Treatment of Long-COVID with systemic ozone therapy: Importance of the 'proper dose'

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Summary

Systemic therapy with medical ozone has proved since the beginning of the pandemic to be a good adjuvant therapeutic approach to the other therapies proposed for the treatment of COVID-19. The joint action of effector molecules generated as a result of the appropriate mixing of the patient's blood with a gaseous oxygen-ozone mixture on capillary and pre-capillary vascular endothelial cells favours the restoration of the coating known as glycocalyx. This action enables greater defence and self-healing of patients against the most dangerous consequence of viral infection, namely endotheliitis at the microcirculatory level.
Indeed, the damage that the cytokines induced by the viral pathology produce at the level of the glycocalyx, especially when this is already damaged by pre-existing pathologies, is such as to generate thrombotic phenomena at a local level, with consequent pre-capillary arterial haemolysis and increased perivascular and intraparenchymal lymphocyte migration, to mention only the most relevant consequences.
These same phenomena, then, in some subjects remain for a very long time due to the poor ability of endothelial cells to repair the damage. An adequate therapeutic treatment with ozone is able to increase the repair processes at the endothelial level, demonstrating efficacy in the therapy of the so-called Long-Covid.

Keywords: Long COVID; Post Acute Sequelae of COVID-19 (PASC); Ozone therapy

Introduction

Current clinical knowledge allows us to state that the patient with severe COVID-19 has a reduced or damaged capillary glycocalyx [Zha et al.. 2022; Patterson et al. 2022]. However, the resulting thrombotic phenomena associated with the reduction of antithrombin 3 in the part of the membrane with a non-physiological glycocalyx and the lymphocyte cell migration phenomena demonstrated by the significant alteration of the lymphatic cell subpopulation count had hinted at such an etiopathogenesis from the earliest clinical observations [Yamaoka-Tojo, 2020; Tricarico et al., 2021].

WHO has developed a clinical case definition of post COVID-19 condition as follows: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time". Moreover, a separate definition may be applicable for children [WHO, 2021]. Long COVID, post-COVID, post-acute COVID-19 syndrome (PACS), or post-acute sequelae of COVID-19 (PASC) are used as synonyms for this pathological condition.

Whatever, the accumulation of free radicals at the level of capillary membranes favours platelet aggregation and subsequently the onset of thrombotic and haemolytic phenomena. Glycocalyx lesions can be long-lasting as the portions that make up this structure require a prompt reparative response from the enzymatic protein production system based on DNA gene transcription. Appropriate therapeutic treatment with medical ozone, as a result of the inductive action of reactive oxygen species (ROS) on the NFkB system and, above all, lipid oxidation products (LOPs) with the consequent production of substances such as 4-hydroxynonenal (4-HNE) is able to stimulate the production of inducers of the Nrf2/KEAP1 cytoplasmic transcriptional pathway, restoring the production of enzymes and proteins useful for reconstructing the damaged portions of the glycocalyx [Tricarico and Travagli, 2021].

Materials and methods

From a diagnostic perspective, parameters that can provide useful information to monitor the evolution of the disease state are shown in Table 1 [Tricarico and Travagli, 2022].

Table 1. Common blood analysis laboratory findings for interpreting the staging criteria of COVID-19

Marker activity	Evaluation parameters
Blood cell count and bone marrow activity for hematopoiesis	red blood cells; red cell distribution width; reticulocytes; white blood cells, with lymphocyte immune-phenotype; thrombocytes.
Inflammatory activity	erythrocyte sedimentation rate; C-reactive protein; superoxide dismutase; cytokines and chemokines
Coagulation activity	antithrombin; fibrinogen; D-dimer
Kidney function	creatinine; uricemia; albumin-to-creatinine ratio; estimated glomerular filtration rate
Assorted activities	haptoglobin; calcemia; ferritin; procalcitonin; troponin; plasmatic proteins; lactate dehydrogenase; B-type natriuretic peptide; electrolytes; blood gas analysis

In addition, to diagnose these cases in the future, the suggestion is to also analyse glycosaminoglucane contents, with special reference to the glycocalyx biomarker syndecan-1 [Madukoro et al. 2022].

Results and discussion

To understand how the laboratory findings of Table 1 should be correctly interpreted, let's take for example haptoglobin and Ca^{2+} arterial blood levels. These parameters indirectly indicate the health condition of the glycocalyx. In COVID-19 patients, calcium blood levels are always below normal values, suggesting an increase in the activity of lymphocyte migration in the phase of "tight" adhesion between lymphocyte and endothelium. On the contrary, the presence of high haptoglobin values even in the absence of hemolysis phenomena suggests a liver release during the pathogenic challenging precapillary erythrocyte hemolysis. Moreover, the role of haptoglobin in the genesis of thrombotic phenomena needs more in-depth study, together with the potential involvement of the ABO blood-group system [Tricarico et al. 2021].

In terms of choosing dosages for *ex-vivo* systemic treatment of the blood of the same patient with oxygen-ozone gas mixtures under appropriate conditions, it must first be considered that the individual's antioxidant responses may vary in accordance with the values given in Table 2.

Table 2. Average ozone molecules/mL in the oxygen/ozone gaseous mixture at the different concentrations used at therapeutic level with respect to molecules/mL of readily available antioxidants and free unsaturated fatty acids (UFA) in human plasma [Tricarico and Travagli, 2021, adapted].

Ozone concentration [µg/ml]	Approximate number of ozone molecules ($x10^{19}$)	Potential approximate antioxidant activity of sample blood [molecules·mL]
10	1.3	Albumin: ~$2.6x10^{19}$ Uric acid: ~1.10^{19} Ascorbic acid: ~$1.7x10^{18}$ Free UFA: ~ $2.1x10^{17}$ Glutathione: ~$1.1x10^{17}$
15	2.0	
20	2.6	
25	3.3	
30	3.9	
35	4.6	
40	5.2	

Furthermore, it is possible that pre-existing lesions of the glycocalyx due to concomitant morbidities or genetic and metabolic modifications of the glycocalyx and its repair by the vascular endothelial cell substantially influence the healing processes and the maintenance of PASC symptoms and signs, as summarized in Figures 1.

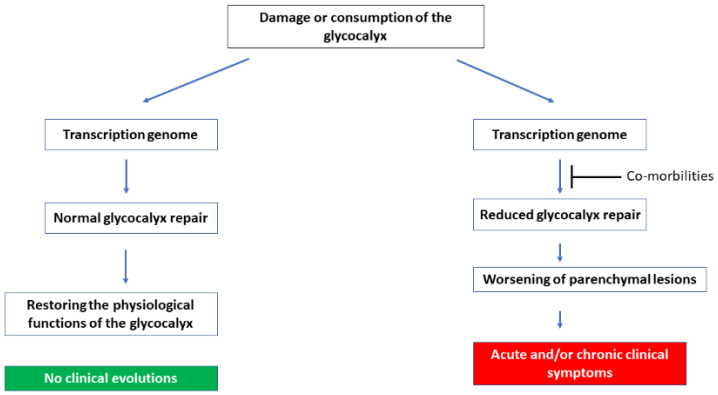

Figure 1. - Impact induced by the viral infection on the vascular endothelium at the glycocalyx level in relation to endothelial senescence conditions

In the course of systemic pathology such as COVID-19, oxidative phenomena are enormously increased and the antioxidant response is certainly reduced. Treatment with systemic oxygen-ozone therapy, thanks to the production of reactive oxygen species (ROS) and lipid oxidation products (LOPs) as effector molecules, can intervene in this imbalance, re-establishing, where possible, a physiological recovery of the vascular endothelial cells. However, this is only conceivable in accordance with the concept of personalized therapy and proper dose, taking into account the overall pattern of the body's antioxidant system. In particular, with reference to Table 2, it is necessary to carefully evaluate the number of ozone molecules in order to act with thought and reason, evaluating all the parameters that can help us in dealing with such serious clinical situations.

As for syndecan-1 is concerned, it is a stronger predictor of respiratory failure in patients with sepsis due to pneumonia, and which could also be useful for a follow-up of the Coronavirus endothelial lesion.

In our experience, early treatments with medical systemic ozone at lower than usual doses and repeated after a short interval of time 12/24 hours have been shown to protect the glycocalyx and reduce the symptoms commonly encountered in Long-COVID.

Conclusions

This presentation is not intended to be an exhaustive review of the state of the art of both the biochemical aspects of redox reactions in the blood and their interaction with the glycocalyx of the vascular endothelium in physiological and etiopathogenetic terms. Rather, the aim is to suggest a different point of view for the understanding and therapeutic treatment of pathologies in which cell and tissue ischemic damage is predominant. They can represent all those organ pathologies in which the improvement of both blood perfusion and intracapillary cell-lumen exchanges is compromised, as can be seen in the peculiar symptoms of Long-Covid.

The role of the vascular endothelium in mechano-transduction, permeability, and angiogenesis, as well as the disruption of this layer lining the luminal surface of vascular endothelial cells that occurs in various pathologies is becoming increasingly evident. We believe that intervention at the level of the glycocalyx is fundamental to refining the mechanism of systemic oxygen-ozone therapy precisely in the direction of being able to determine the concept of 'proper dose' as the cornerstone of a correct therapeutic approach to serious or disabling pathologies such as Covid-19 and its post-acute sequelae.

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