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Case Report

Improvement of Retinal Edema with QIAPI 1™. Case Report

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Received: October 13, 2022; **Published:** September 30, 2022

Abstract

There are anatomic and physiologic conditions that once perturbed predispose to abnormal fluid accumulation within the retina. The breakdown of the blood-retinal barrier both in retinal capillaries and/or the retinal pigment epithelium. The clinical leakage does not always correlate closely with tissue swelling or functional loss. In the literature is cited an active transport across the RPE, but it is poorly defined. Despite the significant impact of retinal edema in visual function, its pathophysiology is not well-understood.

Our discovery about the unsuspected water dissociation capability of eukaryotic cells is marking a before and after.

Keywords: *Retina; Oxygen; Hydrogen; Edema; Leakage; Retinal Pigment Epithelium*

Background

Retinal edema (RE) is a disease characterized by the swelling of the tissue due to the abnormal accumulation of fluid [1]. It is associated with increased retinal thickness and significantly reduced visual acuity, and it may develop in various ocular and systemic conditions. It is thought that topical prostaglandin analogs used for glaucoma treatment may also promote retinal edema, specially in the macular area (Cystoid Macular Edema) [2].

Retinal edema develops not only because protein and fluid coming from blood vessels enter the extracellular space, but because the external limiting membrane and the convoluted extracellular pathway within the retina limit the clearance of albumin and other large osmotically active molecules. These molecules bind water to cause edema [3].

The prevalent theory is hypoxia induces retinal edema primarily caused by vascular lesions, for instance diabetic retinopathy and retinal vein occlusion [4]. The edematous changes occur mainly in intermediate and deep layers of retina because of disruption of the inner blood-retinal barrier (iBRB). However, the effect of direct and acute hypoxia on iBRB remains to be elucidated.

Adult mouse model exposed to experimental atmospheric hypoxia induced iBRB disruption the subsequent edematous change mainly in the superficial layer of the retina. However, the low atmospheric oxygen concentrations don´t have a direct effect on oxygen tissue levels, due to living things do not take oxygen form atmosphere [5].

Low levels of atmospheric oxygen compromise the efficiency of gas exchange in the lung in relation to CO_2, since this gas is constantly formed inside our body, and from which an average adult expels between 900 grams and one kg every 24 hours.

When the usual composition of the atmosphere is modified beyond certain limits, the exchange of gases in the alveolus is depauperated and the levels of CO_2 begin to rise in the blood and tissues, which causes cellular dysfunction and if this disturbance in the expulsion of CO_2 by the alveolar membranes is prolonged enough or is of short duration but intense, edema and hemorrhage will appear in the tissues.

If we, voluntarily, stop or slow our breath rate, CO_2 begin to rise in our blood because cannot be expelled through our lungs.

Hypercapnia always goes with acidosis and hypoxia, due to high concentration of CO_2 inside our body and blood diminishes the efficiency, the efficacy, the astonishing accuracy of water dissociation. Thereby oxygen levels turn down because our body cannot get enough oxygen from water splitting, and not from atmosphere.

Oppositely, it is not possible to increase oxygen blood content through fast breath rate (Taquipnea). Our body goes into respiratory alkalosis due to Carbonic acid is expelled rapidly. However, blood oxygen content cannot be raised more than 98 or 99% of oxygen blood saturation.

Theoretically, Mitochondrial oxidative phosphorylation absolutely requires oxygen to generate the currency of energy in aerobes [6]. The physiologic homeostasis of these organisms is strictly maintained by supposedly optimal cellular and tissue-oxygenation status; however, oxygen levels is an indirect marker of hydrogen availability, because oxygen and hydrogen are obtained simultaneously when water molecule is breaking or dissociated. Thereby, always gone together. And hydrogen is the main carrier of energy in the entire universe, and oxygen is a toxic element that is produced inevitably by dissociating the water molecule, so plants expel it into the atmosphere, but through evolution, nature has optimized its presence.

In studies in climbers, PaO_2 (partial pressure of arterial oxygen) fell with increasing altitude, whereas SaO_2 (arterial oxygen saturation) was relatively stable [7]. Researchers explained that finding in basis that hemoglobin concentration increased, which is the traditional explanation. However, at light that hemoglobin can dissociate the water molecules, we believed that hemoglobin increases to raise the capacity of dissociate water, more than oxygen transportation; beginning with the reported fact, since 1897, that oxygen cannot pass through lung tissues and reach the blood stream [8].

Supposedly, the ability of human body to perform work, diminishes with the decreased availability of atmospheric oxygen for aerobic respiration [9]. Apparently, the important observations of Haldane [10] and Carl Ludwig [11] they have gone unnoticed in the academic world, starting with the people who develop the curricula in universities. And if we overlook that oxygen does not pass through the lung tissues, when planning a research paper, then the methods, results, analysis, and conclusions will be wrong at the very start.

P_ACO_2 partial pressure of alveolar carbon dioxide, was assumed to be equal to $PaCO_2$ partial pressure of arterial carbon dioxide. But in the case of the oxygen, the story is very complicated treating to adjust experimental results to clinical observations. It is not possible to minimize, much less theoretically compensate for, the fact demonstrated since the second half of the nineteenth century, that oxygen it cannot pass through the lung tissues and reach the blood circulation.

Case Report

Female patient dated birth December 1949, Diabetic and hypertensive since 2005, with degenerative osteoarthritis in the knees, as well as tendonitis of the patellar tendon. Take prazosin every 8 hours, metoprolol twice a day, paroxetine, and acetyl salicylic acid every 24 hours.

She comes for low vision in OI that does not allow her to wander alone, she cannot read small print. Vision has continued to decline despite medical treatment.

On examination, it is observed, in the left eye, diffuse edema of the retina, especially in the lower temporal quadrant. The following photographs were taken on the day of the first consultation (10/10/2020).

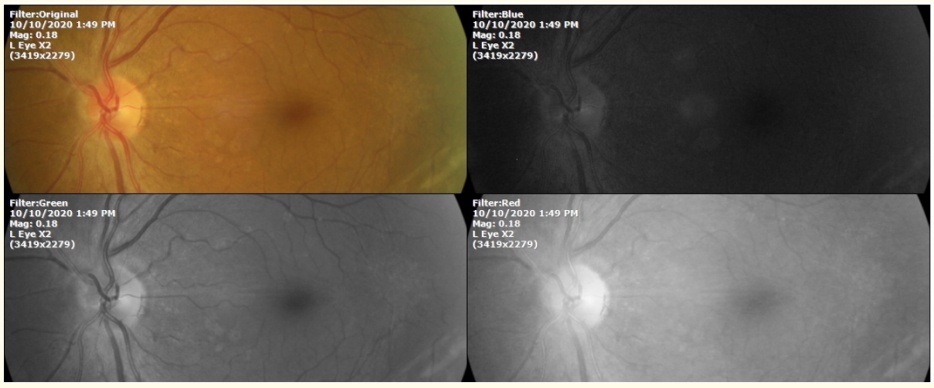

Figure 1: *Left eye. The retina is thickened especially in some areas such as the nasal border of the papilla, the macular region, and especially in the lower temporal quadrant. Careful examination did not find any retinal tears that could explain the predominant location of edema in the lower temporal region.*

Once the patient agreed to our treatment, QIAPI 1 was started, sublingual drops at the dose of three drops every hour, all the time she was awake. Since the body's response to the drug is comprehensive, she was advised to decrease the other medications and was given an appointment in six months. The following photographs were taken in the second consultation (04/17/2021).

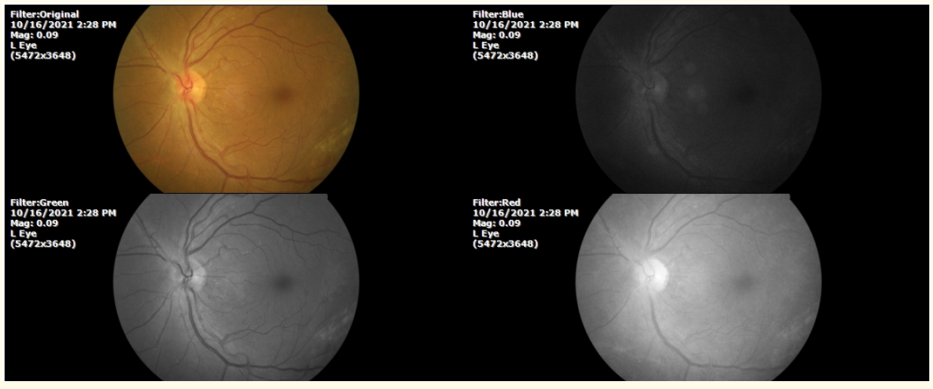

Figure 2: *Left eye. Edema of the retina shows a significant decrease. Both in the macula, as in the nasal border of the optic nerve, as well as in the lower temporal area. Careful exploration of the periphery of the retina did not reveal retinal tears.*

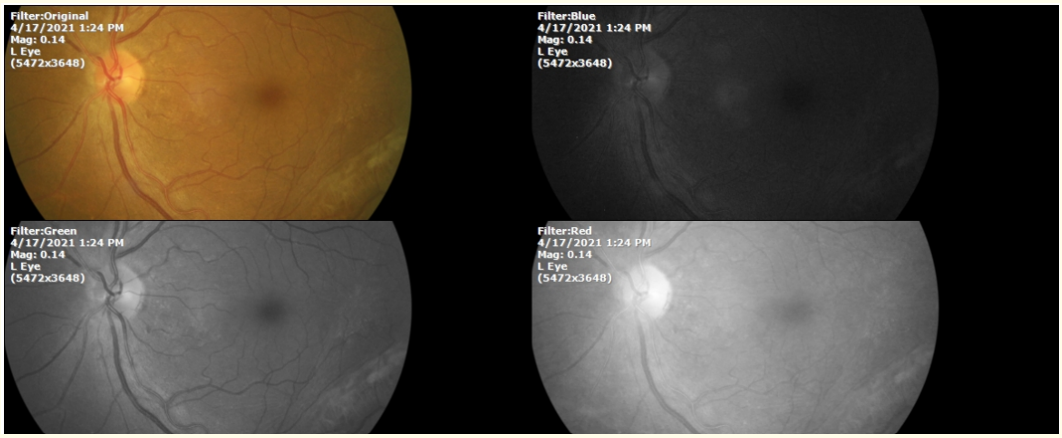

Figure 3: *Left eye. The greater the magnification, the details of the improvement of the retinal tissue are appreciated. The small areas of gliosis that are observed in the path of the maculo-papillary has not increased, and on the contrary, have decreased.*

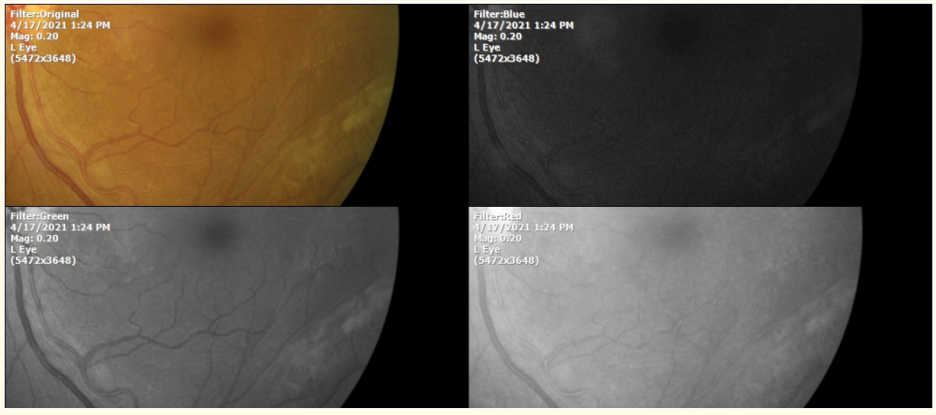

Figure 4: *Increasing the magnification, the anatomical details of the macula show good recovery, and the lower temporal zone of the retina, the most affected by edema, does not show degenerative changes such as the formation of adhesions with the vitreous or the formation of abnormal gliotic or fibrous tissue.*

It was indicated to continue with the same treatment, with the same frequency, and a new appointment was given in six months. The following photographs were taken six months later, in the third consultation (10/16/2021).

It was suggested to continue with the same treatment and return to further review in six months. The following photographs were taken at the fourth consultation (04/23)2022).

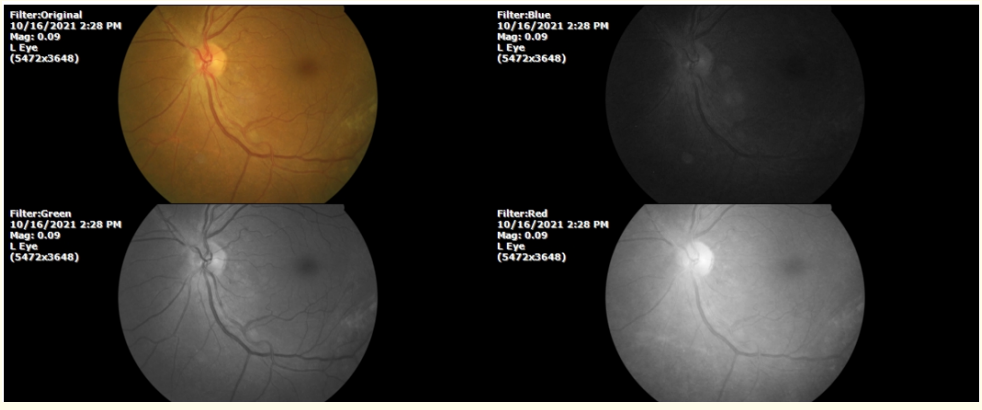

Figure 5: *The retinal structures follow their favorable course; the anatomy seems to be recovering properly. The edema of the lower temporal zone continues to decrease without showing unfavorable changes.*

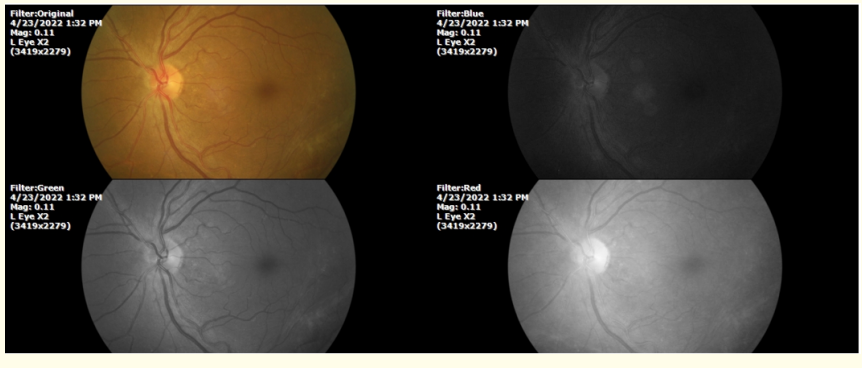

Figure 6: *The general appearance of the fundus continues to improve, the macula is seen in good condition, the small areas of gliosis continue to decrease; and edema of the inferior temporal region continues to fade without forming retinal vitreous adhesions or fibrosis or gliosis.*

Figure 7: *Left eye. Focusing on a wider sector of the lower quadrants, the retina is seen in good condition, the edema of the lower temporal region is more tenuous.*

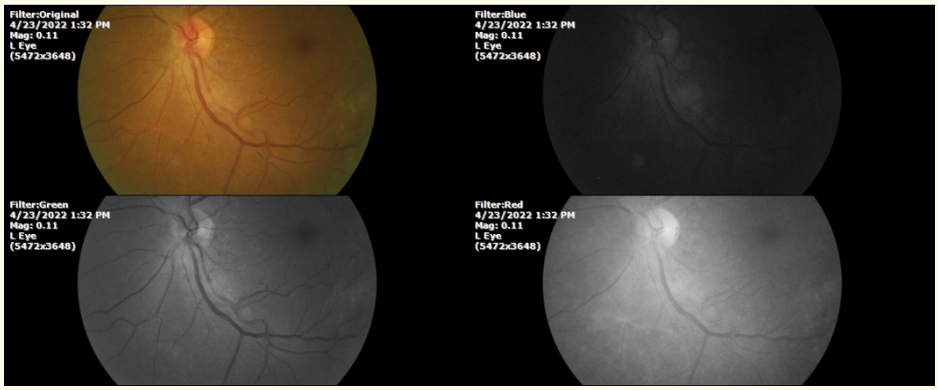

Figure 8: *Left eye. The anatomical features of the retina, macula, and optic nerve are very acceptable. Photographs with different wavelengths do not reveal formations of abnormal structures.*

Comment

Topical steroids, non-steroidal anti-inflammatory eye drops, and ocular steroid injections (sub-tenon or intravitreal) are the main treatment options for edema of retinal tissue [12]. Retinal edema is the most common cause of vision loss in patients with uveitis [13]. Although both regional and systemic steroids are considered the main treatments, other treatment options are available, including immunomodulatory agents and anti-vascular endothelial growth factor (VEGF) intravitreal injections [14].

Retinal edema affects approximately 7 million patients with diabetic retinopathy (DR) and 3 million patients with retinal vein occlusion (RVO) [15]. Cystoid Macular Edema involves fluid accumulation in the outer plexiform layer of the retina due to abnormal perifoveal retinal capillary permeability, whereas Diabetic Macular Edema is associated with the leakage of macular capillaries and is observed in patients suffering from diabetes [16]. Macular and retinal edema is also associated with an increase in VEGF and interleukin 6, which induce vascular permeability and vasodilation [17].

The histological alterations observed in the edema of the retina and the macula have been tried to explain according to the prevailing dogma that glucose is the source of energy and biomass of the tissues. But the results have been unsuccessful because the treatments developed based on these concepts have significant side effects and the visual capacity hardly shows a slight recovery.

Chronic macular and retinal edema leads to permanent visual impairment by altering the outer limiting membrane, affecting photoreceptor segments (outer nuclear layer thinning and outer segment atrophy), and disorganization of inner retinal layers [18].

Macular and retinal edema treatment approaches have changed substantially in recent years but without significative improvement of vision and tissues. Although laser photocoagulation (LP) has long been the gold standard for the treatment of macular edema, it is being replaced by anti-VEGF intravitreal injections, which have been reported as a first line of hope in the treatment for both Diabetic macular edema and Macular Edema due to Retinal vein occlusion (RVO) [19].

Frequent intravitreal injections are required to preserve the effects of anti-Vascular Endothelial Growth Factor (VEGF) therapy, and this treatment is therefore associated with repeated significant risk both local and systemics, high costs and an increasing burden on ophthalmologists and their patients. Despite the reported good efficacy of anti-VEGFs, sadly, many patients do not respond well to treatment. In addition, identifying which treatment regimen is optimal is a constant dilemma.

Intravitreal corticosteroid implants ensure sustained drug release for a specific period and reduce the number of injections needed compared with anti-VEGF treatment. Steroid implants were reported to be effective and safe both in DME and ME due to RVO; however, they are typically used as a second choice in cases resistant to anti-VEGF treatment [20]. The poor efficacy of steroids is worst because they may be associated with increased intraocular pressure (IOP) and cataract formation. The number of patients with edema of the retina or macula is important, otherwise heroic, and expensive treatments would not be tried.

It is a frequent conclusion of scientific articles about retinal edema that resistance to anti-VEGFs and intravitreal steroids treatment methods highlights the need for alternative treatment options. In other words, the problem remains. Therefore, despite the strenuous efforts of clinicians, researchers and laboratories, the underlying problem of edema of the retina and macula is yet to be resolved.

Our results in several retinal diseases that occur with edema demonstrate the importance of water dissociation in the metabolic sequence of the biochemical logic of a tissue as complex as the retina. Each cell of our body is energetically independent because everyone can dissociate water. This allows us to break the dogma that the oxygen present in tissues and blood comes from the atmosphere.

It is a widely accept concept that only a small amount of oxygen is transported in the plasma of the blood because oxygen does not dissolve easily in water, which is the main reason that alveolo-pulmonary tissues repel oxygen from the atmosphere. Thereby, the oxygen our body is produced by water splitting of every cell individually. Oxygen is not transported by the hemoglobin in red blood cells, because hemoglobin, given its enormous similarity with chlorophyll, is also able to dissociate the molecule from water. Therefore, the omnipresent oxygen in the erythrocyte comes from the dissociation of water that happens in hemoglobin, not from the atmosphere.

The supposed combination of CO_2 with hemoglobin forms a strong acid, and this kind of acids dissociate very little, which is incompatible with the pulmonary physiology that is currently proposed, since the transit of the bloodstream through the lung occurs in a second, and the strong acids, when dissociated little, would not allow the very dynamic gas exchange of CO_2 between the blood and the alveolo-pulmonary spaces.

Conclusion

The remarkable response of retinal edema to the treatment of QIAPI 1™ in the case of this patient, without the risks of intravitreal injections or both local and systemic side effects of steroids, allow us to glimpse that not everything is written in the physio-pathogenesis of edema of the macula and retina. The very exact circulation of water, electrolytes, as well as other molecules through the retina and adjoin tissues, depends to a substantial degree on the available energy, which comes from the dissociation of the water molecule, and not glucose.

Glucose is the universal precursor of any organic molecule that makes us up, both in plants and animals, but it is not able to provide the energy that its own metabolism requires.

Ethics Approval and Consent to Participate

The ethics committee of our study center approved the study, the patient signed his informed consent before starting treatment.

Consent for Publication

Not applicable.

Availability of Data and Material

Data and material are available.

Competing Interests

The ability of eukaryotic cells to dissociate water was discovered by researchers at our think tank. The medicines to modulate the process have been developed in our study center.

Funding Support

Our work has been financially supported by the Human Photosynthesis™ Research Centre.

Authors' Contributions

Dr. Arturo Solís Herrera is director and founder of our research centre. Dra. Arias Esparza and Dr. Paola E. Solís Arias are Clinical researchers of our study centre.

Acknowledgments

This work was supported by Human Photosynthesis™ Research Centre. Aguascalientes 20000, México. comagua2000@yahoo.com.

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Volume 13 Issue 11 November 2022