

ORIGINAL RESEARCH

Effect of Ozone Therapy on Pain and Functional Status in Fibromyalgia Patients

Ozlem Kuculmez, MD

ABSTRACT

Introduction • Fibromyalgia is a musculoskeletal disease that is frequently detected in young women, includes symptoms such as fatigue, sleep disturbances, and cognitive dysfunction unrelated to pain, and negatively affects the patient's quality of daily life. Ozone therapy increases tissue oxygenation, activates antioxidant mechanisms, and may be used in patients with fibromyalgia. The aim of this study is to investigate the efficacy of ozone therapy on pain and functional status in fibromyalgia patients.

Methods • It was a longitudinal cross-sectional study. The study was performed by Baskent University Alanya Hospital. Patients, aged between 20 and 65 years, diagnosed with fibromyalgia according to American College of Rheumatology 2010 criteria and had ozone therapy were included to the study. It was hypothesized that the ozonotherapy increases tissue oxygenization, decreases pain level and supplies better quality of life in patients with fibromyalgia. Demographic and three-month follow-up data of fibromyalgia patients who had received 10 sessions of ozone autohemotherapy were obtained from the hospital database. The patients received 10 sessions of ozone autohemotherapy at a concentration of 25 µg/ml (100 ml of blood and 100 ml of ozone gas) 2-3

times per week. The values of the Visual Analog Score and Fibromyalgia Impairment Questionnaire scores in the three-month follow-up were statistically compared, and $P < .05$ was considered statistically significant.

Results • 20 female patients were analyzed. The mean age of patients was 54.8 ± 15.5 years. Patients' median (min-max) baseline score on Visual Analog Score was 9 (5-10), post-treatment score was 3 (0-8), 3 (1-8) in 1st month, and 4 (1-8) in 3rd month. The median (min-max) Fibromyalgia Impairment Questionnaire score of patients was 73.29 (29.2 - 87.2) at baseline, 31.67 (7.01 - 66.99) after treatment, 24.6 (10.7 - 63.3) at 1st month, and 24.67 (10.67 - 66.99) 3rd month. A significant decrease in pain ($P < .001$) and functional improvement ($P < .001$) was observed in the patients after ozonotherapy.

Conclusion • After 10 sessions of ozonotherapy in fibromyalgia patients, the Visual Analog Score and Fibromyalgia Impairment Questionnaire scores decreased significantly and this well-being persisted for three months. Ozonotherapy may be considered for fibromyalgia treatment protocol as complementary therapy. For determining dosage and session standards further studies are needed. (*Altern Ther Health Med.* 2025;31(1):10-14).

Ozlem Kuculmez, MD, Assistant Professor, Baskent University Alanya Hospital, Department of Physical Medicine and Rehabilitation, Antalya, Turkey

Corresponding author: Ozlem Kuculmez, MD
E-mail: akanozlem07@gmail.com

INTRODUCTION

Fibromyalgia (FM) is an extremely interesting disease regarded as a collection of symptoms not directly linked to pain, including widespread discomfort, fatigue, sleep disorders, and problems with cognitive function. It is more prevalent among women, typically between the ages of 30 and 55. This condition is very common with a prevalence of 2-5% in overall

population.¹ It is classified as a chronic pain syndrome in the International Classification of Diseases ICD-11.² For this reason, diagnosis can no longer be made only by tender point palpation. Diagnosis is made by scoring widespread pain and somatic symptoms according to the 2010 American College of Rheumatology criteria. Sometimes it is not easy to diagnose and treat this illness, because of uncertainties and lack of knowledge about the etiopathogenesis of the disease.⁴ Many theories have been proposed for the etiopathogenesis of this disease, such as genetic and environmental factors, traumas, endocrine disorders, antioxidant system deficits, mitochondrial dysfunction, neuroinflammation, small fiber impairment, and central sensitization, but no definite conclusion has been reached. As mitochondrial dysfunction, hypoxia, and lack of

antioxidant mechanisms were blamed for the fatigue symptoms of patients, ozonotherapy has been become more controversial and researched.^{5,6} Ozone therapy is a complementary therapy used to treat some diseases with medical ozone gas (a combination of 3-5% O₃ - 95% O₂). The therapy has been started to be used in medicine since the discovery of ozone generators. Since the ozone molecule is one of the most reactive molecules, it is believed to increase tissue oxygenation and induce antioxidant reactions once it is delivered to the body.⁷ Because of this property, there are several studies suggesting that the therapy may also be effective in patients with fibromyalgia.^{5,8} This study aims to determine the effect of ozone therapy on the pain and functional level of patients who received this therapy in the Baskent University Physiotherapy Clinic. It was hypothesized that FM patients have decreased Visual Analog Score (VAS) and increased Fibromyalgia Impairment Questionnaire (FIQ) scores after ozone major autohemotherapy (MaAHT). This study was the first study that searched efficacy of ozonotherapy in pain and functional status in newly diagnosed, treatment naive FM patients.

MATERIALS AND METHODS

The study was a longitudinal cross-sectional investigation. The study was conducted in accordance with the Declaration of Helsinki, after obtaining approval from the Baskent University Ethics Committee (KA22/352, 22.11.2022). The method of administration, mechanism of action, possible side effects of ozonotherapy was explained in detail and consent form was taken from the patients for ozone therapy as a routine procedure. Sample size was calculated with G*Power 3.0.10. (Franz Faul, Universität Kiel, Kiel, Germany) program. Targeting a medium effect size ($d = 0.25$), 80% power, and a 5% false-positive rate, sample size was revealed as 28. During the last 6 months (01.05.21- 30.10.21), patients who visited the Physical Medicine and Rehabilitation Polyclinic with a diagnosis of fibromyalgia were scanned in the health database. Demographic data such as age, gender, previous diagnoses, medications, ozone sessions, ozone dosages, side effects, control anamnesis, VAS and FIQ scores were obtained from the health database.

Inclusion Criteria

The patients aged between 20-65 years, newly diagnosed as FM according to ACR 2010 diagnostic criteria and who had accepted 10 sessions of ozone major autohemotherapy were included in the study.

Exclusion Criteria

The patients who were previously diagnosed as FM had a diagnosis of another rheumatic or systemic disease that could affect the results, used FM drugs for another indication, had another therapy as physical therapy, injections that could affect the results, and who did not come to ozonotherapy or controls were excluded from the study.

When ozone-resistant materials are not used, ozone becomes carcinogenic by melting plastic material instead of

an antioxidant agent. Because of this issue ozone-resistant vacuum glass citrated bottles (PPS citrated bottles, contain 10 ml citrate), serum sets (PPS serum sets), and injectors (Medivare 50-60 ml injectors), were used for major autohemotherapy protocol. Therapies were performed with the Turkozone Blue S (Ozone Health Services Co. Ltd., Istanbul, Turkey) medical ozone generator (CE 1984) which was approved by the Ministry of National Health. The ozone generator allowed the customization of the treatment via selecting the O₃ dosage in a continuous range, i.e., from 1 to 80 µg of O₃. Ozone dosage was selected by the operator. 100 cc of blood was drawn from patients to citrated bottles with ozone-resistant serum sets. 100 ml of O₃ -O₂ mixture gas was injected into bottles in 5 minutes. Then the bottles were turned upside down and ozonated blood was reinfused to the patients intravenously within 15 minutes using the same serum sets. Sterile disposable materials were used, and antiseptic conditions were maintained during the process. All patients had a concentration of 20-25 µg/ml of 100 ml of blood and 100 ml of O₃ -O₂ mixture gas. In the first session 20 µg/ml, in the second session 22 µg/ml, and between the third and tenth sessions 25 µg/ml were administered, as it was recommended to start the therapy with a low dose and increase it slowly as recommended in Sucuoglu et al.'s study. For the patients of FM, a medium dose range was preferred. Ozone therapy was administered 2-3 times per week for a total of 10 sessions, as recommended in the literature.⁹ VAS and FIQ scores (before ozone therapy, after therapy, at the first and third month of control) were taken from the health database and statistically compared.

Visual Analog Scale is used to digitize some values that cannot be measured numerically. The Turkish validity and reliability of the scale were performed by Yaray et al. in 2011. Patients are shown a pain scale of 10 centimeters (cm) long. On this scale, 0 cm represents no pain and 10 cm represents the most severe pain. Patients look at this scale and indicate the severity of the pain as a point on this scale. The distance between point 0 and the point indicated by the patient is measured in cm, and the value indicates VAS.¹⁰

FIQ is an FM rating scale that consists of 10 questions. The first question evaluates physical functioning, the second and third questions evaluate the severity of the disease and the degree of inability to work, and the fourth to tenth questions evaluate difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. A maximum total of 100 points can be scored. Scores between 50 and 70 points are considered moderately impaired, and scores above 70 points are considered severely impaired. The Turkish validity and reliability of the scale were established by Sarmer et al. in 2000.¹¹

The primary outcome measure was VAS and the secondary outcome was FIQ score in the current study.

Statistical analysis

Data were analyzed with the SPSS program (IBM Corp., Chicago, Illinois, USA 25.00), and all results were interpreted at a significance level of 0.05 and a confidence interval of

95%. Normally distributed values were defined as mean $\pm$ SD, nonnormally distributed values were defined as median (min-max), and categorical variables were defined as frequency and percentage. Because a normal distribution could not be found for VAS and FIQ values, the Friedman test was used to compare VAS and FIQ values between groups. (Values before therapy, after therapy, controls in the first and third month) because the data did not provide normal distribution and repeated measurements were made in the dependent group in the study design. Post hoc analysis was performed with the Bonferroni test to determine between which measurements the statistical difference emerged. $P < .05$ was considered statistically significant.

RESULTS

It was found that 55 patients visited the outpatient clinic with the diagnosis of FM in the last six months and these patients were revealed for the study. 35 patients who did not meet the inclusion criteria were excluded from the study. The consort flow diagram is shown in Figure 1. A total of 20 patients were analyzed who had a new FM diagnosis and 10 MaAHT sessions. All patients included in the study were women, their mean age was 54.8 ± 15.5 years, and their demographics were similar.

The present study revealed that following 10 sessions of MaAHT for patients with FM, there was a notable difference in VAS ($\chi^2 = 37.577$, $P < .001$) and FIQ median scores ($\chi^2 = 48.306$, $P < .001$) at the three-month follow-up.

The initial median (min-max) of the patient's VAS score was determined to be 9 (5-10). After 10 MaAHT sessions, the median VAS score decreases to 3 (0-8). It was observed that this decrease continued as the median VAS scores were 3 (1-8) at the first month and 4 (1-8) at the third month controls. According to the analysis results, a statistically significant difference was observed between the mean values of VAS at different time points ($\chi^2 = 37.577$, $P < .001$). According to post hoc analysis, there was a significant difference between pre-treatment-post-treatment (mdn= 3) ($P = .001$), pre-treatment-first month-follow-up (mdn= 3) ($P = .001$) and pre-treatment-third month follow-up (mdn= 4) ($P = .001$), but there was no difference between post-treatment-first month follow-up (mdn= 3) ($P = 1.000$) or first month-third month follow-up (mdn= 4) ($P = 1.000$) values. These findings indicate that ozonotherapy shows its effect on VAS score significantly in first month after therapy and this well-being persists for three months. The change in VAS values during the three-month follow-up is shown in Figure 2.

The median (min-max) FIQ score of patients was 73.29 (29.2 - 87.2) at baseline, 31.67 (7.01 - 66.99) after treatment, 24.6 (10.7 - 63.3) in the first month, and 24.67 (10.67 - 66.99) in controls at third month. After treatment, a statistically significant difference was found between the mean FIQ scores at different time points ($\chi^2 = 48.306$, $P < .001$). According to posthoc analysis, there was a significant difference between the mean values before treatment and after treatment (mdn= 31.67) ($P = .013$), before treatment

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

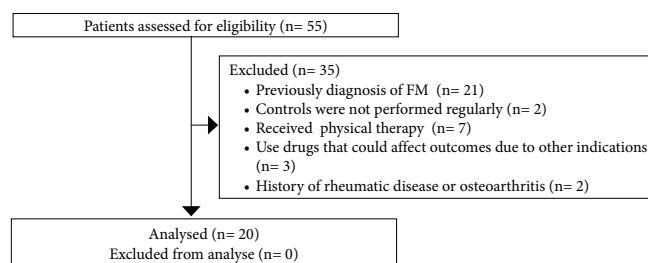


Figure 2. Time dependent change in Visual Analog Score (VAS).

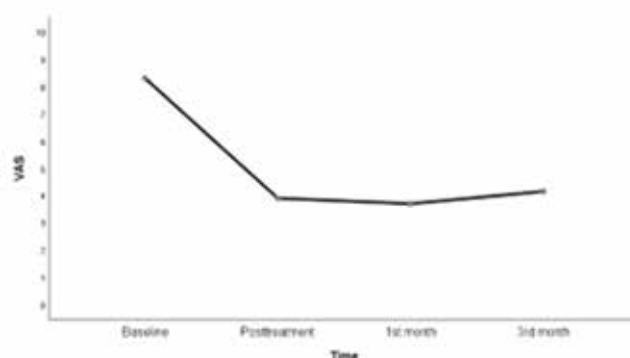
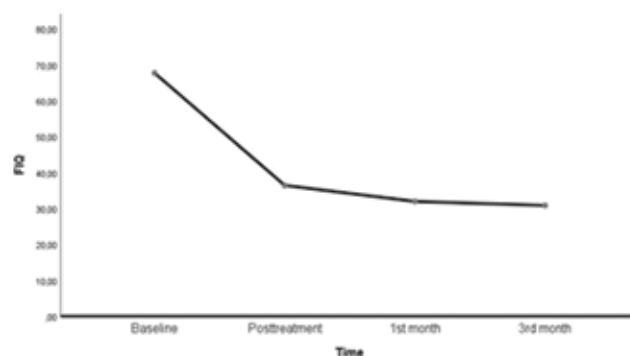


Figure 3. Time dependent change in Fibromyalgia Impairment Scale (FIQ).



and in the first month after treatment (mdn= 24.6) ($P = .001$), before treatment and in the third month after treatment (mdn= 24.67) ($P = .001$) and after treatment in the third month (mdn= 24.67) ($P = .006$), but there was no difference between the values after treatment in the first month (mdn= 24.6) ($P = .165$) or between the first month and the third month (mdn= 24.67) ($P = 1.000$). These results reveal that ozonotherapy shows its effect on FIQ score significantly in first month after therapy and this positive effect persists for three months. The change in FIQ scores during the three-month follow-up is shown in Figure 3.

DISCUSSION

The current study found that after 10 sessions of MaAHT in FM patients, there was a significant difference in VAS ($\chi^2 = 37.577$, $P < .001$) and FIQ median scores ($\chi^2 = 48.306$, $P < .001$) at the three-month follow-up.

.001) at the three-month follow-up. There was a significant difference in the mean scores of VAS and FIQ after the treatment and in first month control. Also these positive effects persisted for three months.

There are a limited number of studies in the literature on this topic. Hidalgo-Tallón et al. applied ozone therapy with rectal insufflation method in 36 FM patients (33 women, 3 men). They performed the therapy 2-5 times per week for 12 weeks and used a dosage of 40 µg/ml 200 ml. After a total of 24 sessions, they showed significant improvement in the patients' Beck Depression scores, Short Form Health Survey (SF-12), and FIQ scores.¹²

The study, designed by Tirelli et al, included 65 FM patients (55 women, 10 men). Disease duration ranged from 0.5 to 33 years. Ozone therapy was administered by MaAHT in 55 patients and by the rectal insufflation method in 10 patients. Patients attended sessions twice a week for the first month, after which therapy was continued twice a month. They were then assessed with a numerical rating scale (0-10) and a fatigue severity scale (1-7), and 70% of patients experienced a 50% improvement in symptoms.¹³ Another study included 200 patients who received MaAHT sessions at a dose of 45 µg/ml 3-4 times per week for one month. a 10-point numerical pain intensity scale was used for assessment, and only 17.5% of patients showed no improvement. They determined a significant decrease in modified 10-points Pain Intensity-Numerical Rating Scale after 3-4 sessions in 1st-month control.¹⁴

Moreno-Fernández et al. administered 10 sessions of MaAHT at 30-60 µg/ml to 20 FM patients. In addition to FIQ and tender point assessment, peripheral blood was drawn from the patients, and reactive oxygen species (ROS), lipid peroxidation (LP), and protein carbonyl content (PC) were also measured. In addition to clinical improvement in patients receiving ozone therapy, levels of oxidative stress markers such as ROS, LC, and PC were also shown to decrease.¹⁵

The first randomized controlled trial of ozone therapy in FM patients was conducted by Sucuoglu et al. A total of 54 patients (26 patients in the ozone therapy group, and 28 patients in the placebo group) were enrolled in the study. They received both MaAHT and minor autohemotherapy twice weekly for a total of 10 sessions. When comparing pre- and post-treatment outcomes, significant improvement was noted in the Fibromyalgia Impact Questionnaire, the Pittsburgh Sleep Quality Index (PSQI), and the Short form-12 (SF-12) in both groups. Because of this issue, Sucuoglu et al. suggested this therapy as an adjuvant therapy to physiotherapy in FM patients.⁹ Türkyılmaz et al performed a prospective cross-sectional study on 40 patients. They applied ozone therapy two times a week for a total of 13 sessions and determined improvement in FIQ, PSQI, and SF-12 scores.¹⁶ Ahi et al performed a retrospective study in 45 FM patients who had ozone therapy and found improvement in VAS, FIQ, and Short form 36 scores.¹⁷ In the current study, we determined that the results support Türkyılmaz's and Ahi's results as we found improvement in VAS and FIQ scores too.

In literature, there is no standard protocol for dosage, frequency, and method of application. As a result, the results are heterogeneous and the level of evidence decreases. Most studies on ozone therapy have been conducted in patients with low back pain and knee osteoarthritis.¹⁸⁻²¹ The number of studies on FM patients is also extremely limited. However, the significant improvement in both VAS and FIQ scores in FM patients after 10 MaAHT sessions in the current study supports the findings of other studies in the literature.

It is well known that ozone is highly reactive and transforms into oxygen and ozonoid once it acts on the body. The ozonoid molecules then transform into reactive oxygen species (ROS) and lipid oxidation products (LOPs). ROS facilitates tissue oxygenation by acting on erythrocytes and delivering oxygen to the tissue. LOPs act on the endothelium and increase the release of nitric oxide. They stimulate the production of erythrocytes resistant to oxidative stress and the activation of stem cells. In addition, they increase the number of antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase, glutathione transferase, glutathione, and glutathione reductase. It also accelerates the Krebs cycle and ATP production and regulates the extent of inflammation.⁸ As known, there are many theories on the pathogenesis of FM, such as neurotransmission disorders, neuroinflammation, peripheral sensitization, central sensitization, small-fiber neuropathy, neuroendocrine factors, sleep disorders, genetic predisposition, oxidative stress factors, mitochondrial dysfunction, environmental and psychosocial factors.²²⁻²⁴ It is suggested that ozone therapy may have antioxidant, anti-inflammatory, and metabolic effects.^{5,7} The study by Moreno-Fernández et al. and the current study also support this hypothesis.¹⁵ If these findings are supported by more comprehensive studies in the future, ozonotherapy may be included in the treatment algorithm of fibromyalgia.

The main limitations of our study are the cross-sectional design, the data obtained from a health database, limited evaluation methods, the short follow-up time, and the small sample size. Another important limitation is the lack of a standard dosage, session, and application protocol for ozonotherapy in FM patients. The fact that many newly diagnosed patients did not meet the study criteria caused the sample size to be limited. This is one of the most important limitations. The strength of the study is including only newly diagnosed FM patients different from other studies that had no previous treatment to evaluate the real efficacy of ozonotherapy. This issue supplies to determine real efficacy of ozonotherapy in FM patients as they are newly diagnosed and treatment naive. The ozotherapy may take place in FM treatment protocol in future. There is a need for prospective, multicenter studies that define standard protocols and dosage in these patients. Also, we need further studies that have longer follow-ups to see the efficacy of ozonotherapy in a long time.

CONCLUSION

After 10 MaAHT sessions in FM patients, VAS and FIQ scores decreased significantly, and this beneficial effect

persisted for three months. The greatest efficacy was found between the pre-post treatment period and first month control. Ozone therapy appears to be a treatment option for FM patients, but prospective and randomized controlled clinical trials with a larger sample size are needed.

FUNDING

The researchers did not take any funding for the study.

ETHICAL APPROVAL

The study was approved by the Baskent University Ethical Committee in 03.02.2022 (E-94603339-604.01.02-180664)

CONSENT FOR PUBLICATION

No need for a consent form because the study was a cross-sectional study. The consent forms for ozone autohemotherapy were obtained from all participants.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ACKNOWLEDGMENT

None

DECLARATION OF CONFLICT OF INTEREST

None

FUNDING

None

REFERENCES

- Giorgi V, Sirotti S, Romano ME, et al. Fibromyalgia: one year in review 2022. *Clin Exp Rheumatol*. 2022;40(6):1065-1072. doi:10.55563/clinexp Rheumatol/i9gk2
- Nicholas M, Vlaeyen JWS, Rief W, et al; IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160(1):28-37. doi:10.1097/j.pain.0000000000001390
- Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. 2010;62(5):600-610. doi:10.1002/acr.20140
- Berwick R, Barker C, Goebel A; guideline development group. The diagnosis of fibromyalgia syndrome. *Clin Med (Lond)*. 2022;22(6):570-574. doi:10.7861/clinmed.2022-0402
- Bazzichi L, Giacomelli C, Consensi A, Giorgi V, Batticciotto A, Di Franco M, Sarzi-Puttini P. One year in review 2020: fibromyalgia. *Clin Exp Rheumatol*. 2020; 38 Suppl 123(1):3-8.
- Alorfi NM. Pharmacological treatments of fibromyalgia in adults; overview of phase IV clinical trials. *Front Pharmacol*. 2022;13:1017129. doi:10.3389/fphar.2022.1017129
- Assavarittirong C, Samborski W, Grygiel-Górniak B. Oxidative Stress in Fibromyalgia: From Pathology to Treatment. *Oxid Med Cell Longev*. 2022;2022:1582432. doi:10.1155/2022/1582432
- de Sire A, Agostini F, Lippi L, et al. Oxygen-Ozone Therapy in the Rehabilitation Field: State of the Art on Mechanisms of Action, Safety and Effectiveness in Patients with Musculoskeletal Disorders. *Biomolecules*. 2021;11(3):356. doi:10.3390/biom11030356
- Sucuoglu H, Soydaş N. Efficacy of ozone therapy as an add-on treatment in fibromyalgia: A randomized double-blind placebo-controlled study. *J Back Musculoskelet Rehabil*. 2023;36(2):357-366. doi:10.3233/BMR-210368
- Yaray O, Akesen B, Ocaklioglu G, Aydinli U. Validation of the Turkish version of the visual analog scale spine score in patients with spinal fractures. *Acta Orthop Traumatol Turc*. 2011;45(5):353-358. doi:10.3944/AOTT.2011.2528
- Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. *Rheumatol Int*. 2000;20(1):9-12. doi:10.1007/s002960000077
- Hidalgo-Tallón J, Menéndez-Cepero S, Vilchez JS, Rodríguez-López CM, Calandre EP. Ozone therapy as add-on treatment in fibromyalgia management by rectal insufflation: an open-label pilot study. *J Altern Complement Med*. 2013;19(3):238-242. doi:10.1089/acm.2011.0739
- Tirelli U, Cirrito C, Pavanello M, Piasentin C, Lleshi A, Taibi R. Ozone therapy in 65 patients with fibromyalgia: an effective therapy. *Eur Rev Med Pharmacol Sci*. 2019;23(4):1786-1788. doi:10.26355/eurrev_201902_17141
- Tirelli U, Franzini M, Valdenassi L, Pandolfi S, Taibi R, Chirumbolo S. Fibromyalgia treated with oxygen-ozone auto-haemotherapy (O2-O3-AHT): a case study on 200 patients with a modified 10-PI-NRS evaluation. *Eur Rev Med Pharmacol Sci*. 2022;26(21):7974-7979. doi:10.26355/eurrev_202211_30150
- Moreno-Fernández A, Macías-García L, Valverde-Moreno R, Ortiz T, Fernández-Rodríguez A, Molini-Estrada A, De-Miguel M. Autohemotherapy with ozone as a possible effective treatment for Fibromyalgia. *Acta Reumatol Port*. 2019; 29;44(3):244-249.
- Gazioglu Türkylmaz G, Rumeli Ş, Bakır M. Effects of Major Ozone Autohemotherapy on Physical Functionality and Quality of Life in Fibromyalgia Syndrome: A Prospective Cross-sectional Study. *Altern Ther Health Med*. 2021;27(5):8-12.
- Ahi E, Afsar SI. The effectiveness of major ozone autohemotherapy in the treatment of fibromyalgia syndrome. *Journal of Surgery & Medicine*. 2022;6(8):746-750. doi:10.28982/josam.1032050
- Bocci V, Borrelli E, Zanardi I, Travagli V. The usefulness of ozone treatment in spinal pain. *Drug Des Devel Ther*. 2015;9:2677-2685. doi:10.2147/DDDT.S74518
- Rimeika G, Saba L, Arthimulam G, et al. Metanalysis on the effectiveness of low back pain treatment with oxygen-ozone mixture: comparison between image-guided and non-image-guided injection techniques. *Eur J Radiol Open*. 2021;8:100389. doi:10.1016/j.ejro.2021.100389
- Anil U, Markus DH, Hurley ET, et al. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. *Knee*. 2021;32:173-182. doi:10.1016/j.knee.2021.08.008
- Noori-Zadeh A, Bakhtiyari S, Khooz R, Haghani K, Darabi S. Intra-articular ozone therapy efficiently attenuates pain in knee osteoarthritic subjects: A systematic review and meta-analysis. *Complement Ther Med*. 2019;42:240-247. Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update. *Int J Mol Sci*. 2021;22(8):3891. doi:10.1016/j.ijms.2018.11.023
- Cordero MD, de Miguel M, Carmona-López I, Bonal P, Campa F, Moreno-Fernández AM. Oxidative stress and mitochondrial dysfunction in fibromyalgia. *Neuroendocrinol Lett*. 2010;31(2):169-173.
- Cordero MD, De Miguel M, Moreno Fernández AM, et al. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. *Arthritis Res Ther*. 2010;12(1):R17. doi:10.1186/ar2918
- Shukla V, Kumar DS, Ali MA, Agarwal S, Khandpur S. Nitric oxide, lipid peroxidation products, and antioxidants in primary fibromyalgia and correlation with disease severity. *J Med Biochem*. 2020, 23;39(2):165-170. doi:10.2478/jomb-2019-0033.