

Research article

Ozone Therapy as a Therapeutic Option in Rheumatoid Arthritis with Severe Inflammatory Syndrome

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Abstract: Rheumatoid arthritis is a chronic autoimmune inflammatory disease characterized by systemic inflammatory activity and progressive joint involvement, in which corticosteroid therapy is frequently used to control severe inflammatory syndrome. However, its use is limited in patients with metabolic comorbidities, such as diabetes mellitus. This case report analyzes the clinical course of a 67-year-old female patient with type II diabetes mellitus, initially diagnosed with bilateral knee osteoarthritis, in whom clinical, biological, and imaging reassessment led to the diagnosis of severe active rheumatoid arthritis, with elevated Disease Activity Score (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) values. Given the contraindication to corticosteroid therapy, disease-modifying treatment with methotrexate was initiated and combined with systemic ozone therapy administered via major autohemotherapy, used as an adjuvant immunomodulatory intervention. The therapeutic protocol was conducted over a 12-month period, and the patient remains under clinical follow-up. Clinical and biological outcomes were favorable, with a marked reduction in inflammatory markers (ESR and CRP) and disease activity scores (DAS28, CDAI, SDAI) observed as early as the first month of treatment, followed by complete clinical remission at 12 months, normalization of glycated hemoglobin, and absence of adverse events. The findings of this case suggest that ozone therapy may represent a safe and effective therapeutic alternative in the management of rheumatoid arthritis with severe inflammatory syndrome in patients with contraindications to corticosteroid therapy, supporting the need for controlled clinical studies on larger patient cohorts to validate this therapeutic approach.

Keywords: rheumatoid arthritis, ozone therapy, severe inflammatory syndrome

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease of autoimmune origin that primarily affects small joints and leads to both local inflammation and systemic manifestations [1]. It is characterized by a persistent inflammatory process that results in joint deformities, destruction of synovial tissue, severe disability, and, in some cases, premature mortality [2]. Between 1980 and 2018, the global prevalence of RA was estimated at 460 cases per 100,000 individuals [3]. Age at onset varies according to disease stage, most commonly occurring between 35 and 50 years, with women accounting for approximately 80% of affected patients. Disease progression is frequently associated with a substantial degree of disability, reported in 61.3% of cases [4], resulting from the progressive destruction of articular cartilage, subchondral bone, and the joint capsule, which is why rheumatoid arthritis has been metaphorically described as a “cancer that never dies” [3, 4]. Beyond its impact on health status,

RA imposes a significant socioeconomic burden due to associated morbidity, the need for long-term care, and the high costs of medical management [7].

In the absence of a specific curative treatment for degenerative or inflammatory joint diseases, therapeutic management primarily aims to alleviate symptoms and preserve joint function [8]. Available treatment options include pharmacological therapies, such as analgesics and nonsteroidal anti-inflammatory drugs, alongside non-pharmacological interventions, including physical exercise, rehabilitation therapies, and the use of assistive devices [9]. In patients with an insufficient response to these measures who are not candidates for major surgical interventions, minimally invasive procedures may be considered, particularly intra-articular injections with various agents, such as corticosteroids, hyaluronic acid, platelet-rich plasma, or medicinal ozone [10, 11].

In this context, ozone therapy has been proposed as an alternative or adjuvant therapeutic option due to its reported anti-inflammatory and analgesic effects, especially in situations where corticosteroid therapy is limited or contraindicated, as in patients with diabetes mellitus [12, 13].

Medicinal ozone is an oxygen–ozone mixture administered at low concentrations, capable of restoring cellular redox balance and modulating the inflammatory response through an oxidative pre- and postconditioning mechanism, which has been validated in various pathological conditions, including ischemic syndromes, diabetes mellitus, pain-related disorders, and degenerative diseases of the musculoskeletal system [14]. Oxygen–ozone therapy (OOT) is regarded as a complementary, and in some cases alternative, therapeutic procedure that is safe and minimally invasive, administered via multiple routes depending on the clinical indication, with demonstrated effects on pain reduction, inflammation control, improvement of microcirculation, and enhancement of quality of life [15, 16].

Clinical studies have demonstrated the efficacy of OOT in degenerative disorders of the spine and in knee osteoarthritis, both as monotherapy and in comparison with established treatments such as nonsteroidal anti-inflammatory drugs, corticosteroids, hyaluronic acid, or platelet-rich plasma (PRP) [17, 18]. Although the reported outcomes indicate improvements in joint mobility and reductions in pain and inflammatory scores, the literature emphasizes the need for further comparative research to more clearly define the role of ozone therapy relative to standard treatments [15]. Considering the central involvement of chronic inflammation, oxidative stress, and immune dysregulation in the pathogenesis of rheumatoid arthritis, ozone therapy emerges as a promising adjuvant therapeutic option, particularly in patients with contraindications to conventional anti-inflammatory treatments, thereby justifying its clinical exploration in this setting.

2. Materials and Methods

2.1. Case presentation

The patient, a 67-year-old normoweight woman with a medical history significant for type II diabetes mellitus, first presented to our hospital in December 2024 with a diagnosis of bilateral knee osteoarthritis, which had been established at another medical facility approximately one month earlier. She had previously undergone rehabilitation treatment consisting of bilateral intra-articular knee injections with a viscoelastic agent (hyaluronic acid). The subsequent clinical course was unfavorable, with persistent pain symptoms and no improvement in the degree of functional impairment.

The initial clinical examination revealed pain of predominantly inflammatory character in both knee joints. Ultrasonographic evaluation of the knees demonstrated a small amount of intra-articular fluid in the bilateral suprapatellar recesses, in the absence of Doppler signal, associated with bilateral medial meniscal extrusion. Initial treatment consisted of physiotherapy applied to the knee joints, including magnetotherapy, laser therapy, ultrasound, and interferential currents. The clinical evolution

was initially favorable; however, after approximately one month, the patient reported recurrence of the initial symptoms, prompting a reassessment of the diagnosis of bilateral knee osteoarthritis.

A detailed medical history provided additional information regarding the prior course of the disease, including morning stiffness persisting throughout the entire day, loss of appetite, moderate weight loss, and an increased degree of impairment in activities of daily living compared with the initial assessment.

Clinical examination revealed pain of predominantly inflammatory character involving the right tibiotalar joint, the carpal joints, and the bilateral carpometacarpal joints of the thumbs.

Biological samples were collected to evaluate the inflammatory and immunological status, with the results indicating a severe inflammatory syndrome, characterized by marked elevations in acute-phase reactants and disease-specific serological markers. The detailed values of the biological parameters are summarized in Table 1.

Tabel 1. Biological parameters at the time of initial evaluation

Parameter	Value	Units
Complete blood count	Within normal limits	-
Blood glucose	151	mg/dL
Erythrocyte sedimentation rate (ESR)	108	mm/h
C-reactive protein (CRP)	145	mg/L
Fibrinogen	908,2	mg/dL
Rheumatoid factor (RF)	434	IU/mL
Anti-CCP antibodies	27,2	U/mL
Tumor markers (CA, CA19-9, CA125, AFP)	Within normal limits	-
TSH, T4	Within normal limits	-

Ultrasonographic examination continued to demonstrate a small amount of intra-articular fluid in both knee joints, as well as a reduced amount of fluid in the right tibiotalar joint, in the absence of Doppler signal.

Based on the clinical, biological, and imaging findings, the established diagnosis was rheumatoid arthritis, with a diagnostic score of 8 points according to the criteria presented in Table 2.

Tabel 2. Diagnostic criteria

Diagnostic criteria	Reason	Score
Affected joints	4 small joints and 3 large joints	3 point
Serology	Anti-CCP antibodies = 27,2 U/mL Rheumatoid factor (RF) = 434 IU/ml	3 point
Acute-phase reactants	C-reactive protein (CRP) = 145 mg/L	1 point
Symptom duration	More than 6 weeks	1 point

Disease activity was evaluated using validated composite indices developed within the collaboration between the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR). The diagnosis of rheumatoid arthritis was established based on the clinical presentation, laboratory findings, and exclusion of alternative conditions with similar manifestations, in accordance with current standards in rheumatology practice. The obtained results are presented in Table 3.

Table 3. Disease activity assessment scores

Score	Value	Motivation
DAS 28 (Disease Activity Score)	6,64	7 tender joints 3 swollen joints VAS = 10 VSH = 108mm/h
CDAI (Clinical Disease Activity Index)	30	7 tender joints 3 swollen joints Patient global assessment (VAS) = 10 Physician global assessment (VAS) = 10
SDAI (Simplified Disease Activity Index)	44,5	CDAI + CRP (145 mg/L) = 44,5
Steinbrocker Functional Classification	Class II	Ability to perform daily activities in the presence of pain and functional limitation

The Disease Activity Score was 6.64, corresponding to a high level of disease activity. Similarly, the Clinical Disease Activity Index yielded a value of 30, and the Simplified Disease Activity Index a value of 44.5, both indicating high disease activity. Functional assessment according to the Steinbrocker classification placed the patient in Class II, characterized by the ability to perform daily activities in the presence of pain and functional limitation.

2.2. Therapeutic Management

Considering the diagnosis of rheumatoid arthritis with high disease activity and the presence of type II diabetes mellitus, a comprehensive therapeutic management strategy was initiated, consisting of disease-modifying therapy with methotrexate, folic acid supplementation, hepatoprotective therapy, and systemic ozone therapy with an immunomodulatory role. Methotrexate was administered subcutaneously at a dose of 10 mg once weekly, using a prefilled syringe (Metorthrit®), with the addition of folic acid 5 mg, administered 24 hours after each methotrexate dose. Hepatoprotective therapy included silymarin (Lagosa®), initially administered at a dose of 150 mg twice daily for 14 days, followed by 150 mg once daily for an additional 14 days.

Ozone therapy was employed as an adjuvant immunomodulatory treatment in the form of major autohemotherapy, following a progressive dose-escalation protocol, as detailed in Table 4.

Table 4. Ozone therapy protocol

Day	Ozone dose (µg/mL)	Blood volume	Day	Ozone dose (µg/mL)	Blood volume
1	25	250 mL	49	45	250 mL
4	25	250 mL	56	45	250 mL
7	25	250 mL	63	45	250 mL
10	30	250 mL	70	45	250 mL
13	30	250 mL	84	45	250 mL
16	30	250 mL	98	45	250 mL
19	35	250 mL	128	45	250 mL
21	35	250 mL	158	45	250 mL
24	35	250 mL	188	45	250 mL
27	40	250 mL	218	45	250 mL
30	40	250 mL	248	45	250 mL
33	40	250 mL	278	45	250 mL
36	45	250 mL	318	45	250 mL
39	45	250 mL	248	45	250 mL
42	45	250 mL	368	45	250 mL

As part of the overall therapeutic strategy described above, the ozone therapy protocol was implemented over a 12-month period and comprised a total of 30 treatment days distributed throughout the follow-up interval.

Table 4 provides a detailed presentation of the intervention schedule, including the day of administration, the ozone dose used ($\mu\text{g/mL}$), and the blood volume processed during each session of major autohemotherapy. The blood volume was kept constant at 250 mL for all procedures, while the ozone concentration followed a progressive dose-escalation scheme, starting at 25 $\mu\text{g/mL}$ in the initial phase, subsequently increasing to 30 $\mu\text{g/mL}$, 35 $\mu\text{g/mL}$, and 40 $\mu\text{g/mL}$, and ultimately reaching 45 $\mu\text{g/mL}$, which was maintained during the later stages of the protocol.

This gradual escalation strategy was designed to ensure progressive adaptation and tolerability, while supporting the intended immunomodulatory effect of ozone therapy as an adjuvant to standard disease-modifying treatment.

3. Results

The total duration of patient follow-up was 12 months, spanning from December 2024 to December 2025. The clinical and biological evolution under the instituted treatment is summarized in Table 5. Values not recorded at that visit are indicated as not available.

Table 5. Evolution of clinical and biological parameters during follow-up

Date	VAS	DAS 28	CDAI	SDAI	ESR (mm/h)	CRP (mg/L)	HbA1c (%)
15 January	10	6,64	30	44,5	108	145	6,26
1 March	5	4,95	18	20,6	36	26	-
30 April	2	3,07	8	8,4	-	4	-
27 June	1	2,64	4	4,6	30	6	-
29 September	1	2,24	3	3,4	-	4	-
3 December	0	1,61	0	0,5	-	5	5,35

During the follow-up period, a progressive and sustained reduction in pain was observed, as reflected by a decrease in the VAS score from 10 at the initial assessment to 0 at the end of follow-up. Disease activity showed a marked improvement, with the DAS28 score decreasing from 6.64, indicative of high disease activity, to 1.61, consistent with clinical remission. Similarly, the CDAI and SDAI scores demonstrated a continuous decline, from initial values of 30 and 44.5, respectively, to 0 and 0.5 at the end of the follow-up period.

Biological markers of inflammation also showed significant improvement, with the erythrocyte sedimentation rate (ESR) decreasing from 108 mm/h to values approaching the normal range during follow-up, and C-reactive protein (CRP) levels declining from 145 mg/L to 5 mg/L at the end of the evaluated period. The evolution of biological parameters was concordant with the observed clinical improvement.

No adverse events related to ozone therapy were recorded throughout the treatment period. At present, the patient continues disease-modifying therapy with methotrexate and folic acid supplementation at the same doses, while hepatoprotective therapy with silymarin was administered for a total duration of 28 days, and ozone therapy was discontinued. At the final evaluation, the patient's clinical status was optimal, with no pain and no functional limitations in the previously affected joints. Notably, glycated hemoglobin values normalized by the end of the follow-up period.

4. Discussion

Rheumatoid arthritis is a chronic inflammatory rheumatic disease, initially characterized by an exudative process followed by an infiltrative–proliferative stage, which symmetrically affects the synovial membrane, particularly in the small joints of the limbs. The pathogenesis involves the initiation of a complex cascade of immune

reactions triggered by an exogenous etiological agent or an altered endogenous structure, sometimes on a genetically predisposed background. These immunological mechanisms become self-perpetuating, with the synovial membrane as the primary site, where interactions among macrophages, B lymphocytes, T helper lymphocytes, endothelial cells, and fibroblasts lead to activation of inflammatory mediators and increased levels of proinflammatory cytokines, ultimately responsible for the progressive destruction of joint structures.

In this pathogenic context, the control of both systemic and local inflammation represents a major therapeutic objective. Ozone therapy has been proposed as an adjuvant treatment in rheumatoid arthritis due to its reported anti-inflammatory, immunomodulatory, antioxidant, and analgesic effects. These effects are mediated through the regulation of cellular redox balance, reduction of oxidative stress, endothelial protection, and improvement of tissue oxygenation—mechanisms that are highly relevant to the pathogenesis of chronic synovial inflammation. In addition, the analgesic and myorelaxant properties of ozone therapy may contribute to pain relief and improvement of joint function.

The presented clinical case exhibited several particular features that influenced both the diagnostic process and the therapeutic strategy. The onset of rheumatoid arthritis at the age of 67 years, in the absence of a family history of autoimmune diseases, initially directed the diagnostic approach toward a degenerative pathology, namely primary bilateral knee osteoarthritis. This assumption was initially supported by the localization of symptoms and the patient's age, leading to the implementation of osteoarthritis-specific treatment, including intra-articular injections with a viscoelastic agent and physiotherapy procedures.

The unfavorable clinical course and the emergence of features suggestive of a systemic inflammatory process necessitated a reassessment of the diagnosis, supplemented by biological and imaging investigations, which confirmed rheumatoid arthritis with high disease activity. The coexistence of type II diabetes mellitus in a normoweight patient represented a key factor in therapeutic decision-making, as corticosteroid therapy was contraindicated due to metabolic risk. In this context, the addition of ozone therapy as an adjuvant immunomodulatory treatment to standard disease-modifying therapy with methotrexate was considered appropriate.

The favorable clinical and biological evolution observed during follow-up—characterized by a progressive reduction in disease activity scores, normalization of inflammatory markers, and the absence of adverse events—supports the potential role of ozone therapy as a useful adjuvant therapeutic option in the management of rheumatoid arthritis with severe inflammatory syndrome, particularly in patients with contraindications to corticosteroid therapy. Nevertheless, given the nature of the presented case, these findings should be interpreted with caution, and controlled clinical studies involving larger patient cohorts are required to validate the efficacy and safety of this therapeutic approach.

5. Conclusions

Ozone therapy may represent a valuable therapeutic alternative to long-term corticosteroid therapy in the management of rheumatoid arthritis with severe inflammatory syndrome, particularly in patients with associated chronic diseases that contraindicate the use of corticosteroids. In the presented case, the addition of ozone therapy as an adjuvant immunomodulatory intervention to standard disease-modifying treatment was associated with a favorable clinical and biological outcome, characterized by reduced disease activity, normalization of inflammatory markers, and absence of adverse events.

Nevertheless, given the nature of a case report, generalization of these findings should be approached with caution. Prospective, randomized clinical studies conducted on larger patient cohorts are required to evaluate the efficacy and safety of

ozone therapy in patients with severe inflammatory syndrome. The present case report provides a premise for future research aimed at clarifying the role of ozone therapy within the therapeutic algorithm of rheumatoid arthritis.

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Abbreviations

AFP	Alpha-fetoprotein
CA	Cancer antigen
CA125	Carbohydrate antigen 125
CA19-9	Carbohydrate antigen 19-9
CDAI	Clinical Disease Activity Index
CRP	C-reactive protein
DAS28	Disease Activity Score
ESR	Erythrocyte sedimentation rate
HbA1c	Glycated hemoglobin
OOT	Oxygen–ozone therapy
PRP	platelet-rich plasma
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SDAI	Simplified Disease Activity Index
T4	Thyroxine
TSH	Thyroid-stimulating hormone
VAS	Visual Analog Scale

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