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Effect of Hyperbaric Oxygen Therapy on Diabetic Foot Ulcer; a Clinical Study

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ABSTRACT

Introduction: One of the most common diabetes complications is diabetic foot ulcer (DFU). Besides conventional treatments, hyperbaric oxygen therapy (HBOT) is known as an adjunctive therapy for DFU. This study aimed to investigate the efficacy of HBOT and possible risk factors.

Methods: This study was conducted in two hyperbaric clinics of Bahar and Khatam, respectively in Isfahan and Tehran, Iran, between September 2016 and September 2017. Eligible participants underwent 100% oxygen at 2 to 2.5 atmosphere absolute for 90 to 120 minutes daily (five days per week). Data were analyzed with SPSS version 24.0.

Results: The recovery rate was 69% in 58 enrolled patients and had a significant direct association with good glycemic control status, before (P<0.01) and during HBOT (P < 0.01), and low-grade ulcers (P= 0.04). The mean number of HBOT sessions of the cured patients (21.5±17.1) was significantly higher than that of the not cured patients (11.3 ± 7.9) (P= 0.02). However, the recovery rate had no significant association with the type of ulcer (P= 0.1).

Conclusion: HBOT had good efficacy and a high recovery rate in DFU treatment. Given the fact that good glycemic control status reduces the incidence of ulcers, this study showed that it increased the DFU recovery rate under HBOT.

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Introduction

Diabetes mellitus (DM) affects around 463 million people worldwide in 2019 and is one of the most common chronic metabolic diseases. It is estimated that the DM prevalence will rise up to 10.9%, by 2045 worldwide. Besides, a study estimated that DM prevalence may affect 5.2 million people in Iran, by 2025 (1-7). DM has multiorgan complications. The increase of the level of blood sugar (BS) raises the susceptibility to infection and ischemia occurrence, thus leads to damage in vessels and nerves. Diabetic foot ulcer (DFU) is one of the most common complications of diabetes. It is defined as a type of wound in diabetes patients, a good surface for developing infections. DFU occurs in 15% to 25% of diabetes patients during their life. Recent studies estimated the prevalence of DFU to be 6.3% worldwide and declared that it has 2% growth per year (1, 4, 8-13).

DFU has high mortality and morbidity including osteomyelitis, local infections, sepsis, amputation, and psychological disorders, and 84% of lower leg amputations are due to the progression of DFU (14, 15). A study showed that the mortality rate of diabetes patients was three times high-

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er in those with DFU (16).

Surgical and non-surgical treatments, such as maggot therapy, growth factor therapy, and hyperbaric oxygen therapy (HBOT), are used for DFU treatment. Choosing the best therapeutic method with a highly satisfactory and low adverse outcome is still a matter of debate. HBOT, as one of the safest methods, has attracted more attention recently. Some studies showed high acceptability and significant efficacy of HBOT in decreasing the number of amputations among diabetes patients (2, 3, 17-19). HBOT was introduced by Gottlieb in 1977 for the first time for treating DFU, but it is still used as an adjunctive method (4, 16, 19).

Oxygen is an indispensable part of tissue repair, and HBOT uses 100% oxygen with a pressure of two to three atmosphere absolute (ATA). HBOT can increase angiogenesis, enhance the leukocytes and stem cell functions, release the growth factors, decrease the hypoxic area and edema, and finally heal the wounds (1, 3, 18-20). Studies showed that HBOT improved DFU prognosis over long-term use (21-24). In contrast, other studies declared that HBOT could not significantly improve the healing process or decrease the amputation rate (25). A study among 28 patients with DFU reported no significant difference between the case and control groups in terms of using HBOT (26).

Note that the duration for HBOT to be effective varies in different studies, based on the type, size, and condition of the wound, and it mostly reached 40 sessions during 4 to 6 weeks (1).

As very few studies have already investigated the efficacy of HBOT among Iranian patients with DFU, this study aimed to assess the recovery rate of using HBOT for treating DFU and possible associatedriskfactors.

Methods

Study design

This was a two-center clinical study among diabetes patients with DFU from two private hyperbaric clinics of Bahar in Isfahan and Khatam in Tehran, Iran, between September 2016 and September 2017. The protocol of this study was approved by the ethics committee of Islamic Azad University, Tehran Faculty of Medicine. It was conducted in accordance with the Declaration of Helsinki (7th revision, 2013). The participants were included only after obtaining written informed consent. All information was used anonymously. This study imposed no additional costs to the patients or the healthcare system.

Study population

Diabetes patients over 18 years old who had ulceration of foot tissue associated with neuropathy and/or peripheral artery disease (27) and gave informed consent for using HBOT based on physicians' decision were enrolled in this study. Patients with a non-diabetic infected ulcer, history of seizure, claustrophobia, or untreated pneumothorax were excluded. We used a convenience sampling method. HBOT was applied using a monoplace hyperbaric oxygen chamber (Sechrist 3600H, Sechrist Industries, Inc., Anaheim, CA). The patients were treated with 100% oxygen at 2 to 2.5 ATA for 90 to 120 minutes per day, 5 days per week (from Saturday to Wednesday).

Data gathering

The patients' baseline and disease-related information was collected from their medical file, including gender, type of DM (one or two), duration of DM, type of DM treatment (oral medications, insulin therapy, or both), previous history of DFU, and grade of DFU. The grade of the ulcer was also determined for all patients based on the classic Wagner grading system (CWGS) (28).

They underwent a physical examination by a vascular surgeon, infectious disease specialist, endocrinologist, and orthopedist before and after each HBOT session, and the decision for the required HBOT sessions, antibiotic therapy, and debridement was taken by these experts.

The level of blood sugar (BS) and hemoglobin A1C (HbA1c) was measured at the beginning of the treatment and noted as initial laboratory findings. The glycemic control status was assessed before and during HBOT. The desirable and undesirable glycemic control status were defined as HbA1c < 8% and HbA1c ≥ 8%, respectively (29). The levels of BS and HbA1c were measured based on the enzymatic glucose oxidase method. The primary outcomes were defined as the glycemic control status during the treatment and the recovery of DFU (cured and not cured). Cured ulcers were defined as ulcer's grade reduction to zero, based on CWGS. Significant pain or feeling of popping in ears, pulmonary barotrauma, central nervous system toxicity, and claustrophobia after each session of HBOT were considered as adverse effects and secondary outcomes.

Finally, the frequency of different causes of no improvement (failed cure) including treatment abstinence, and not respecting the guideline, and the reasons of treatment abstinence including physicians' decision, no trust in the treatment method, high expenses of the procedure, and elongation of the procedure were assessed.

Statistical analysis

Data was analyzed by SPSS version 24 (SPSS Inc., Chicago, IL., USA). Quantitative variables

were described using mean ± standard deviation and qualitative variables were described using frequency (percent). Chi-square test, One Way ANOVA test, and independent sample T-test were applied to evaluate the association between different variables. P<0.05 was considered statistically significant.

Result

Totally, 58 patients with a mean age of 62 ± 10.5 and range of 43 to 87 years were enrolled (of whom, 43 (74.1%) were men). The mean duration of DM was 16.5 ± 10 years. The mean number of completed HBOT sessions was 18.3 ± 15.5. Forty patients (69%) were cured. The baseline information of patients is shown in Table 1. The majority of patients had type 2 DM, DFU grade two, undesirable glycemic control status before HBOT, and desirable glycemic control status during HBOT. They were mostly under insulin therapy and had a negative history of DFU. None of the patients experienced any significant adverse effects after HBOT.

Those with desirable glycemic control status before and during HBOT had a significantly higher recovery rate (P < 0.05). The recovery rate was also significantly higher in those with grade one DFU (P < 0.05). There was no significant association between the outcome and gender, history of DFU, type of treatment, and the type of DM (P > 0.05) (Table 1).

Table 1. Association between categorical variables and outcome

Variables		Total	Outcome		p-value*
			Cured (n=40)	Not cured (n=18)	
Gender	Male	43(74.1)	30(75)	13(72.2)	0.8
	Female	15 (25.9)	10(25)	5(27.8)	
Type of DM	One	12(20.7)	7(17.5)	5(27.8)	0.3
	Two	46(79.3)	33(82.5)	13(72.2)	
Type of treatment	Oral	16(27.6)	11(27.5)	5(27.8)	0.6
	Insulin	41(70.7)	28(70)	13(72.2)	
	Both	1(1.7)	1(2.5)	0	
Glycemic control status before HBOT	Desirable	24(41.4)	22(55)	2(11.1)	<0.01
	Undesirable	34(58.6)	18(45)	16(88.9)	
DFU history	Positive	17(29.3)	13(32.5)	4(22.2)	0.4
	Negative	41(70.7)	27(67.5)	14(77.8)	
Grade of DFU	1	17(29.3)	14(35)	3(16.7)	0.04
	2	26(44.8)	18(45)	8(44.4)	
	3	7(12.1)	5(12.5)	2(11.1)	
	4	8(13.8)	3(7.5)	5(27.8)	
Glycemic control status during HBOT	Desirable	51(87.9)	40(100)	11(61.1)	<0.01
	Undesirable	7(12.1)	0	7(38.9)	

Data was described as frequency (percent). DM: Diabetes Mellitus; HBOT: Hyperbaric Oxygen Therapy; DFU: Diabetic Foot Ulcer.
*p-value refers to the association between outcome and each variable.

The mean number of completed HBOT sessions in cured patients (21.4 ± 17.1) was significantly higher than in those who did not cure (11.3 ± 7.9) (P = 0.02). Even though the mean duration of DM in cured patients (16.3 ± 10.6 years) was also lower than that of not cured patients (16.9 ± 8.7 years), the difference was not significant (P = 0.822). The mean age in cured patients (62.2 ± 10.3 years) was higher than in not cured ones (61.6 ± 11.4 years), but the difference was not significant either (P = 0.838).

The studied causes of cure failure (in not cured patients), including treatment abstinence, not respecting the guideline, and multiple reasons, were observed in 12 (68.4%), 1 (5.3%), and 5 (26.3%) patients, respectively. Considering different causes of treatment abstinence, including physician's decision, no trust in the treatment method, high expenses of the procedure, elongation of the procedure, and multiple reasons were respectively reported in 5 (41.7%), 1 (8.3%), 2 (16.7%), 3 (25%), and 1 (8.3%) patients.

The mean level of initial BS was 212.5 ± 53.5 mg/dL, which was significantly lower in those who high grade of DFU had higher level of initial BS but the difference was not statistically significant (p>0.05) (Table 2).

Table 2. Association between categorical variables and outcome

Variables		Initial BS level,(mg/dL)	p-value*
Glycemic control status during HBOT	Desirable	202.2 (47.3)	<0.01
	Undesirable	287.4(33.7)	
Grade of DFU	1	193.3(56.6)	0.3
	2	216.1(52.9)	
	3	231.4(42)	
	4	224.9(55.1)	
Outcome	Cured	190.7(41.2)	<0.01
	Not cured	260.9(45.8)	

Data was described as frequency (percent). DM: Diabetes Mellitus; HBOT: Hyperbaric Oxygen Therapy; DFU: Diabetic Foot Ulcer.
*p-value refers to the association between outcome and each variable.

Discussion

DFU causes physical and psychological discomfort which needs long-term and expensive interventions. It causes multiorgan involvement and requires the simultaneous control of nutrition and glycemic status, infection, and regeneration of residual non-contaminated tissue (17, 30). In this regard, HBOT has highly been appreciated in patients with DFU as one of the modern adjuvant treatment options (31,32).

In this study, the recovery rate was high, which was significantly associated with desirable glycemic control status before and during HBOT, grade one DFU, more completed HBOT sessions, and lower initial level of BS. Consistent with our results, other studies showed that DFU was more widespread in males and the elderly. Age and prolongation of DM were associated with increased risk of neural and vascular damages that led to an aggravation of diabetes complications like cardiovascular defects, retinopathy, neuropathy, and DFU (11,16,33-35).

Baroni et al. showed a significant increase in the recovery rate of patients with DFU using HBOT (36). A systematic review of 9 studies, including 585 patients with DFU, showed that HBOT had significant high efficacy in the healing of wounds (37). Perren et al. stated that HBOT could significantly reduce the ulcer area and depth after four weeks of treatment in type two diabetes patients with new ischemic DFU (11). HBOT had also good efficacy in the healing of DFU in Poland (33).

Consistent with our findings, Ennis et al. reported a DFU recovery rate of 70.9% with HBOT among 462,888 patients (38). Londahl et al. declared that the recovery rate of DFU using HBOT was significantly higher in the case group (61%, 38 patients) compared to their control group (27%, 37 patients) (39). Kaya et al. also calculated a recovery rate of 62.5% in their patients with DFU using HBOT (32).

Failure in DFU cure mostly occurs due to a high concentration of pro-inflammatory cytokines and high level of matrix metalloproteinases at the ulcer site, which subsequently decrease growth factors, the receptors, and matrix proteins required for wound healing (33,40,41).

Contrary to our results, Kawecki et al. reported only a 27.7% recovery rate in 94 patients with ischemic and neurogenic DFU using HBOT (4).

A systematic review of 9 articles with 526 patients with DFU showed that HBOT decreased the wound size but had no significant effect on the wound healing process (25). This diversity of results could also be related to different study populations and case groups. We studied all kinds of DFU but most articles focused more specifically on ischemic and neurogenic DFU. Moreover, having more completed HBOT sessions and high-quality chambers in our study increased the recovery rate of DFU, compared to others.

Consistent with our study, Jira et al. reported a similar effective mean number of HBOT sessions for treating DFU among 80 patients, in a 10-year study (42). However, Salama et al. declared that 35 sessions of HBOT were effective for treating DFU in their 30 patients (43). Kessler et al. showed that 20 HBOT sessions had no significant effect on wound healing among 28 patients with DFU (44). The low age average, low grade of DFU, and having a well-trained team in our study helped to have a

high DFU recovery rate with minimum sessions of HBOT and without any adverse effects.

HBOT increases the oxygen pressure of local blood vessels by 15-fold and plays an important role in wound healing. Providing an oxygen-rich environment for keratinocytes, fibroblasts, epithelial cells, and leukocytes precipitates the healing process. In addition, the high oxygen pressure enhances phagocytosis by timely reducing the hypoxic area. The difference in the effective (required) number of HBOT sessions for treating DFU could also be related to the time of starting HBOT, patients' medical history, and physicians' assessment about the condition of the ulcers (2-4, 11,1, 45, 46).

Consistent with our findings, Vinkel et al. showed that HBOT could significantly decrease the grade of ulcer (16). However, Huang et al stated that only ulcers with grade three or higher could significantly benefit from HBOT (31).

Good glycemic control status is of paramount importance in treating DFU. Dhatariya et al. in a study among 629 patients stated that the good glycemic control status was positively associated with the recovery rate and inversely with the duration of DFU recovery (47).

This study examined the association between the type of DM and the recovery rate of DFU using HBOT, for the first time in Iran, and we found no significant association. Consistent with our findings, Londah et al. also showed no significant association between them (39). Erdogan et al. asserted that the recovery rate of DFU was not significantly associated with age, gender, and duration of DM among 130 patients (34). However, another study showed that the mortality rate of patients with DFU was two times more than the diabetes patients without DFU (17, 48).

Our study was conducted in two private hyperbaric clinics, and all patients had been referred to receive HBOT. Because of the study settings, we were unable to recruit a control group. It was also impractical to have a follow-up with the patients and assess the recurrence rate. The small sample size was mostly because of the high expenses of HBOT and the long duration of treatment. It is highly recommended to perform further studies with larger sample size and use modern hyperspectral imaging techniques to measure the microscopic hypoxia for early diagnosis of ischemia and inflammation, to decrease the comorbidities of DFU.

Conclusion

HBOT had good efficacy and a high recovery rate in DFU treatment. Given that good glycemic control status reduces the incidence of ulcers, this study showed that it increased the DFU recovery rate under HBOT.

References

1. Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcers: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017;17:1-142.
2. Harrison LE, Giardina C, Hightower LE, et al. Might hyperbaric oxygen therapy (HBOT) reduce renal injury in diabetic people with diabetes mellitus? From preclinical models to human metabolomics. Cell Stress Chaperones. 2018;23:1143-1152.
3. Irawan H, Semadi IN, Widiana IGR. A Pilot Study of Short-Duration Hyperbaric Oxygen Therapy to Improve HbA1c, Leukocyte, and Serum Creatinine in Patients with Diabetic Foot Ulcer Wagner 3-4. ScientificWorldJournal. 2018;2018:6425857.
4. Kawecki M, Pasek J, Cieslar G, et al. Computerized planimetry evaluation of hyperbaric oxygen therapy in the treatment of diabetic foot. Adv Clin Exp Med. 2018;27:39-44.
5. Moradi Y, Baradaran HR, Djalalinia S, et al. Complications of type 2 diabetes in Iranian population: An updated systematic review and meta-analysis. Diabetes Metab Syndr. 2019;13:2300-2312.
6. Babaniamansour S, Aliniagerdroudbari E, Niroomand M. Glycemic control and associated factors among Iranian population with type 2 diabetes mellitus: a cross-sectional study. J Diabetes Metab Disord. 2020;19:933-940.
7. Alavi SF, Abasian P, Eslami H. Synthesis and characterization of polystyrene/poly(ethyl acrylate) mushroom-like Janus particles. Polymers for Advanced Technologies. 32.2021. 1712-1726.
8. Izadi M, Kheirjou R, Mohammadpour R, et al. Efficacy of comprehensive ozone therapy in diabetic foot ulcer healing. Diabetes Metab Syndr. 2019;13:822-825.
9. Yazdanpanah L, Shahbazian H, Nazari I, et al. Incidence and Risk Factors of Diabetic Foot Ulcer: A Population-Based Diabetic Foot Cohort (ADFC Study)-Two-Year Follow-Up Study. Int J Endocrinol. 2018;2018:7631659.
10. Grigoropoulou P, Eleftheriadou I, Jude EB, et al. Diabetic Foot Infections: an Update in Diagnosis and Management. Curr Diab Rep. 2017;17:3.
11. Perren S, Gatt A, Papanas N, et al. Hyperbaric Oxygen Therapy in Ischaemic Foot Ulcers in Type 2 Diabetes: A Clinical Trial. Open Cardiovasc Med J. 2018;12:80-85.
12. Babaniamansour P, Mohammadi M, Babaniamansour, S et al. The Relation between Atherosclerosis Plaque Composition and Plaque Rupture. J Med Signals Sens. 2020;10:267-273.
13. Roshandel M, Sotudeh-Gharebagh R, Mirzakhanlouei S, et al. Statistical Optimization of Production Conditions of Polycaprolactone-Chitosan-Curcumin Particles. Journal of Chemical and Petroleum Engineering. 2018;52:181-191.
14. Hitchman LH, Totty JP, Raza A, et al. Extracorporeal Shockwave Therapy for Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis. Ann Vasc Surg. 2019;56:330-339.
15. Babaniamansour P, Ebrahimian-Hosseinabadi M, Zargar-Kharazi A. Designing an Optimized Novel Femoral Stem. J Med Signals Sens. 2017;7:170-177.
16. Vinkel J, Lohse N, Hyldegaard O. The clinical use of hyperbaric oxygen in the treatment of Danish patients with diabetic foot ulcers. Dan Med J. 2019;66:A5528.
17. Kilicoglu OI, Demirel M, Aktas S. New trends in the orthopaedic management of diabetic foot. EFORT Open Rev. 2018;3:269-277.
18. Heyboer M, Sharma D, Santiago W, et al. Hyperbaric Oxygen Therapy: Side Effects Defined and Quantified. Adv Wound Care (New Rochelle). 2017;6:210-224.
19. Howell RS, Criscitelli T, Woods JS, et al. A Perioperative Approach to Increase Limb Salvage When Treating Foot Ulcers in Patients With Diabetes. AORN J. 2018;107:431-440.
20. Babaniamansour S, Aliniagerdroudbari E, Afrakhteh M, et al. Can fasting plasma glucose replace oral glucose-tolerance test for diagnosis of gestational diabetes mellitus? Diabetology International. 2021.
21. Fagher K, Löndahl M. The impact of metabolic control and QTc prolongation on all-cause mortality in patients with type 2 diabetes and foot ulcers. Diabetologia. 2013;56:1140-1147.
22. Hayes P, Alzuhir N, Curran G, et al. Topical oxygen therapy promotes the healing of chronic diabetic foot ulcers: a pilot study. J Wound Care. 2017;26:652-660.
23. Oliveira N, Rosa P, Borges L, et al. Treatment of diabetic foot

complications with hyperbaric oxygen therapy: a retrospective experience. Foot Ankle Surg. 2014;20:140-143.
24. Driver VR, Reyzelman A, Kawalec J, et al. A Prospective, Randomized, Blinded, Controlled Trial Comparing Transdermal Continuous Oxygen Delivery to Moist Wound Therapy for the Treatment of Diabetic Foot Ulcers. Ostomy Wound Manage. 2017;63:12-28.
25. Zhao D, Luo S, Xu W, et al. Efficacy and safety of hyperbaric oxygen therapy used in patients with diabetic foot: a meta-analysis of randomized clinical trials. Clin Ther. 2017;39:2088-2094.e2.
26. Leslie CA, Sapico FL, Ginunas VJ, et al. Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. Diabetes Care. 1988;11:111-115.
27. van Netten JJ, Bus SA, Apelqvist J, et al. Definitions and criteria for diabetic foot disease. Diabetes Metab Res Rev. 2020;36:e3268.
28. Wagner FW, Jr. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle. 1981;2:64-122.
29. Glycemic Targets: Standards of Medical Care in Diabetes-2019.Diabetes Care. 2019;42:S61-S70.
30. Babaniamansour S, Hematyar M, Babaniamansour P, et al. The Prevalence of Vitamin D Deficiency Among One to Six Year Old Children of Tehran, Iran. Journal of Kermanshah University of Medical Sciences. 2019;23.
31. Huang ET, Mansouri J, Murad MH, et al. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med. 2015;42:205-247.
32. Kaya A, Aydin F, Altay T, et al. Can major amputation rates be decreased in diabetic foot ulcers with hyperbaric oxygen therapy? Int Orthop. 2009;33:441-446.
33. Glik J, Cholewka A, Englisz B, et al. Thermal imaging and planimetry evaluation of the results of chronic wounds treatment with hyperbaric oxygen therapy. Adv Clin Exp Med. 2019;28:229-236.
34. Erdogan A, Duzgun AP, Erdogan K, et al. Efficacy of Hyperbaric Oxygen Therapy in Diabetic Foot Ulcers Based on Wagner Classification. J Foot Ankle Surg. 2018;57:1115-1119.
35. Niroomand M, Babaniamansour S, Aliniagerdroudbari E, et al. Distress and depression among patients with diabetes mellitus: prevalence and associated factors: a cross-sectional study. Journal of Diabetes & Metabolic Disorders. 2021.
36. Baroni G, Porro T, Faglia E, et al. Hyperbaric oxygen in diabetic gangrene treatment. Diabetes Care. 1987;10:81-86.
37. Golledge J, Singh TP. Systematic review and meta-analysis of clinical trials examining the effect of hyperbaric oxygen therapy in people with diabetes-related lower limb ulcers. Diabet Med. 2019;36:813-826.
38. Ennis WJ, Huang ET, Gordon H. Impact of Hyperbaric Oxygen on More Advanced Wagner Grades 3 and 4 Diabetic Foot Ulcers: Matching Therapy to Specific Wound Conditions. Adv Wound Care (New Rochelle). 2018;7:397-407.
39. Londahl M, Landin-Olsson M, Katzman P. Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. Diabet Med. 2011;28:186-190.
40. Lobmann R, Zemlin C, Motzkau M, et al. Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. J Diabetes Complications.2006;20:329-335.
41. Ershadinia N, Mortazavinia N, Babaniamansour S, et al. The prevalence of autoimmune diseases in patients with multiple sclerosis: A cross-sectional study in Qom, Iran, in 2018. Current Journal of Neurology. 2020;19:98-102.
42. Jira M, El Omri N, Sekkach Y, et al. [Hyperbaric oxygen therapy in the treatment of diabetic foot: experience in the management of 80 cases at a department of internal medicine]. Pan Afr Med J. 2018;30:100.
43. Salama SE, Eldeeb AE, Elbarbary AH, et al. Adjuvant Hyperbaric Oxygen Therapy Enhances Healing of Nonischemic Diabetic Foot Ulcers Compared With Standard Wound Care Alone. Int J Low Extrem Wounds. 2019;18:75-80.
44. Kessler L, Bilbault P, Ortega F, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. Diabetes Care. 2003;26(8):2378-82
45. Fagher K, Katzman P, Londahl M. Hyperbaric oxygen therapy reduces the risk of QTc interval prolongation in patients with diabetes and hard-to-heal foot ulcers. Journal of diabetes and its complications. 2015;29(8):1198-202.
46. Jahromi S, Amani E, Movahed S. An improved hybrid continuum-atomistic four-way coupled model for electrokinetics in nanofluidics. ELECTROPHORESIS. 2019;40(12-13):1678-90.
47. Dhatariya KK, Li Ping Wah-Pun Sin E, Cheng JOS, et al. The impact of glycaemic variability on wound healing in the diabetic foot - A retrospective study of new ulcers presenting to a specialist multidisciplinary foot clinic. Diabetes research and clinical practice. 2018;135:23-9.
48. Andrews KL, Houdek MT, Kiemele LJ. Wound management of chronic diabetic foot ulcers: from the basics to regenerative medicine. Prosthetics and orthotics international. 2015;39(1):29-39