

Meta-Analysis: Effect of Hyperbaric Oxygen Therapy on Diabetic Foot Ulcer Recuperation

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ABSTRACT

Background: Diabetes mellitus (DM) is a global phenomenon due to the high morbidity and mortality, especially in developing countries such as Indonesia. An ulcer is a wound and is usually found in patients who experience increased blood sugar and can cause peripheral blood vessel disorders, blood vessel disorders will result in peripheral neuropathy or a combination of both, diabetic ulcers are a condition often experienced by diabetes sufferers. Hyperbaric Oxygen Therapy (HBOT) is a therapy that is considered effective in healing diabetic ulcers and has been proven by many studies conducted. This study aims to analyze the effect of HBO therapy on the improvement of diabetic ulcer wounds.

Subjects and Method: This was a systematic review and meta-analysis of primary studies. Article searches were carried out based on the PICO model. Population: diabetic ulcer patients. Intervention: Hyperbaric Oxygen Therapy. Comparison: placebo. Outcome: diabetic ulcers condition. Article searches were carried out from Google Scholar, MEDLINE/PubMed, Science Direct, Scopus, Hindawi, BMC, and Spinger Link databases. Keywords used "diabetic foot ulcers" AND "hyperbaric oxygen therapy". The inclusion criteria were full paper, RCT, and reporting risk ratio (RR). Selected studies were analyzed using the RevMan 5.3.

Results: 9 RCTs from China, Canada, the Netherlands, Sweden, Egypt, Taiwan, England, and Turkey were selected for meta-analysis. HBO therapy increased diabetic ulcers condition (RR= 1.91; 95% CI= 1.17 to 3.12; p= 0.01).

Conclusion: HBO therapy improves diabetic ulcers condition.

Keywords: hyperbaric oxygen, diabetic foot ulcer, meta analysis.

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BACKGROUND

Diabetes mellitus (DM) is a global phenomenon due to the high morbidity and mortality of DM, especially in developing countries such as Indonesia. This disease is a metabolic disease characterized by chronic

hyperglycemia caused by damage/deficiency in insulin secretion, damage to the response to the insulin hormone or both (IDF, 2021).

Neuropathic symptoms were observed in 28.5% of DM 6500. Damage to the peripheral circulation of the legs in DM patients

was characterized by the presence of peripheral arterial disease (PAD). Tissue ischemia that occurs as a complication of diabetic foot ulcers (UKD) is caused by delayed refilling of the refill capillaries (Arif 2020). According to Decroli (2019), hyperglycemia can cause damage to nerves by 3 mechanisms, namely metabolic effects, mechanical conditions, and compression effects of the lower limb compartment, while UKD itself is caused by decreased tissue oxygen levels and disruption of sensory and motor nerve function.

According to the International Diabetes Federation (IDF) report in 2021, 537 million adults (20-79 years) live with diabetes worldwide. This number is expected to increase to 643 million (1 in 9 adults) in 2030 and 784 million (1 in 8 adults) in 2045. Diabetes mellitus caused 6.7 million deaths in 2021. It is estimated that 44% of adults who living with undiagnosed diabetes (240 million people). 541 million adults worldwide, or 1 in 10, have impaired glucose tolerance, placing them at high risk of developing type 2 diabetes (IDF, 2021). The Ministry of Health of the Republic of Indonesia reports that the number of diabetes mellitus sufferers in 2021 will be 19.47 million people (Ministry of Health of the Republic of Indonesia, 2022). The East Java Provincial Health Service reported that the number of diabetes mellitus sufferers in East Java Province in 2021 reached 929,535 cases. Of this number, it is estimated that 867,257 sufferers (93.3%) have been diagnosed and received health services (East Java Health Office, 2022). The results of medical records obtained from 6 Community Health Centers in Mojokerto City, it was reported that the number of diabetes mellitus sufferers in Mojokerto City was 4,936 patients. For diabetes mellitus sufferers who received health services according to standards, it was reported that there were

7,021 patients (142.2%) (East Java Health Office, 2022).

An ulcer is a wound and is usually found in patients who experience increased blood sugar and can cause peripheral blood vessel disorders, blood vessel disorders will result in peripheral neuropathy or a combination of both, diabetic ulcers are a condition often experienced by diabetes sufferers (Ünal, 2018) . Meanwhile (Hinchliffe et al., 2020), said that diabetic foot ulcers can occur without signs of neuropathy, even in the presence of severe tissue loss.

Technological advances in the health sector support achieving the highest level of health. Hyperbaric oxygen (HBO) is one of the adjuvant therapy options in the treatment of UKD (Aghili, 2016). HBO is the administration of 100% oxygen where the patient is in a high-pressure room and breathes pure oxygen at an air pressure greater than normal atmospheric air, namely 1 ATA (Absolute Atmosphere). The role of HBO is to improve the amount of oxygen delivered to the wound area, both bound to hemoglobin and dissolved in plasma. Thus, the rate of wound healing is directly related to oxygen levels in the tissue (Carls, et al, 2013).

The effectiveness of HBO therapy in treating UKD has been widely documented in various health centers around the world. Based on the results of several Randomized Control Trials (RCTs) that have been conducted, HBO is recommended as an additional therapy that is immediately given to UKD sufferers, to prevent major amputations and increase wound repair (Huang et al., 2015). With a fast wound repair process, it can reduce the risk of amputation, minimize the risk of death, and reduce treatment costs for UKD patients.

This study was conducted to analyze the effect of Hyperbaric Oxygen Therapy

(HBOT) on improving Diabetic Foot Ulcer (DFU).

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis carried out using the PRISMA flow diagram. Article searches from Google Scholar, BMC, MEDLINE/PubMed, Science Direct, Scopus, Hindawi, and Springer Link. Literature search using "diabetic foot ulcers" AND "hyperbaric oxygen therapy".

2. Inclusion Criteria

The inclusion criteria were full paper, RCT, and reporting risk ratio.

3. Exclusion Criteria

The exclusion criteria were articles using language other than Indonesian or English. Articles published before 2000 also excluded.

4. Operational Definition of Variables

Hyperbaric Oxygen Therapy Hyperbaric oxygen therapy is a treatment modality in which a person breathes 100% oxygen in a chamber with increased atmospheric pressure. Diabetic Foot Ulcer Repair The wound repair process is a natural wound restoration process that involves a complex,

dynamic and integrated process in tissue due to damage.

5. Instrument

Assessment of the quality of research articles was carried out using the critical appraisal checklist tool randomized controlled trial (RCT) published by CEBM University of Oxford 2014.

6. Data Analysis

Data analysis in this research used the Review Manager application (RevMan 5.3). In this study, I² is used to quantify dispersion. The results of data analysis are in the form of effect size values, which will then be interpreted in the form of forest plots and funnel plots.

RESULTS

Research from primary studies regarding the effect of Hyperbaric Oxygen Therapy (HBOT) on improving Diabetic Foot Ulcer (DFU) contained 9 articles from 4 continents, namely 1 study from America, 3 studies from Europe, 1 study from Africa, and 3 studies from Asia.

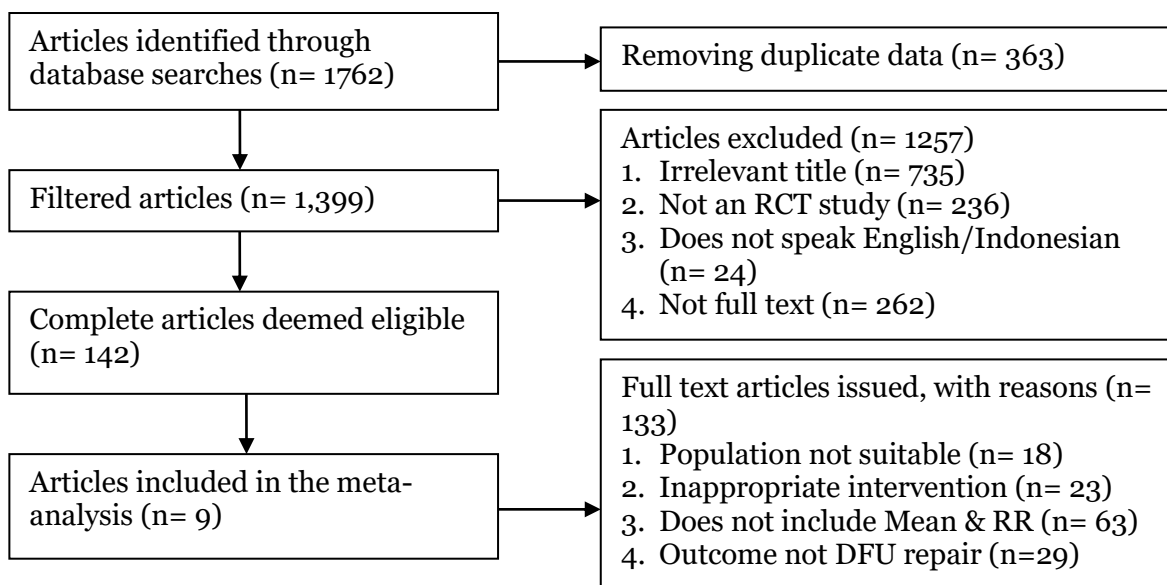


Figure 1. PRISMA flow diagram

Article searches were carried out using a database based on the PRISMA flow diagram which can be seen in Figure 1. Assessment of study quality was carried out qualitatively and quantitatively. Assessment of research quality using critical appraisal checklists tools randomized controlled trials (RCT) published by CEBM

University of Oxford 2014. In Table 1. Each of the 11 questions is answered with answer choices: if Yes, value 1 and No, value 0. After A study quality assessment was carried out, a total of 9 articles included in the meta-analysis quantitative synthesis process were analyzed using RevMan 5.3.

Table 1. Research Quality Assessment (Critical Appraisal)

Studies	Assessment Items												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Ma <i>et al.</i> , 2013	1	1	1	1	1	1	1	1	1	1	1	1	12
Ferdoko <i>et al.</i> , 2016	1	1	1	1	1	1	1	1	1	1	1	1	12
Santema <i>et al.</i> , 2017	1	1	1	1	1	1	1	1	1	1	1	1	12
Ying <i>et al.</i> , 2019	1	1	1	1	1	1	1	1	1	0	1	1	11
Londahl <i>et al.</i> , 2010	1	1	1	1	0	1	1	1	1	1	1	1	11
Salama <i>et al.</i> , 2019	1	1	1	1	1	1	1	1	1	1	1	1	12
Chen <i>et al.</i> , 2017	1	1	1	1	1	1	1	1	1	1	1	1	12
Abidia <i>et al.</i> , 2003	1	1	1	1	0	1	1	1	1	1	1	1	11
Duzgun <i>et al.</i> , 2008	1	1	1	1	0	1	1	1	1	1	1	1	11

Description of question criteria:

- 1 = Does the research address a clearly focused statement/problem?
- 2 = Is the randomized controlled trial research method appropriate for answering the research questions?
- 3 = Were there enough subjects in the study to determine that the findings did not occur by chance?
- 4 = Are subjects randomly allocated to experimental and control groups? If not, could this introduce bias?
- 5 = Are inclusion/exclusion criteria used?
- 6 = Were the two groups comparable at the start of the study?
- 7 = Are objective and unbiased outcome criteria used?
- 8 = Are objective and validated measurement methods used to measure the results? If not, were the results assessed by someone blind to group assignment (i.e. were assessments blinded)?
- 9 = Is effect size practically relevant?
- 10 = How precise is the effect estimate? Is there a confidence interval?
- 11 = Could there be confounding factors that have not been taken into account?
- 12 = Can the results be applied to your research?

Description of Answer Score:

- 0 = No
- 1 = Yes

Table 2. PICO (Population, Intervention, Comparison and Outcome) for each study

Author (year)	Country	Sample size	P	I	C	O
Ma <i>et al.</i> , 2013	China	36	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Ferdoko <i>et al.</i> , 2016	Canada	157	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Santema <i>et al.</i> , 2017	Netherlands	60	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Ying <i>et al.</i> , 2019	China	34	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Londahl <i>et al.</i> , 2010	Sweden	37	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Salama <i>et al.</i> , 2019	Egypt	15	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Chen <i>et al.</i> , 2017	Taiwan	38	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Abidia <i>et al.</i> , 2003	United Kingdom	25	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair
Duzgun <i>et al.</i> , 2008	Turkey	50	Patient of Diabetic Foot Ulcer	HBOT	Placebo	Foot Wound Repair

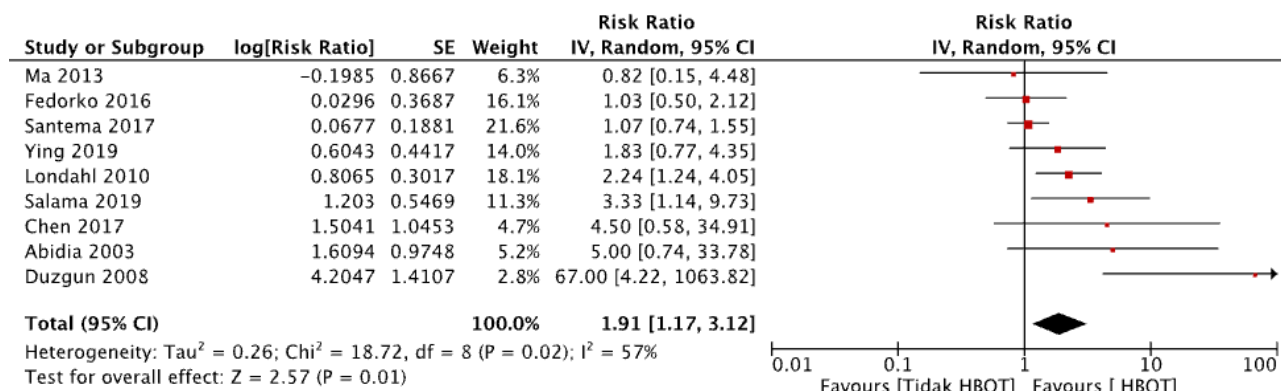


Figure 2. Forest Plot of the effect of HBO therapy on improvement of diabetic ulcers

The forest plot in Figure 2 shows that there is an influence of Hyper-baric Oxygen Therapy (HBOT) in efforts to repair Diabetic Foot Ulcer (DFU). DM patients who received HBOT had an average improvement in leg ulcers with a score of 1.91 units better than DM patients who did not receive HBOT (placebo) (RR= 1.91; 95% CI = 1.17 to 3.12; p= 0.01).

The forest plot also shows moderate heterogeneity of effect estimates (I²= 57%; p

<0.001). This moderate heterogeneity is because the research samples that were meta-analyzed experienced significant variations. This study has a varied sample size for each article, a large sample range, and there are differences in characteristics across age ranges and gender. Thus, the calculation of the average estimated effect is carried out using a random effects model approach.

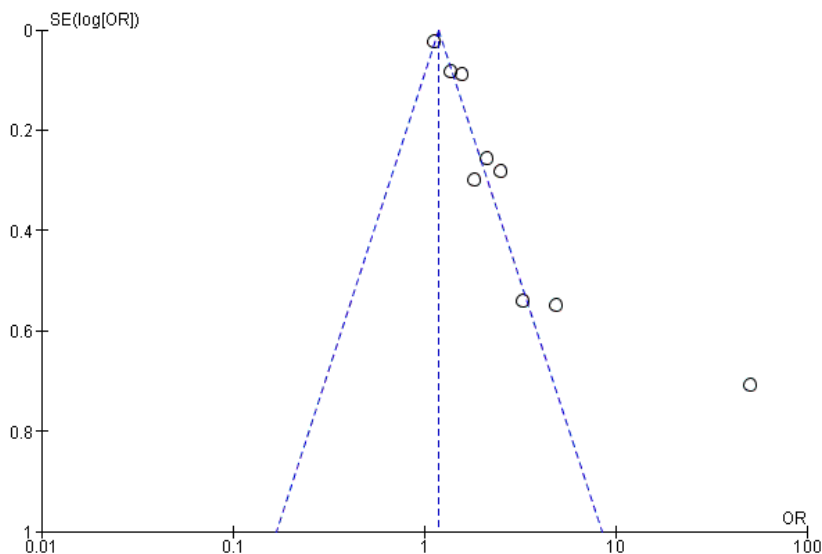


Figure 3. Funnel Plot of the effect of HBO therapy on diabetic ulcers

The funnel plot in Figure 3 shows that the distribution of estimated effects is more to the right than to the left of the vertical line of average estimates. Thus the funnel plot shows publication bias. Because the distribution of effects for primary studies with small samples in the funnel plot is to the right of the vertical line of the mean which is the same as the location of the diamond shape in the forest plot which is also to the right of the vertical line of hypothesis 0, publication bias tends to exaggerate the effect. actually (over estimate).

DISCUSSION

There are 9 randomized controlled trials as a source of meta-analysis of the effect of Hyperbaric Oxygen Therapy (HBOT) on Diabetic Foot Ulcer (DFU). There is an effect of HBOT on DFU repair which is 1.81 times better than DFU patients who did not undergo HBOT therapy, and this result is statistically significant

A study by Stoekenbroek et al. (2014) did not get the results that were in line with expectations because there were several obstacles that occurred, including the data collection process which was considered inappropriate, and in this study there were no

reports of DFU improvements, and there were also no differences. in the possibility of amputation. This research is not in line with research currently being conducted, where in this study there is an effect of HBOT in repairing DFU.

A similar study was conducted by (Zhang et al., 2022) however, in this study it was concluded that HBOT offers great benefits in repairing DFUs and reducing the risk of amputation due to DFUs. In this study, researchers focused on improving the quality of life of DFU patients by making improvements with the HBOT method.

Different from research conducted by (Sharma et al., 2021). In this study, it was explained that HBOT therapy was effective in influencing DFU repair, and research was carried out again to find out how effective the effect was. This complication of DFU usually occurs in type 2 diabetes patients. This DFU is very dangerous and poses a very strong threat of increasing the risk of amputation in patients. This will greatly contribute to reducing a person's quality of life. Foot ulcers in diabetes patients are infected by polymicrobial agents that can weaken the immune sys-

tem, and the high level of resistance or immunity to antibiotics makes the ulcers difficult or even incurable (Sharma et al., 2021).

Hyperbaric Oxygen Therapy (HBOT) is one of the therapies recommended as an effort to improve DFU disease. This therapy has the potential to improve ulcer repair, and reduce amputation rates in DFU patients, especially non-ischemic ones (Wenhui et al., 2021).

The use of HBOT therapy for DFU repair is carried out in the hope that the abnormally low tissue oxygen pressure in the wound area can be corrected. Löndahl (2013) conducted a study on HBOT therapy as an additional treatment for DFU patients. In this study, results were similar to those currently being conducted by researchers, where HBOT therapy was effective in repairing DFU.

Not all of the research discussed by the author agrees with the research being conducted, but it is explained in many articles that HBOT has a high possibility of being able to cure DFU. HBOT is carried out by placing the patient in a room filled with pure oxygen at quite high pressure. The pressure used is 1.5 times atmospheric pressure or more than 1 atm. The hope is that by receiving pure oxygen at high pressure, the body can absorb more oxygen, especially in the wound area (Rosyanti et al., 2019)

Based on the research conducted, the results showed that hyperbaric oxygen therapy (HBOT) had an effective effect on improving diabetic foot ulcers (DFU). For HBOT to continue, reevaluation at 30-day intervals must demonstrate continued progress in healing. 1 The usual treatment protocol for HBOT in diabetic wounds is HBOT given at 2.0 to 2.4 ATA for 90 minutes daily for 30 to 40 days (Shaha, 2010).

AUTHOR CONTRIBUTION

Faried Effendi Surono is the main researcher who chose the topic, explored and collected research data. Didik Gunawan Tamtomo and Rita Benya Andriani analyzed data and reviewed research documents.

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This study is self-funded.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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