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Case Study

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# On the Clinical Uses of Medical Ozone

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## Abstract

In light of some new protocols of administration of medical ozone, a global vision on the scientific data concerning the topic is proposed together to the more recent international literature. The interpretations of the molecular mechanisms induced by adequate oxidative stress, called eustress, will be discussed and interpreted in the light of the latest discoveries in the field of epigenetics and the metabolic pathway NRF2/ARE

**Keywords:** Medical Ozone; Oxidative Stress; Nrf2; Epigenetic; Protocols

## Discussion

Medical Ozone (MO) began to arouse the interest of the scientific community already at the end of the 19th century when its disinfectant and highly oxidizing action had allowed the first uses in the medical field and the first observations both in favour [1] and against [2], an endless debate that continues to this day. From that moment to today, interest has grown exponentially as indicated by the number of publications that have addressed the topic, reaching a total of 4,997 citations on PubMed (Fig. 1, May, 2025):

But it is above all in the early years of this century that a real re-evaluation of this integrative approach, the former Oxygen Ozone Therapy, began.

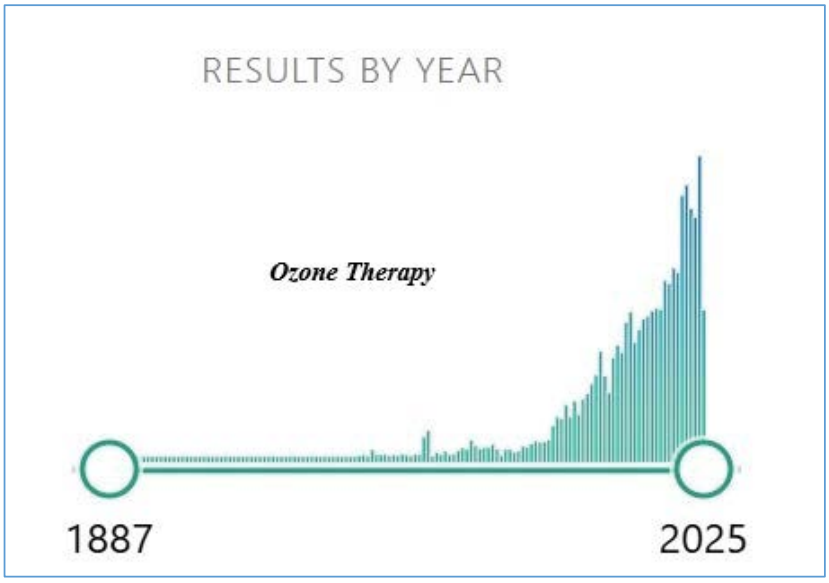


**Figure 1:** PubMed references using the key Ozone Therapy on May 2025. Total of 4997 citations.

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In fact, thanks to the studies of numerous scientists, including Prof. Velio Bocci [3, 4], it was possible to scientifically explain the apparently paradoxical effect resulting from the activation of a response that is exactly the opposite in qualitative terms to the effects of an agent such as ozone with high oxidizing properties.

This phenomenon, called the hormetic effect, was already known [5], but the more intimate mechanisms that would help us understand how an antioxidant response could be achieved by living beings on this planet, equipped with an oxygen-dependent energy mechanism that is finalized in the engine of mammalian cells, the mitochondria, were at that time largely unknown. We now have evidence that this cellular response can be understood as an adaptive reaction to a xenobiotic stimulus through the activation of metabolic pathways capable of counteracting the effect suffered by generating an exactly opposite one.

The hormetic concept was firstly associated to MO in 2008 [6]. Basically, after the administration of an oxidizing agent, graduated in intensity and duration similarly a physiological eustress that does not exceed the threshold of possible biological damage, a powerful antioxidant response is activated, capable of restoring redox homeostasis.

Therefore, unlike the well-known dose/effect relationship underlying classical pharmacological activity on receptors, in the case of the hormetic adaptive response there is no linear dose-effect relationship and therefore no effect at very low doses and toxic damage at higher doses, sometimes not easy to evaluate and quantify, both in the acute and chronic phase. This is one of the main reasons why some new techniques recently proposed for the administration of MO cannot find a place in the field of medical integration as they are not supported by adequate scientific literatures both for the lack of clinical studies but above all for the possible toxicity deriving from the continuous and prolonged administration of oxygen-ozone mixtures as in the case of the recently and hastily introduced techniques such as those called multi-passes (10, 20 or even more).

Not only that, the technique described as the most effective in producing an unidentified *Bioenergetic Metabolism* with activation of *Stem Cells* and an unclear *Mitochondrial Biogenesis*, is not supported by scientific literature and is based on a single, mostly anecdotal publication [7], also lending itself to other critical issues due to possible side effects that have not yet been fully considered and studied. Indeed, at each pass performed by taking a certain amount of blood, treating it with ozone, and infusing it back into the patient, the amount of anticoagulant needed for all passes must be taken into account, which could lead to serious consequences in terms of blood coagulation in addition to the risk of possible contamination if performed in unsuitable places.

To complete the topic, it is clear that these new techniques, far from being considered innovative or harbingers of prodigious clinical effects, differ greatly from what is described in the numerous scientific works produced in the case of the use of MO according to the techniques already described in the literature and which are regulated by a hormetic mechanism and by the involvement of surprising metabolic pathways such as the nuclear (erythroid-derived 2)-like transcription factor 2 (Nrf2) [8, 9, 10]. Furthermore, the repeated administration of a highly oxidizing substance cannot be considered a hormetic mechanism and paradoxically is more in line with conventional medical treatment being more related to the dose and proposing, in my opinion erroneously, that higher doses can induce a superior result to a single dose, thus introducing new interpretative models not in line with the scientific literature produced in the last 50 years and more.

Regarding the molecular mechanism activated by a standard MO treatment, mainly recommended for prevention and multidisciplinary integration, new insights into the multiple actions at the biochemical level have recently appeared in prestigious scientific journals, giving this technique, which can no longer be considered outside the consolidated schemes of medical treatments, non-negligible therapeutic potential: "*Life expectancy has almost doubled in the last century and diseases specific to aging are becoming frequent. However, the pathological mechanisms underlying most of them are not well understood and are treated more with symptomatic therapies than with prevention and correction of risk factors*." [11].

In the same article cited above, the authors described the complexity of a series of diseases called "*the Nrf2 diseasome*" that share the same mechanism linked to Nrf2: "*Interestingly, this network includes heterogeneous phenotypes such as autoimmune, respiratory, digestive, cardiovascular, metabolic and neurodegenerative diseases, along with cancer and many other conditions*."

Unfortunately, the lack of multicenter, randomized, well-coordinated clinical trials makes it difficult to introduce these integrative approaches, including that with MO which has been shown to also activate the Nrf2 metabolic pathway [9, 12] together with other activators agents (Fig. 2).

Furthermore, the complexity of the mechanisms involved in moderate eustress introduces numerous variables that play a fundamental role in the molecular processes that lead to the final clinical outcome. A recent study [18] describes Nrf2 as one of the most important transcription factors that controls more than 2000 genes.

In most cases, Nrf2-dependent genes are related to oxidative stress and are involved in redox balance, although new metabolic pathways seem to be involved by this plethora of genes, and not only in the regulation of oxidative stress.

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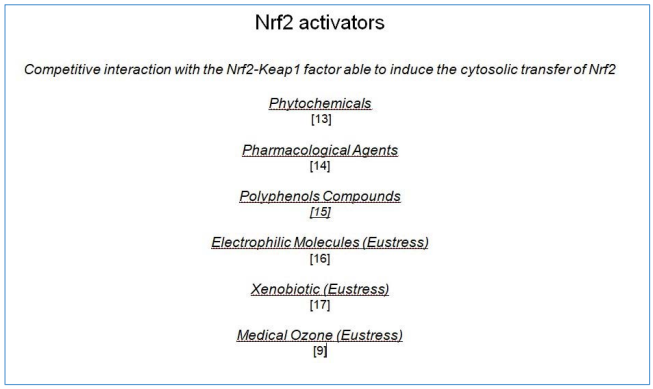



**Figure 2:** Activators list of the Nrf2 metabolic pathway.

In fact, in recent years, Nrf2-dependent genes have increased considerably, both in quantity and quality, especially with regard to the modality of specific functions that follow its activation. In their paper, McCord, Gao and Hybertson introduced some concepts that could help to better understand the real importance in the control of many functions of our body, but also their complexity: "*The purpose of this review is to provide an overview of the remarkable complexity of the tortuous sequence of stop-and-go signals that not only regulate expression or repression, but may also modify transcriptional intensity as well as the specificity of promoter recognition, allowing fluidity of its gene expression profile depending on the various structural modifications the transcription factor encounters on its journey to the DNA*."

They continue, "*At present, more than 45 control points have been identified, many of which represent sites of action of the so-called Nrf2 activators. The complexity of the pathway and the synergistic interplay among combinations of control points help to explain the potential advantages seen with phyto-chemical compositions that simultaneously target multiple control points, compared to the traditional pharmaceutical paradigm of one-drug, one-target*."

Furthermore, the same authors have underlined the evolutionary importance of this metabolic pathway for the numerous activities controlled by its activation, thus opening a new scenario on the possibility of controlling the damages of aging and improving the quality of life in the elderly and not only.

They argued also on some still unresolved questions regarding the quantification of the effect linked to the degree of activation, which can be better defined as a binary effect, or "*all or none*". Interesting is the reflection of the authors on the dominant paradigm of the pharmacological research of the last decades and aimed mainly to discover a single compound capable of "*inducing, activating, repressing, inhibiting or antagonizing the putative target of a disease*".

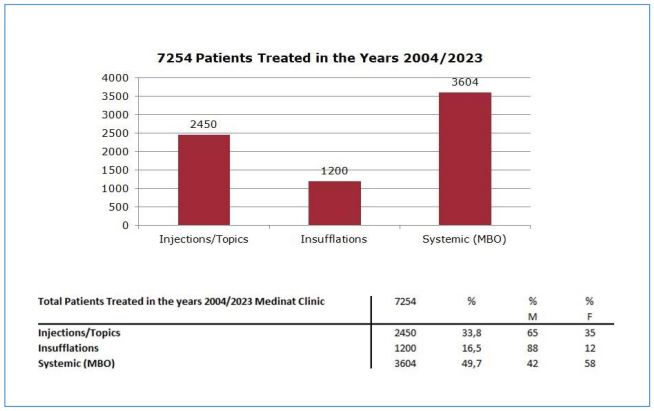
The epigenetic mechanism described in their work can be surprisingly compared to pharmacological *agonism* and *antagonism*, precisely in light of the fluidity of gene activity and the modification of transcriptional intensity that, as proposed by the authors themselves, will be able to modulate gene expression either by activating it, *agonism*, or by inhibiting it, *antagonism*. We agree completely with the sentence: "*It is now evident that more and more scientists so-called "thinking outside the box" see in the metabolic pathway of Nrf2 enormous potential in relation to the possibility of being of help in multiple pathological states including the damages of aging*".

The paper conclude pointed out the following suggestion: "*We certainly hope to see more human clinical trials to utilize and extend what has been learned in the laboratory regarding the potential therapeutic benefits that this transcription factor has to offer*."

In our opinion, in light of the latest knowledge acquired on this topic, and without ever forgetting that only the best scientific characterization can support and must always accompany any new hypothesis relating to new treatments as in the case of MO, it is essential to continue with strength and tenacity by promoting more in-depth studies, especially after the discovery of the involvement of the metabolic pathway Nrf2/ARE as possible interpretation of its therapeutic activity.

Despite the lack of randomized and controlled clinical studies, MO treatments are widespread throughout the world in a large number of the population both for prevention and integration with other specialties, and above all with the almost absolute absence of side effects other than small transitory reactions such as redness.

Our personal clinic activity began more than thirty years ago and only in the last 20 years about 2,700 people have been treated with MO through systemic treatment with single Major Blood Ozonation (MBO), previously Autohemotherapy [Fig. 3].




| Total Patients Treated in the years 2004/2023 Medinat Clinic | 7254 | % | % M | % F |
|---|---|---|---|---|
| Injections/Topics | 2450 | 33,8 | 65 | 35 |
| Insufflations | 1200 | 16,5 | 88 | 12 |
| Systemic (MBO) | 3604 | 49,7 | 42 | 58 |

**Figure 3:** Patients treated at Medinat clinic in the period 2004/2023 according to the administration protocol.

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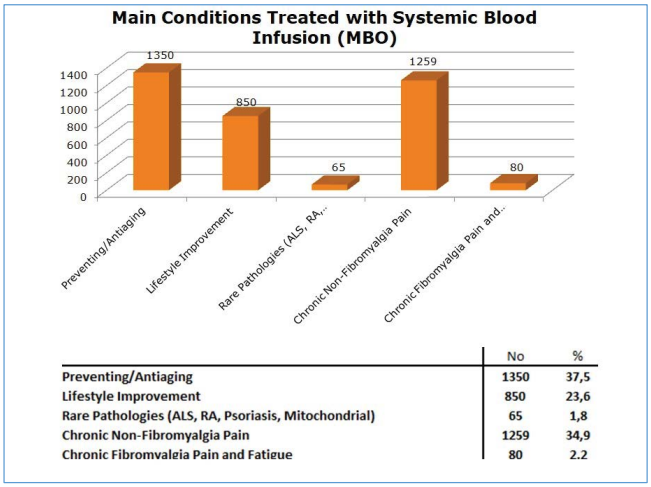
In the same period, 76,428 single MBOs have been performed without significant side effects. All clinical data have been collected and will be the subject of a future report in preparation [Fig. 4, 5].




| | No | % |
|---|---|---|
| Preventing/Antiaging | 1350 | 37,5 |
| Lifestyle Improvement | 850 | 23,6 |
| Rare Pathologies (ALS, RA, Psoriasis, Mitochondrial) | 65 | 1,8 |
| Chronic Non-Fibromyalgia Pain | 1259 | 34,9 |
| Chronic Fibromyalgia Pain and Fatigue | 80 | 2.2 |

**Figure 4:** Main conditions treated with systemic treatment (MBO) at Medinat clinic in the period 2004/2023.

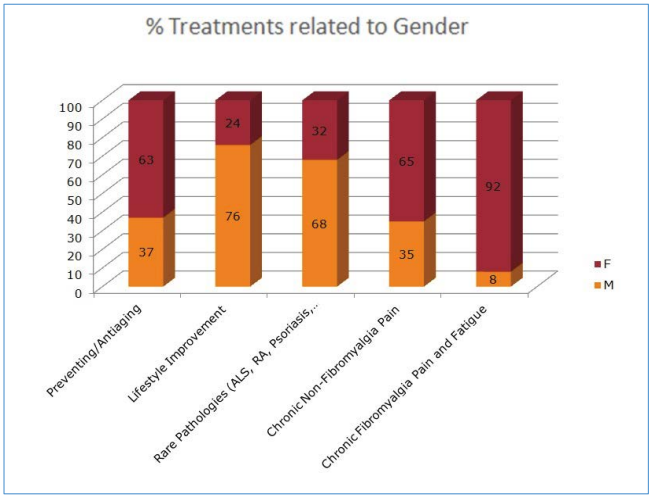



**Figure 5:** Percentage of patients treated with systemic treatment (MBO) at Medinat clinic in the period 2004/2023, divided by gender.

One of the most representative International Ozone Society, the WFOT [19], other than supporting the scientific development of MO proposing the best protocols in relation to its administrations, strongly suggests once again that the use of innovative techniques that deviate from the protocols used to date in the MO field and that have demonstrated the absence of any adverse effects on a highly significant world population with consolidated scientific support, are not recommended because they lack two fundamental aspects:

- Verification of possible acute and chronic toxicity;
- Adequate scientific and clinical studies on the possible induced mechanisms which, in the case of MO, depend mainly from the adaptive response of any individual patient.

## Conflict of interest

The authors declare no conflict of interest.

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