diyabetik hastalarda yılda % 2.5 oranında ayak ülseri gelişir ve bunun sonucunda da diyabetik olmayanlara göre diyabetli hastalarda 15-40 kat daha fazla alt ekstremitte amputasyonu gerekir. Bu çalışmanın amacı, hiperbarik oksijen tedavisi (HBO), lazer ve ultrason tedavilerinin hangisinin medikal tedaviye eklenmesinin en iyi ayak ülseri iyileşme oranını sağlayacağını belirlemektir. Ayak ülseri grade II ile komplike her iki cinsten kırk beş insüline bağımlı olmayan diyabet hastası alındı. Yaşları 35 ila 50 yıl arasında değişmekteydi ve üç eşit gruba dahil edildiler; (A) grubu lazer tedavisi aldı, (B) grubu HBO ve grup (C) tıbbi tedaviye ek olarak darbeli ultrason tedavisi aldı. Ülser yüzey alanı ve hacmi her üç grupta tedavi öncesi ve 2 ay sonrasında değerlendirildi. Tedaviden sonra lazer tedavisi grubu ve HBO grubu ve ayrıca HBO grubu ile darbeli ultrason tedavi grubunda incelenen parametrelerin ortalama değerleri arasında istatistiksel olarak anlamlı bir fark saptandı. Lazer tedavisi grubu ve darbeli ultrason terapi grubu ( $p >0.05$ ) arasında anlamlı bir fark yoktu. Diyabetik hastaların ayak ülserlerinin iyileşme hızını artırmak için, tıbbi tedaviye ilave olarak HBO kullanılması tavsiye edilir.

**Anahtar Kelimeler:** Hiperbarik oksijen tedavisi, lazer, ultrason, diyabetik ayak ülseri

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## INTRODUCTION

World Health Organization stated that about 347 million people suffer from diabetes worldwide and effective diabetes disease management now represents one of the single greatest pressures on healthcare systems (1). In 2012, treating diabetes cost the American healthcare system an estimated ulcer diabetic foot 245 billion, representing 20% of the total healthcare expenditure (2). The cost of diabetic foot ulcer treatment consumes 25-50% of the total cost of diabetes treatment (3). Approximately 15% of diabetic patients develop a foot ulcer during their lifetime, and 20% of these ulcers result in lower extremity amputation. A large majority (84%) of lower extremity amputations in diabetic patients are preceded by a foot ulcer (4). Diabetic foot ulcers appear to be due to abnormal pressure distribution secondary to diabetic neuropathy, vascular disease with diminished blood supply contributes to the development of the ulcers and infections are common often with multiple organisms (5).

Ultrasound can improve tissue repair by increasing protein synthesis, mast cell degranulation and growth factor production, uptake of calcium and fibroblast mobility. Also, Low-level laser therapy is a safe and effective method for treatment of diabetic foot ulcers (6). Hyperbaric oxygen therapy (HBO) is defined as a treatment in which patients breathe 100% oxygen intermittently under a pressure of greater than sea level or one atmosphere. HBO for venous ulcers could improve healing at six weeks (7). Hyperbaric oxygen (HBO) therapy has been used as an adjunct in the management of chronic diabetic wounds. In spite of the increasing evidence supporting its use and its cost-effectiveness (8), there is still a lack of awareness about its benefits (9). Access to HBO2 therapy remains limited by the lack of facilities offering this treatment (10). The aim of this study was to determine the best therapeutic

modality out ultrasound, low intensity laser therapy and HBO which can accelerate the healing rate in diabetic patients with foot ulcers.

## MATERIAL AND METHODS

### Subjects

Forty-five non-insulin dependent diabetic patients of both sexes with grade II foot ulcer according to Wagner classification (11), their age ranged between 35-50 years, free from renal failure, myocardial infarction, cardiac, respiratory problems or ulcer rather than diabetes and included into 3 equal groups; group (A) received laser therapy; group (B) received HBO and group (C) received the pulsed ultrasound therapy in addition to medical treatment. Informed consent was obtained from all participants. All participants were free to withdraw from the study at any time. If any adverse effects had occurred, the experiment would have been stopped. However, no adverse effects occurred, and so the data of all the participants were available for analysis. Ethical approval for this study has been obtained by the Scientific Research Ethical Committee, Faculty of Applied Medical Sciences at King Abdulaziz University, Saudi Arabia.

### Methods

#### Evaluated parameters

**Foot Ulcer Surface Area:** Sterilized transparency will be placed directly over the ulcer, and ulcer area was traced with a fine tipped indelible pen. Three tracing of each ulcer was made by the same investigator to establish measurement reliability. Then the traced transparency film was placed over carbon paper with a white paper in between and transcribed the tracing onto metric of graph paper. To calculate surface area the numbers of

**Table 1.** Mean value of demographic and clinical data for participants in the three groups before treatment

	Hyperbaric oxygen therapy group	Laser therapy group	Ultrasound therapy group	p value
Age (year)	48.91±6.15	47.45±6.32	49.67±7.13	> 0.05
Weight (kg)	82.76±7.42	84.83±6.69	85.54±8.03	> 0.05
Height (cm)	173.23±7.01	172.88±7.01	175.40±5.23	> 0.05
BMI (kg/m <sup>2</sup> )	28.97±2.65	29.14±2.51	28.51±2.34	> 0.05
HBA1c (%)	7.56 ± 1.35	7.86 ± 1.74	7.79 ± 1.63	> 0.05
CRP (mg/l)	8.12 ± 1.19	7.81 ± 1.26	8.15 ± 1.14	> 0.05
Initial ulcer area (mm <sup>2</sup> )	2819.24 ± 583.16	2727.13± 636.52	2868.32± 591.27	> 0.05

HBA1c: Glycosylated Hemoglobin; BMI: Body Mass Index; CRP: C-reactive protein.

**Table 2.** Analysis of variance of ulcer surface area before treatment in the three groups.

	Source of variation	Sum of squares	Degree of freedom mean of squares	F-ratio	p value
Between groups	0.837	2	0.418	2.79	> 0.05
Within groups	6.303	42	0.150		
Total	7.14	44			

mm<sup>2</sup> within the wounds tracing were accounted (12).

**Foot Ulcer Volume Measurement:** Patient was seated in a position according to the site of ulcer allowing complete filling of the ulcer. A 5 cm<sup>2</sup> syringes with removal needle was filled with normal saline (13). The ulcer was injected with saline to measure ulcer volume (14).

**Low intensity laser therapy:** The patients were in a comfortable position on an adjustable height bed, and the ulcered leg was putted on a pillow and covered with sterile towels. The patient and the operator used the protective eye glasses using a long arm goniometer; laser cylinder was adjusted to be perpendicular to the ulcer. Frequency of He-Ne scanning type of laser (Asa, Australia) was used, its frequency was 50-60 Hz and ulcers were treated for 20 min at intensity of 4 J/cm<sup>2</sup>. After application of laser the ulcer was covered with sterile gauze. Patient received three sessions every week for two months.

**Ultrasound treatment:** The ultrasonic therapy (Sonosan 100) was applied to the intact skin surrounding the wound using coupling gel for contact for 5 minutes 3 times per week, for a total period of two months, treatment was delivered at a frequency of 3 MHZ, at spatial average intensity of 0.5 w/ cm<sup>2</sup> and the pulse ratio was set at 1:5. The ultrasound head was cleaned with alcohol to avoid any infection transmitted to the patient

**Hyperbaric oxygen therapy:** The patients seated comfortably in air pressured chamber (Multiplace decompression chamber, ATC, USA), and breathe oxygen through a face mask within the chamber for 90 min at 2.5 absolute temperature air (ATA). Treatment was applied 5 days per week for 8 weeks.

### Statistical analysis

The mean values of ulcer surface area and volume were measured before treatment and after two months at the end of the study for the three groups, then the analysis of variance was used for comparison between groups (p<0.05).

### RESULTS

Forty- five non-insulin dependent elderly diabetic patients of both sexes complicated with foot ulcer grade II. Their age ranged from 35 to 50 years. were included into 3 equal groups ; Group (A) received laser therapy, group (B) received HBO and group (C) received the pulsed ultrasound therapy in addition to medical treatment. Measurements of ulcer surface area and volume for all patients in the three groups were done before treatment and after two months at the treatment program. The three groups were considered homogeneous regarding the demographic and clinical variables (Table 1).

Analysis of variance of ulcer surface area and ulcer volume in the three groups before treatment had a no statistical significant improvement , "F" value was 2.79, p<0.05 (F 0.05 = 3.23) and "F" value was 0.953, p<0.05 (F 0.05 = 3.23) respectively (Table 2,3). The was a significant differences in the final ulcer area between the three groups after treatment (Table 4). However, analysis of variance of ulcer surface area in the three groups after treatment had a statistical significant improvement, "F" value was 28, p<0.05 (F 0.05 = 3.23) (Table 5).The least significant difference of ulcer surface area after treatment between HBO group and laser group and HBO group

**Table 3.** Analysis of variance of ulcer volume before treatment in the three groups.

	Source of variation	Sum of squares	Degree of freedom mean of squares	F-ratio	p value
Between Groups	0.204	2	0.102	0.953	>0.05
Within Groups	4.96	42	0.107		
Total	4.7	44			

**Table 4.** Mean value of clinical data for participants in the three groups after treatment

	Hyperbaric oxygen therapy group	Laser therapy group	Ultrasound therapy group	p value
BMI (kg/m <sup>2</sup> )	29.12±2.73	29.24± 2.55	28.65±2.41	>0.05
HBA1c (%)	7.61±1.38	7.87 ± 1.69	7.83±1.61	>0.05
CRP (mg/L)	8.25±1.16	7.93 ± 1.18	8.21±1.21	>0.05
Final ulcer area (mm <sup>2</sup> )	1134.64±368.27	2142.41 ± 413.35	2318.15±431.41	<0.05

HBA1c: Glycosylated Hemoglobin; BMI: Body Mass Index; CRP: C-reactive protein.

& ultrasound therapy group was statistical significant difference, but between laser group & ultrasound therapy group wasn't statistical significant difference (table 6 and figure 1). Analysis of variance of ulcer volume in the three groups after treatment had a statistical significant improvement, "F" value was 25, P < 0.05 (F0.05 = 3.23) (table 7). The least significant difference of ulcer volume after treatment between HBO group & laser group and HBO group & ultrasound therapy group was statistical significant difference, but between laser group & ultrasound therapy group wasn't statistical significant difference (table 8, figure 2). These results of changes in the ulcer volume and ulcer surface area proved that addition hyperbaric oxygen therapy to the clinical management of diabetic foot ulcers accelerates healing better than either addition of either laser or ultrasound therapy.

## DISCUSSION

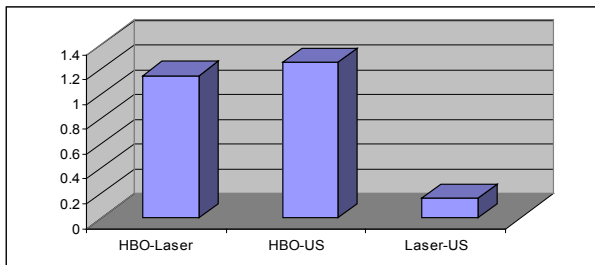
The results of this study indicated that there was a significant improvement in values of ulcer surface area and volume for all patients in the three groups after treatment. There was a statistically significant difference between mean levels of the investigated parameters in laser therapy group & HBO group and HBO group & pulsed ultrasound therapy group after treatment. Where there was no significant difference between laser therapy group & pulsed ultrasound therapy group. Helium-Neon laser can penetrate in the granulation tissue 2.5 times higher than its penetration in the normal skin which gives the advan-

tage of using He-Ne laser in treating ulceration and non-healing wounds (15). Low intensity laser therapy of 4 J/c m<sup>2</sup> increased the cell number about three to six folds compared to control cultures (16). Laser can be used for acceleration of wound healing as the biostimulation of laser accelerate the inflammatory phase of wound healing by altering the levels of various prostaglandins, increasing ATP synthesis by enhancing electron transfer in the inner membrane of the mitochondria and acceleration of collagen and fibroblasts synthesis and vascularization of the healing tissue (6).

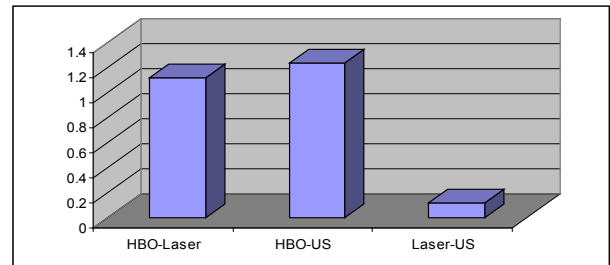
Ultrasound may work at several levels in the early stages of healing, it may decrease edema, increases blood flow, increases the delivery of oxygen & macrophages to the area, stimulates collagen deposition and remodeling (17). Ultrasound therapy increases intracellular calcium and permeability of cell membrane which lead to faster tissue healing at intensities of 0.5 to 0.75 w/c m<sup>2</sup> with pulsed frequency of 20% (18). Ultrasound therapy applied at pulsed mode, frequency 3 MHz, intensity 0.5 w/c m<sup>2</sup>, duration of 5 minutes per session and for three weeks can promote healing of diabetic foot ulcers (19). Tissue hypoxia can be a significant factor in the etiology of non-healing foot ulcers in diabetic patients. Through its correction of peripheral ischemia, HBOT may be useful in promoting healing when other modalities fail. HBOT promotes healing in a variety of ways, it promotes the formation of new vessels required for wound healing, and increases fibroblast proliferation and collagen production, its bactericidal and bacteriostatic effects on both

**Table 5.** Mean value of clinical data for participants in the three groups after treatment

Source of variation	Sum of squares	Degree of freedom	mean of squares	F-ratio	p value
Between Groups	14.04	2	7.02	28	<0.05
Within Groups	10.5	42	0.25		
Total	25.54	44			



**Figure 1.** Mean difference of ulcer surface area after treatment in the three groups.



**Figure 2.** Mean difference of ulcer surface area after treatment in the three groups.

aerobic and anaerobic bacteria (4). White blood cells that fight the infection in the ulcer use 20 times more oxygen when they are killing bacteria (5). High oxygen levels make red blood cells more flexible which enable them to get through the capillaries and get to where are needed (19). The difference in the percentage of improvement in healing rate between laser, ultrasound and HBO was high which means that HBO is faster as increased level of oxygen increased resistance to infection, decreased level of lactic acid and maintained level of ATP. HBO affected immune system and vascular tone leading to release of collagen and fibroblast and vascular growth factors by macrophages (20).

While HBO has an admirable safety record, When used in standard protocols, HBO is safe (21). However, those recommending HBO in wound care should be aware of potential side effects and complications (22). Middle ear barotrauma is the most common side effect of HBO (23). The paranasal sinuses are also a possible site of barotrauma on descent. Because of this, patients with a cold, upper respiratory tract infection or allergic rhinitis are not suitable candidates for HBO (24). Some patients receiving HBO will develop reversible myopia that may be due to oxidative change of the lens proteins (25, 26) and the amount of change in the lens is related to the dose and frequency of HBO sessions (27). After cessation of therapy, the refraction usually returns to the pretreat-

ment state within a few weeks (28). Also, HBO causes increased peripheral vascular resistance from its vasoconstrictive effects lead to decrease in heart rate, cardiac output (29) and blood flow to the left ventricle so that patients with severe congestive heart failure suffer a precipitous decline in cardiac function after receiving HBO. Because of this we generally do not accept patients with a cardiac ejection fraction of less than 35% for HBO (30). Moreover, oxygen is capable of causing grand mal seizures if breathed under pressure for a long enough period of time. , the incidence of oxygen induced seizure is quite rare, 1:10,000 dives (31). The mechanism is unclear but may be due to increased delivery of oxygen free radicals to the brain (32).

The reported adverse events of ultrasound therapy for diabetic foot ulcers included cellulitis, development of additional wounds on the index foot, pain, wound drainage, and erythema (33). While, lasers can be extremely cost effective approach as a therapy towards chronic wounds as they induce healing in a short span of time and further elude patients from coming under tremendous economical obligation which is commonly seen with surgical alternatives (34).

Hyperbaric oxygen therapy improves rate of healing of diabetic foot ulcers and had better results than laser and ultrasound.

**Table 6.** Least significance difference ulcer surface area after treatment in the three groups.

Program	statistical values		
	Mean difference±Standard deviation	L.S.D. value	p value
HBO-Laser	1.15±0.07	1.15	<0.05
HBO-US	1.26±0.05	1.26	<0.05
Laser-US	0.16±0.02	0.16	>0.05

HBO -Laser: Hyperbaric oxygen therapy versus Laser; HBO-US: Hyperbaric oxygen therapy versus Ultrasound therapy; Laser-US: Laser versus Ultrasound therapy

**Table 7.** Analysis of variance of ulcer volume after treatment in the three groups.

Source of variation	Sum of squares	Degree of freedom	mean of squares	F-ratio	p value
Between Groups	14.03	2	7.02	25	<0.05
Within Groups	11.76	42	0.28		
Total	25.79	44			

**Table 8.** Least significance difference ulcer volume after treatment in the three groups.

Program	Mean difference±Standard deviation	statistical values	
		L.S.D. value	p value
HBO-Laser	1.12±0.05	1.12	<0.05
HBO-US	1.24±0.06	1.24	<0.05
Laser-US	0.12±0.01	0.12	>0.05

HBO-Laser: Hyperbaric oxygen therapy versus Laser; HBO-US: Hyperbaric oxygen therapy versus Ultrasound therapy; Laser-US: Laser versus Ultrasound therapy

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