

## General on Glaucoma and Oxidative Stress. Comments on Study Design: “Biomarkers of Lipid Peroxidation in the Aqueous Humor of Primary Open-angle Glaucoma Patients”

Francisco Javier Hernández-Martínez\*

Hospital San Juan de Dios del Aljarafe, Bormujos, Sevilla Spain

\*Corresponding author: Francisco Javier Hernández-Martínez, Hospital San Juan de Dios del Aljarafe, Bormujos, Sevilla Spain, Tel: 8602984777422; Fax: 8602984777422; E-mail: fjhernandezm@hotmail.com

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### Commentary

Glaucoma is an optic neuropathy that causes progressive changes in the visual field and whose main known risk factor is the increased IOP [1]. Primary open-angle glaucoma (POAG) is associated with asymptomatic and irreversible vision loss, although its cause is unknown, it is known that in the presence of elevated intraocular pressure (IOP) occurs sequentially death of retinal ganglion cells by apoptosis and optic nerve fibres in its evolution cause glaucomatous optic atrophy and permanent loss of vision [2]. There has never been unanimously to establish which of the two injuries, structural or functional, it can first be detected. However, experts generally agree that early diagnosis is critical to improving the prognosis of glaucomatous patient.

It is true that the latest acquisitions in image analysis technology (Optical Coherence Tomography -OCT-) have provided objective and quantifiable data of morphological damage, in any way eliminates the subjectivity and variability of the methods previously employed. If we speak from the functional point of view, computerized perimetry remains the method most commonly used scanning glaucomatous damage worldwide. While exploring the optic disc remains the way easier to assess the damage to the optic nerve, the great variability in the interpretation and errors derivatives thereof, the OCT has become critical in monitoring patients with glaucoma.

However, they are not used in clinical usually, the data obtained from the biochemical analyses to manage the progression of glaucoma, although molecules that have been linked to this disease through pathogenetic processes such as inflammation, cytotoxicity, apoptosis, vascular damage, and oxidative stress, among others. This is because the cellular and molecular mechanisms by which the ocular hypertension (OHT) produced in the ocular anterior segment induces an irreducible neurodegenerative process with damage to the noble structures of the eye posterior segment and the optical path, are yet to be elucidated. Therefore, this has been one of the objectives of our study, we find risk factors that can monitor the progression of glaucoma using biomarkers easily applicable in clinical practice.

As mentioned, there is evidence in the scientific literature of the connection between oxidative stress and POAG [3,4]. We know that stress causes oxidative damage to biomolecules, especially lipids, nucleic acids and proteins. Our research group has worked for the last 12 years on this subject, demonstrating metabolites increased lipid peroxidation and decreased antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione enzyme system (GSHPx), and total antioxidant activity in the aqueous humor of patients with POAG, compared to subjects in the comparison group [5-12]. Other authors have demonstrated oxidative DNA damage in the course of glaucoma

by determining the increase of 8-hydroxy-2-deoxyguanosine [5]. In addition, oxidative damage to proteins has a complex chemistry. Forming reactive oxygen species (ROS), such as  $\text{Cl}_2\text{Fe}/\text{ascorbic acid}$ , xanthine/xanthine oxidase and  $\text{H}_2\text{O}_2$ , cause the appearance of many carbonyl groups and other alterations in different proteins, and although the mechanisms differ in each of these systems, they may also vary due to the type of affected protein. In fact, from damaged proteins as the protein intermediates hydroperoxides which are relatively stable and can generate new ROS by reacting with transition metals are generated. For example, in opacified crystal has chymotryptic activity seen lower proteasome, which can cause the accumulation of altered proteins as described in the lens in relation to age [13,14]. Various methods exist for determination of oxidized proteins, which include measurement carbonylated proteins, generated by oxidation many amino acid side chains. This is the marker of severe protein oxidation most used.

Furthermore, supporting the hypothesis of oxidative damage in glaucoma patients are descriptions of an increased resistance of aqueous humor outflow from the anterior chamber in the presence of high levels of  $\text{H}_2\text{O}_2$ , intense antioxidant activity detected in the trabecular meshwork, increased SOD activity and GSHPx in aqueous humor of glaucoma patients and lesions that induces oxidative stress on the trabecular meshwork [15].

As discussed above, besides the peroxides, it is also known that isoprostanes products lipoperoxidation catalytic action of ROS on arachidonic acid, can affect synaptic neurotransmission in the tissues of the ocular anterior segment. Currently determining F2 isoprostanes (due to its stability) is considered one of the best methods for determining oxidative stress by mass spectrometry, although determinations are also made by assaying for enzyme-linked immunosorbent assay (ELISA). F2 Isoprostanes are compounds containing a ring F prostane (F2 type prostaglandins) and are formed from ROS by non-enzymatic reactions. In fact, peroxidation of esterified arachidonic acid is produced and secreted into the circulation. After phospholipases act before eliminated in urine as free isoprostanes. Its half-life is very short and are prostaglandin antagonists [16].

It described that ROS are also released in processes where activation of polymorphonuclear occurs. These release different types of ROS that interact with pro-metalloproteinases and activating them extracellular matrix producing cell and tissue damage [17]. This information is apparent that remodeling of the extracellular matrix of the trabecular meshwork correlates with increased IOP, although this process seems to be controlled exogenously by water-soluble antioxidants such as

glutathione (GSH), having been identified presence of this tripeptide and its related iris, ciliary body and trabecular meshwork enzymes.

In addition to antioxidant enzyme (SOD, CAT, GSHPx, etc.) must consider the importance of antioxidants that can be provided exogenously, such as vitamins and minerals we eat with our food [18]. In recent years they have appeared different jobs relating to nutrition and its influence on the development and progression of glaucoma. In addition to the observational and interventional studies on the subject, a review about vitamins and minerals, carotenoids and essential fatty acids in relation to eye health by Brown et al., University of Oxford (UK) confirmed that vitamins A, C and E have a protective effect on the oxidative damage of the lens [19]. Epidemiological studies carried out by West and Oren [20] argue that eating fruits and vegetables that contain nutrients such as vitamins C, E and various carotenoids is inversely related to the risk of cataracts. Anyway, keep in mind that these studies were based on observation of consumption, and in fact could not prove that eating these foods in the diet can actually prevent cataracts. With regard to glaucoma, there are research groups worldwide that have linked diet and nutritional supplementation with the course of glaucoma [21-23].

It is difficult, from the molecular point of view addressing the role of nutrition in the management of patients with POAG. Ramdas et al. [23] showed that a diet with a low intake of antioxidants, particularly retinol and vitamin B1, was associated with an increased risk of glaucoma. Coleman et al., [24] assessed the risk of progression of glaucoma (by analyzing photographs of the optic disc and visual field) in 95 women diagnosed among 1155 participants in the study of osteoporotic fractures, which the influence was studied consumption of fruits and vegetables. The study showed less progression of glaucoma in women who frequently ate carrots, cabbage, green leafy vegetables and apricots, compared to those who did not. These results are really interesting and support the interest of nutrition and antioxidant defense system in glaucoma. Another study examined the relationship between consumption of dietary fat and POAG, including 25199 women Health Study of US nurses and 40306 men chosen from the Health Professionals [25] concluded that increased the proportion of polyunsaturated fatty acids (PUFAs) w-3/w-6 appears to increase the risk of POAG.

Our research group has studied the activity of enzymes transporters antioxidant vitamins in patients with POAG [26-28]. Zanon-Moreno et al. suggested that genetic factors may play a key role in the effect of the intake of antioxidants from the diet, glaucoma. They studied first the association between polymorphisms in key vitamins A and C and POAG carrier proteins. They included 300 subjects (150 cases with POAG and 150 controls) in a Mediterranean population to determinarles plasma concentrations of vitamins C and A and polymorphisms of a single nucleotide (SNPs) in genes related to these concentrations of vitamins: rs176990 and rs190910 in gene 1 retinol-binding protein (RBP1); rs1279683 rs10063949 and in and genes 1 and 2 of conveyors L-ascorbic acid Na + dependent, SLC23A1 and SLC23A2 genes respectively). POAG group subjects had significantly lower concentrations of vitamin C in plasma controls in association with the SNPs associated with genes that cofician for carriers of the vitamin. The same group analyzed the association of polymorphisms associated with vitamin E, vitamin C and GSHPx with serum biomarkers and the risk of POAG genes. In this study 250 cases and 250 controls with POAG also a Mediterranean population were selected. POAG patients had significantly lower plasma levels of vitamin E ( $p < 0.001$ ) and vitamin C ( $p < 0.001$ ) than control subjects.

However, activity was found in significantly higher plasma GPx enzyme in subjects with POAG compared to controls ( $p < 0.001$ ). The rs1279683 polymorphisms were also analyzed gene 2 transporter L-ascorbic acid Na+-dependent (SLC23A2), rs6994076 in gene transfer protein alpha tocopherol (APTT), rs737723 in gene associated protein tocopherol (SEC14L2/TAP) gene, and the gene rs757228 glutathione peroxidase 4(GPX4). SLC23A2 gene expression was also analyzed in a subsample. The results show an increased risk of POAG rs1279683 polymorphism associated polymorphism rs737723 and also. Likewise, the results also suggest a gene-gene interaction between the two polymorphisms that significantly increases the risk of developing POAG.

Given that in some respects there is still controversy about the theory of oxidative stress in the development and progression of chronic diseases, and remain unresolved many issues particularly with regard to the sequence of events that involves the time when the ROS formation alters the balance between pro-oxidant and antioxidant forces for the first and start the chain reaction and cell and tissue damage in POAG, we designed this project with the main objective to analyze the presence biomarkers of oxidative stress, quantifying the concentration of Malonil dialdehyde and Total antioxidant status in the aqueous humor of a population of patients with POAG and compared with the results obtained from a group of non-glaucomatous subjects underwent uncomplicated cataract (considered as comparative group).

This research was designed as a study, observational, transversal, analytical and non-experimental case control including a group of patients diagnosed with POAG and a comparison group (not healthy control) consisted of patients with no pathological cataract (GC). Both groups of participants were chosen to conform to the criteria of inclusion and exclusion defined in section Material and Methods and require surgery because of his eye disease (glaucoma vs cataracts), as we aim to find new risk factors for glaucoma, and therefore one of our goals has been the identification of biomarkers of oxidative stress in the aqueous humor, which of course can not be removed in healthy patients on ethical issues. Our main objective has been to identify new risk factors for the progression of glaucoma, so that they can introduce as biomarkers applicable in ophthalmology practice and improve monitoring of glaucomatous patient.

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