The Journal of Foot & Ankle Surgery 57 (2018) 1115–1119

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Efficacy of Hyperbaric Oxygen Therapy in Diabetic Foot Ulcers Based on Wagner Classification

Ahmet Erdoğan, MD[1], Arife Polat Düzgün, MD[2], Kubra Erdoğan, MD[3], Murat Bulut Özkan, MD[1], Faruk Coşkun, MD[2]

[1] *Medical Doctor, Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey*
[2] *Medical Doctor and Professor, Department of General Surgery, Ankara Numune Training and Research Hospital, Ankara, Turkey*
[3] *Medical Doctor, Department of Internal Medicine, Ankara Numune Training and Research Hospital, Ankara, Turkey*

ARTICLE INFO

Level of Clinical Evidence: 3

Keywords:
amputation
chronic wounds
diabetic foot ulcer
hyperbaric oxygen therapy
Wagner classification
wound healing

ABSTRACT

Diabetic foot ulcer is a common chronic complication of diabetes mellitus. In addition to conventional primary therapy, there are adjuvant therapy methods such as hyperbaric oxygen therapy for the healing of diabetic foot ulcer wounds. The present study aimed to determine the efficacy of hyperbaric oxygen therapy in diabetic foot ulcers based on Wagner classification. It was performed retrospectively from prospectively collected data. One hundred thirty patients with diabetic foot ulcers were assessed in 2 groups: 1 group received hyperbaric oxygen therapy; the other group did not. Patients were examined according to age, sex, ulcer grade based on Wagner classification; ulcer healing status; whether hyperbaric oxygen therapy was received; duration of diabetes in years; HbA1C, sedimentation, C-reactive protein levels; and presence of accompanying diseases, including peripheral arterial disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, neuropathy, and retinopathy. The mean follow-up period was 19.5 ± 4.45 months (range 12 to 28 months). Seventy-one (54.6%) patients received hyperbaric oxygen therapy, and 59 (45.4%) patients did not. All patients in Wagner grade 2 healed in both groups. In the group that received hyperbaric oxygen therapy for grade 3 and 4 patients, 35 (87.5%) and 11 (84.6%) healed, respectively. In total, 60 (84.5%) patients in the group that received hyperbaric oxygen therapy healed. The subgroup comparison conducted according to Wagner classification revealed no differences between the 2 groups of grades 2 and 5 patients. It also revealed that treatment had higher levels of efficacy in the healing of ulcers in grade 3 and 4 patients.

Diabetes mellitus (DM) is a chronic disease that is prevalent worldwide. As of 2013, the number of global adult DM patients was 381 million, which is estimated to reach up to 591 million by 2035 (1). Diabetic foot ulcer (DFU) is induced by peripheral neuropathy, peripheral arterial disease (PAD), and foot trauma, which are chronic complications of diabetes. Furthermore, motor and autonomous function deficits play a central role in development of DFU. It is reported that 12% to 15% of DM patients develop DFU, which accounts for 40% to 60% of nontraumatic foot amputations as the most common reason (2).

DFU is a chronic complication that has a detrimental effect on the quality of life of patients, is restrictive for patients and relatives, and places a heavy burden on society due to the high costs associated with its treatment. Therefore, the purpose, starting from the diagnosis of diabetes, should be delivery of training to patients and relatives and prevention of DFU development (3).

Although classification of DFU is important for standardization and further determination of therapy, a universally recognized classification has not yet been developed. The Wagner classification is currently one of the most commonly used classification systems, although it remains a controversial issue (4). This classification includes cases with risk factors as well and consists of grades from 0 to 5 based on presence, depth, infection status, and gangrenes of ulcer (5).

The primary requirements for DFU are cleansing of the wound, removal of necrotic tissue from the wound, examination of the wound in relation to bone, and deep tissue sampling that should be received for culture. DFU patients should be evaluated with a multidisciplinary approach; primary therapy includes debridement, daily care and dressing of the ulcer, suitable antibiotic therapy, protection of the foot from pressure, and strict glycemic control. Furthermore, hypertension (HT) and hyperlipidemia should be controlled, and tobacco smoking should be ceased (2,4).

In addition to conventional primary therapy, there are adjuvant therapy methods for wound healing in DFU. Adjuvant therapy

Financial Disclosure: None reported.
Conflict of Interest: None reported.
Address correspondence to: Ahmet Erdoğan, MD, Department of General Surgery, Ankara Numune Research and Training Hospital, Talatpaa Bulvar Altindag, 06010, Altindag, Ankara, Turkey.
E-mail address: erdogannumune@hotmail.com (A. Erdoğan).

1067-2516/$ - see front matter © 2018 by the American College of Foot and Ankle Surgeons. All rights reserved.
https://doi.org/10.1053/j.jfas.2018.05.011

alternatives reported in the literature are increasing; negative pressurized wound closure, locally applied growth factor, specific debriding wound dressings, and hyperbaric oxygen therapy (HBOT) are commonly employed methods in the present approach (6–9). The use of HBOT in nonhealing chronic wounds, particularly in DFU, has increased. The employment of HBOT in DFU is intended for increasing tissue oxygenation in wounds to eliminate tissue hypoxia, control infection with antibacterial effects, and optimize healing of wounds (7).

The aim of this study was to determine the efficacy of HBOT in DFUs based on the Wagner classification.

Patients and Methods

The study was carried out retrospectively from prospectively collected data. Scientific and ethical approval were obtained from the Ankara Numune Training and Research Hospital Scientific Research Evaluation Board (2015/985).

Patient Selection

The present study was conducted based on the file data of 166 DFU patients who received inpatient treatment in Ankara Numune Training and Research Hospital General Surgery Department Chronic Wound Treatment Center between September 2013 and January 2015. Inclusion criteria were as follows: >18 years old; Wagner grades 2, 3, 4, and 5; at least 2 weeks after local and systemic wound care; and diabetic feet. Of 166 patients, 16 were excluded due to death from various reasons during ongoing treatment, and 20 were excluded due to receiving less than 10 sessions of HBOT (range 0 to 10).

Review of the records of 130 patients included in the study revealed that foot dressings were opened, wounds were cleansed, wound samples were received for culture, wounds were photographed at the time of admission, and wounds were graded according to the Wagner classification and recorded on a computer with respective grades. Blood glucose regulation was maintained through consultation with the endocrinology or internal medicine departments.

Standard clinical treatment includes debridement, grafting or flap application, amputation as necessary, antibiotic therapy through consultation with the infectious diseases department in response to the presence of infection, and revascularization as appropriate through consultation with the cardiovascular surgery department.

In addition to standard treatment for DFU, HBOT was administered to every patient who was eligible for HBOT as adjuvant therapy in the chronic wound treatment center. Patients with known ineligibility are not referred for HBOT, but the decision of HBOT administration regarding all other patients is given through consultation with underwater and hyperbaric medicine specialists. Patients who are deemed eligible are administered HBOT for a total of 120 minutes daily under 2.4 ATM pressure at the Akyurt Hyperbaric Oxygen Therapy Center.

Before discharge, wound images of the patients were taken, and the recovery status of the wounds was evaluated according to clinical photos of the wound when patients came for outpatient clinics. The mean follow-up period was 19.5 ± 4.45 (range 12 to 28) months.

Patient Grouping

Patients were divided into 2 groups, namely those receiving and those not receiving HBOT, according to the criteria specified above. Patient ulcers were graded into 4 groups including grades 2, 3, 4, and 5 according to the Wagner classification. Patients were divided into 2 groups as those with healed and those with nonhealing ulcers at the time of discharge. The nonhealing ulcer group consisted of patients whose ulcer was not reduced in the follow-up period, as well as those with major amputations, including under and above the knee. The healed ulcer group consisted of patients whose ulcer was fully epithelized with secondary healing, closed with grafting, and healed after minor amputations, including finger, finger + metatarsal, and Chopart.

Statistical Method

Obtained data were expressed as mean ± standard deviation and assessed with IBM SPSS 21.0 software. Analyses were conducted with the chi-square test, Fisher's exact test, the Mann-Whitney *U* test, and the independent sample *t* test. Confidence interval for statistical data was 95%, and the *p* value for statistical significance was $p < .05$.

Results

One hundred thirty patients included 99 (76.2%) males and 31 (23.8%) females. Mean age of the patients was 62 years; age range was between 30 and 96 years. According to the Wagner classification, 19 (14.6%) patients had grade 2, 53 (40.8%) patients had grade 3, 47 (36.1%) patients had grade 4, and 11 (8.5%) patients had grade 5 foot ulcers. Seventy-one (54.6%) patients received HBOT, and 59 (45.4%) patients did not. Of 59 patients who were not administered HBOT, 26 were excluded from therapy through consultation with underwater and hyperbaric medicine specialists, whereas 33 patients were excluded without consultation. Six patients with claustrophobia, 9 patients with obstructive pulmonary disease, 4 patients with pulmonary embolism, 10 patients with cardiac failure, 4 patients with post-tuberculosis sequela, 7 patients with cardiac risk, 9 patients with dyspnea, and 10 patients with overall poor condition were not administered therapy.

Upon examination of the healing status of ulcers, the ulcers of 84 (64.6%) patients were healed and those of 46 (35.4%) patients were not. All patients in grade 2 according to the Wagner classification healed in both groups. As for grade 3 patients, 35 (87.5%) healed in the HBOT group, whereas 7 (53.8%) healed in the non-HBOT group; 11 (84.6%) and 12 (35.2%) of grade 4 patients healed in HBOT and non-HBOT groups, respectively. No healing was observed in both groups of grade 5 patients. In total, 60 (84.5%) HBOT group patients and 24 (40.6%) non-HBOT group patients healed.

The 2 groups that were and were not administered HBOT were compared with respect to age, sex, duration of diabetes in years, presence of PAD, presence of chronic obstructive pulmonary disease (COPD), presence of HT, presence of chronic kidney disease (CKD), presence of neuropathy, and presence of retinopathy, as well as levels of sedimentation (erythrocyte sedimentation rate [ESR]), C-reactive protein (CRP), and HbA1C, with statistical analysis by the chi-square test, the Mann-Whitney *U* test, and the independent sample *t* test. No difference was observed with respect to duration of diabetes in years ($p = .497$), HbA1C level ($p = .546$), sex ($p = .536$), presence of CKD ($p = .086$), presence of neuropathy ($p = .587$), or presence of retinopathy ($p = 0.27$), whereas age ($p = .001$), ESR ($p = .001$), CRP ($p = .047$) levels, presence of HT ($p = .002$), presence of COPD ($p = .005$), and presence of PAD ($p = .007$) differed between the 2 groups (Table 1).

Patients who were graded according to the Wagner classification were divided into 2 groups as those administered and those not administered HBOT to study the effect of HBOT on the healing of wounds. Statistical analysis was conducted with Fisher's exact test. The confidence interval for statistical data was 95%, and the *p* value for statistical significance was $p < .05$. Statistical results indicated that HBOT caused a statistically significant increase in healing of grade 3 ($p = .017$) and grade 4 ($p = .003$) ulcers, but it did not have a statistically significant effect on

Table 1
Comparison of 2 groups of patients that respectively were and were not administered hyperbaric oxygen therapy according to demographic, laboratory, and additional medical situations (N = 130)

	HBOT Administered Mean/Std. Value	HBOT Not Administered Mean/Std. Value	*p* Value
Age	58.35 ± 10.53	66.41 ± 11.17	.001
Years of diabetes	14.45 ± 8.25	16.17 ± 9.04	.497
HbA1C	8.93 ± 2.53	8.49 ± 1.61	.546
ESR	57.33 ± 30.51	76.36 ± 33.51	.001
CRP	43.73 ± 75.11	69.94 ± 69.52	.047
Sex	15 F/56 M	16 F/43 M	.536
	Present/Total(%)	Present/Total(%)	
HT	37/71(52.11%)	47/59(79.66%)	.002
COPD	1/71(1.40%)	9/59(15.25%)	.005
PAD	36/71(50.70%)	44/59(74.57%)	.007
CKD	7/71(9.85%)	13/59(22.03%)	.086
Neuropathy	64/71(90.14%)	51/59(86.44%)	.587
Retinopathy	21/71(29.57%)	23/59(38.98%)	.271

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; HBOT, hyperbaric oxygen therapy; HT, hypertension; M, male; PAD, peripheral arterial disease; Std., standard.

Table 2
Fisher's exact test analysis of healing status of wounds of patients who were graded according to the Wagner classification based on administration of hyperbaric oxygen therapy (N = 130)

			Healing Status of Ulcer			
Wagner Stage	HBOT Administration		Healed	Nonhealing	Total	*p* Value
Grade 2	Was HBOT administered?	Yes	14	0	14	–
		No	5	0	5	
	Total		19	0	19	
Grade 3	Was HBOT administered?	Yes	35	5	40	.017
		No	7	6	13	
	Total		42	11	53	
Grade 4	Was HBOT administered?	Yes	11	2	13	.003
		No	12	22	34	
	Total		23	24	47	
Grade 5	Was HBOT administered?	Yes	0	4	4	–
		No	0	7	7	
	Total		0	11	11	
Total	Was HBOT administered?	Yes	60	11	71	.001
		No	24	35	59	
	Total		84	46	130	

Abbreviation: HBOT, hyperbaric oxygen therapy.

healing of grade 2 and grade 5 ulcers, because all patients in grade 2 healed and all patients in grade 5 did not heal (Table 2).

Discussion

DM is a globally and nationally common health problem. Warning signs are present that the number of diabetic patients will further increase in the coming years. Increased diabetic patients will cause complications as well. The fact that actual treatment comprises preventive medicine and prevention of complications should be remembered.

In the present study, 130 DFU patients were evaluated to compare the efficacy of HBOT. Most patients (76%) were male, which is consistent with the literature (9,10). HBOT is in high demand by patients, patient relatives, and even physicians due to apprehension of eventual amputation and the perception that HBOT is an effective treatment method that may prevent it.

Treatment for DFU requires a multidisciplinary approach. Treatment includes training of patients, foot care, wound care, and debridement as necessary, glycemic control, revascularization, antibiotic therapy in response to the presence of infection, and, in some cases, elimination of life-threatening foot ulcers, which can result in major or minor amputation (11,12). In the present study, the mean HgA1C level of patients (8.77 ± 2.22), the determination of infection in 40.8% of patients, and the presence of PAD in 80 patients clearly revealed the requirement for a multidisciplinary therapy approach for this patient group.

Patients should be strictly administered the standard therapy formed through a multidisciplinary approach for the wounds to heal. Several adjuvant therapy methods are recommended and employed to increase the ratio and rate of healing. Topical growth factor, biotechnical biologic dressings, colony-stimulating growth factor, and HBOT may be used accordingly (13,14). Literature review reveals that the ratio of healing in 1 year is $<60\%$ despite optimal care with standard therapy (15). HBOT involves administration of 100% oxygen to patients in hyperbaric chambers with >1 ATM of pressure. HBOT has a distinctive importance when compared with other adjuvant therapies in terms of being a systemic therapy and in its practicability in any period regardless of whether the DFU is infected (16).

Additionally, HBOT is recommended over conventional therapies for several indications, including delayed radiation injury, necrotizing soft tissue infections and chronic wounds, and particularly DFU (17).

The first study demonstrating the efficacy of HBOT in healing of DFU was conducted in 1979 by Hart and Strauss (18). This study was retrospective and included only a limited number of patients. In the study, it was reported that 10 of 11 patients healed after HBOT.

The first prospective controlled study was conducted in 1987 by Baroni et al (19). Patients were divided into 2 groups. Eighteen patients with foot ulcer grades Wagner 3 and Wagner 4 were administered standard therapy and HBOT in the first group, whereas 10 patients in the second group served as the control and received only standard therapy. A statically significant difference was reported in the healing status of ulcers of patients who were administered HBOT compared with that of patients in the control group.

In their prospective study conducted to demonstrate the efficacy of HBOT on DFU, Doctor et al (20) reported that HBOT reduced the major amputation ratio with statistical significance. Furthermore, they demonstrated that propagation of *Escherichia coli* and *Pseudomonas* was reduced in wound samples collected from the group with HBOT administration.

In the study conducted by Faglia et al (21), 70 patients whose foot ulcer grades ranged between Wagner 2 and Wagner 4 were divided into 2 groups. Patients in the first group were administered standard therapy and HBOT, and patients in the second group were administered only standard therapy. They demonstrated that major amputation was reduced in the patients in the HBOT-administered group. In their study of 38 DFU patients, Kalani et al (22) reported that HBOT led to a statistically significant increase in wound healing. In a study of 18 Wagner 1 and Wagner 2 DFU patients, Abidia et al (23) divided the patients into 2 groups according to administration of HBOT or hyperbaric air therapy. They reported that the healing of wounds in the HBOT-administered group was better in a statistically significant manner by indicating the reduction of the wound surface area. In the same study, they reported that amputation ratio did not differ between the 2 groups. In the study conducted by Kessler et al (24) of 28 patients, patients whose wounds did not heal for 3 months were randomized and divided into 2 groups according to whether HBOT was administered. Upon evaluation of the wound surface of patients who were administered 20 sessions of HBOT, no statistically significant difference was observed with respect to reduction of wound surface area.

In a study conducted in our clinic, Düzgün et al (25) randomized and divided 100 patients into 2 groups based on administration of standard therapy and standard therapy + HBOT. They reported that the healing status of wounds was better in the patient group that was administered standard therapy + HBOT and that the progression of amputations to the distal metatarsophalangeal joint decreased in this group. In another study of 184 DFU patients, full healing was observed in 115 patients, and it was emphasized that HBOT may reduce the major amputation ratio (26). In the study conducted by Löndahl et al (27), DFU patients were divided into 2 groups according to administration of HBOT and hyperbaric air. After a 1-year follow-up period, it was demonstrated that the healing status of the HBOT-administered group was statistically significantly increased. No difference was observed between the 2 groups with respect to amputation ratios. In a prospective randomized study conducted by Ma et al (28), 36 patients were divided into 2 groups according to whether they were administered HBOT. In the study, the effect of HBOT on the healing status of wounds and resulting oxidative stress were evaluated. A reduction in wound diameter was observed at the end of a 2-week evaluation; however, it was reported that oxidative stress will balance this in the long term.

Other studies do not support ours. Margolis et al (29) conducted a study of 6259 patients and found that HBOT did not heal ulcers or decrease the amputation rate. In their prospective randomized study, Fedorko et al (30) reported that HBOT did not provide an additional advantage when compared with comprehensive wound care in terms of decreasing amputation indications and ensuring wound healing.

DFU is a chronic wound that is difficult to heal. Although the scientific basis for employing HBOT for these wounds is poor, Löndahl (12), in a review evaluating its broad use, emphasized the need for new studies. Stoekenbroek et al (31) reviewed 669 studies of HBOT. Although the efficacy of HBOT on DFU was demonstrated in 376 patients in the 7 studies included in the evaluation, the need for larger-scale studies with higher quality was noted. In clinical practice, administration of HBOT in the treatment of DFU may be justified.

In the patient group that presents difficulty in randomization and patient selection for prospective randomized controlled studies, it is highly challenging to determine in clinical practice which patients should receive HBOT and which should not. As it may be observed in the present study as well, 2 groups were formed because some patients were unable to receive HBOT. In cases of DFU, HBOT is administered for 120 minutes once a day under 2 to 3 ATM of pressure. Wounds are evaluated after 30 sessions, and another 30 sessions are administered if benefits are observed (32). There are also studies in the literature that evaluated the healing of wounds after 20 sessions (8). Doctor et al (20) evaluated patients after the administration of 4 sessions of HBOT; Abidia et al (23) administered 30 sessions of HBOT; Düzgün et al (25) administered 30 to 45 sessions of HBOT; and Lindahl et al (27) administered 40 sessions of HBOT. In our study, patients were administered 10 to 60 sessions of HBOT, with a mean administration of 23.70 (±12.40) sessions. In the study conducted by Akgül et al (10) of 126 DFUs, it was reported that HBOT had a poorer course in the presence of coronary artery disease, cerebrovascular disease, and retinopathy. Although surgical treatment is primarily recommended in circumstances where PAD is located above the knee, it was suggested that patients with PAD located below the knee received benefits from HBOT. In a study of 54 DFU patients with Wagner grades 3 and 4, Tongson et al (33) observed that HBOT increased the healing of wounds in a dose-dependent manner (5–10,10–20,20–30). Although efficacy, quantity of sessions, and harms of HBOT remain controversial, recent studies have compared HBOT with new methods such as extracorporeal shock wave lithotripsy and ozone therapy (8,9).

Because of the high comorbidity of DFU patients, it is particularly difficult to homogenize 2 patient groups through classification of patients based merely on ulcer. In our study, we observed no differences with respect to duration of diabetes in years, HbA1C level, sex, presence of CKD, or presence of retinopathy, whereas age, ESR and CRP levels, presence of HT, presence of COPD, and presence of PAD differed between the 2 groups. We also observed that randomization between groups to determine the effect of HBOT on healing of DFU poses a challenge. Considering that it would be impossible to equalize all systems and complications for DM, which is a systemic disease, it is more important to focus on preventive medicine, early diagnosis, and precautions intended to prevent complications of diabetic disease rather than on studies conducted on therapy alternatives and effects for wounds that are difficult to heal.

Since there are no definite results yet about the effects of HBOT on the healing of chronic wounds, particularly DFU, HBOT is being researched to determine whether it may prove useful or, in the long term, harmful. Several clinicians perceive HBOT as a last chance for ulcers that are difficult to heal, to avoid amputation, due to the insufficiency of study designs and the varying numbers of application sessions (11,28,32).

Our study had some limitations. First, it was a retrospective study, and obtained data of the 2 groups were not distributed homogeneously. Second, the number of HBOT sessions administered to the patients were not equal, which may have affected wound healing.

In conclusion, we found that in addition to standard therapies for the treatment of DFU, administration of HBOT as adjuvant therapy has proven efficacy in the healing of wounds. The subgroup comparison conducted according to the Wagner classification revealed no differences between the 2 groups of grade 2 and grade 5 patients, all of which healed or not, whereas HBOT treatment was effective in healing ulcers of grade 3 and grade 4 patients. Studies in other centers are needed to verify our results.

References

1. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014;103:137–149.
2. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, Deery HG, Embil JM, Joseph WS, Karchmer AW, Pinzur MS, Senneville E. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132–173.
3. Prompers L, Huijberts M, Schaper N, Apelqvist J, Bakker K, Edmonds M, Holstein P, Jude E, Jirkovska A, Mauricio D, Piaggesi A, Reike H, Spraul M, Van Acker K, Van Baal S, Van Merode F, Uccioli L, Urbancic V, Ragnarson Tennvall G. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia 2008;51:1826–1834.
4. Snyder RJ, Kirsner RS, Warriner RA, Lavery LA, Hanft JR, Sheehan P. Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. Ostomy Wound Manage 2010;56:1–24.
5. Wagner FW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981;2:64–122.
6. Isaac AL, Armstrong DG. Negative pressure wound therapy and other new therapies for diabetic foot ulceration: the current state of play. Med Clin North Am 2013;97:899–909.
7. Marti-Carvajal AJ, Gluud C, Nicola S, Simancas-Racines D, Reveiz L, Oliva P, Cedeno-Taborda J. Growth factors for treating diabetic foot ulcers. Cochrane Database Syst Rev 2015(10):CD008548.
8. Wang CJ, Wu RW, Yang YJ. Treatment of diabetic foot ulcers: a comparative study of extracorporeal shockwave therapy and hyperbaric oxygen therapy. Diabetes Res Clin Pract 2011;92:187–193.
9. Wainstein J, Feldbrin Z, Boaz M, Harman-Boehm I. Efficacy of ozone-oxygen therapy for the treatment of diabetic foot ulcers. Diabetes Technol Ther 2011;13:1255–1260.
10. Akgul EA, Karakaya J, Aydin S. Role of comorbidities as limiting factors to the effect of hyperbaric oxygen in diabetic foot patients: a retrospective analysis. Diabetes Ther 2014;5:535–544.
11. Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, Londahl M, Price PE, Jeffcoate WJ. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. Diabetes Metab Res Rev 2012;28(suppl 1):119–141.
12. Londahl M. Hyperbaric oxygen therapy as adjunctive treatment for diabetic foot ulcers. Int J Low Extrem Wounds 2013;12:152–157.
13. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, Lemaster JW, Mills Sr JL, Mueller MJ, Sheehan P, Wukich DK. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679–1685.
14. Jeffcoate WJ, Lipsky BA, Berendt AR, Cavanagh PR, Bus SA, Peters EJ, van Houtum WH, Valk GD, Bakker K. Unresolved issues in the management of ulcers of the foot in diabetes. Diabet Med 2008;25:1380–1389.
15. Hinchliffe RJ, Andros G, Apelqvist J, Bakker K, Friederichs S, Lammer J, Lepantalo M, Mills JL, Reekers J, Shearman CP, Valk G, Zierler RE, Schaper NC. A systematic review of the effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral arterial disease. Diabetes Metab Res Rev 2012;28(suppl 1):179–217.
16. Çimşit M. Diyabetik ayak sağaltımında hiperbarik oksijen tedavisi. In: Güncel Yönleri ile Kronik Yara. pp.85–92, edited by M Topalan, Ş Aktaş, Aygül Ofset, Ankara, Turkey. 2010.
17. Thackham JA, McElwain DL, Long RJ. The use of hyperbaric oxygen therapy to treat chronic wounds: a review. Wound Repair Regen 2008;16:321–330.
18. Hart G, Strauss M. Responses of ischemic ulcerative conditions to OHB. In: Hyperbaric Medicine, Aberdeen. pp.312–314, edited by G Smith, Aberdeen University Press, 1979.
19. Baroni G, Porro T, Faglia E, Pizzi G, Mastropasqua A, Oriani G, Pedesini G, Favales F. Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care 1987;10:81–86.
20. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. J Postgrad Med 1992;38:112–114.
21. Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, Michael M, Campagnoli P, Morabito A. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. Diabetes Care 1996;19:1338–1343.
22. Kalani M, Jorneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. J Diabetes Complications 2002;16:153–158.
23. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, Masson EA, McCollum PT. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 2003;25:513–518.

24. Kessler L, Bilbault P, Ortega F, Grasso C, Passemard R, Stephan D, Pinget M, Schneider F. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care 2003;26:2378–2382.
25. Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. J Foot Ankle Surg 2008;47:515.
26. Kaya A, Aydin F, Altay T, Karapinar L, Ozturk H, Karakuzu C. Can major amputation rates be decreased in diabetic foot ulcers with hyperbaric oxygen therapy? Int Orthop 2009;33:441–446.
27. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes Care 2010;33:998–1003.
28. Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. Ostomy Wound Manage 2013;59:18–24.
29. Margolis DJ, Gupta J, Hoffstad O, Papdopoulos M, Glick HA, Thom SR, Mitra N. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. Diabetes Care 2013;36:1961–1966.
30. Fedorko L, Bowen JM, Jones W, Oreopoulos G, Goeree R, Hopkins RB, O'Reilly DJ. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016;39:392–399.
31. Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, van den Brink A, Koelemay MJ. Hyperbaric oxygen for the treatment of diabetic foot ulcers: a systematic review. Eur J Vasc Endovasc Surg 2014;47:647–655.
32. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2012(6):CD004123.
33. Tongson L, Habawel DL, Evangelista R, Tan JL. Hyperbaric oxygen therapy as adjunctive treatment for diabetic foot ulcers. Wounds International 2013;4:8–12.