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Review Article

Glaucoma and Systemic Diseases with Vascular Compromise

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Abstract

Intraocular pressure (IOP) is the only potentially modifiable causal factor for the purpose of preventing glaucoma blindness, this being a multifactorial disease and although it is the most important risk factor in its development, the reduction of its non-guaranteed values the progression of glaucomatous damage. Some patients experience disease progression despite adequate IOP levels, and others with higher- than-normal values remain stable without risk to the visual field. Primary Open Angle Glaucoma (POAG) and Normal Pressure Glaucoma (GPN) share similar risk factors in pathogenesis and can be classified into mechanical and vascular categories. In recent decades, the deficit in the ocular circulation of patients with this disease has been well established, which could explain the continuous progression of glaucomatous damage in these cases.

Current scientific evidence has shown that there is an important association between systemic diseases with vascular compromise such as Migraine, Obstructive Sleep Apnea, Hypotension from different causes, High Blood Pressure, Cerebrovascular disease, Ischemic heart disease and Diabetes Mellitus with the findings at the ocular level in patients with glaucomatous optic neuropathy. This correlation guides to consider these diseases together so that each professional dedicated to visual health always considers it essential to evaluate the aspects that link these diseases in order to act accordingly.

Keywords: *Glaucoma; Systemic Diseases; Vascular Risk*

Introduction

Glaucoma affects more than 66 million people worldwide, and approximately 6.8 million of them are bilaterally blind. The loss of vision caused by this disease is irreversible and is the second leading cause of blindness worldwide [1].

Intraocular pressure (IOP) is considered the only potentially modifiable causal factor for the purpose of preventing glaucoma blindness. The multicenter clinical trial, Collaborative Normal Tension Glaucoma Study (CNTGS), demonstrated the effectiveness of IOP reduction in preventing the progression of glaucomatous damage, while the Ocular Hypertension Treatment Study (OHTS) demonstrated the benefit of reducing the IOP to avoid the conversion of the ocular hypertensive patient to glaucomatous. Medical treatment has undergone a surprising evolution, new hypotensive eye drops appear and different firms are currently investigating simpler, effective and more tolerable therapeutic options for patients [2].

Glaucoma is a multifactorial disease, but its precise pathogenesis is not yet clear. Although IOP is the most important risk factor in its development, its reduction does not guarantee the cessation of the progression of the damage. Some patients show progression of the disease despite maintaining IOP stability and others with IOP higher than normal remain stable without visual field deterioration [3].

Primary Open Angle Glaucoma (POAG) and Normal Pressure Glaucoma (NPG) share similar risk factors in pathogenesis, which can be largely classified into mechanical and vascular categories. In addition to IOP, age, suspicious characteristics of the excavation of the optic nerve, high myopia, decreased central corneal thickness, black race and family hereditary history, among others, are factors involved in the genesis of glaucomatous damage [2].

As the world's population ages, this disease will become more prevalent and advances in the diagnosis and treatment of glaucomatous optic neuropathy (NOG) will be of utmost importance to protect and improve the quality of life of our aging population [1]. An attempt has been made for some years to elucidate the etiology of NOG deterioration despite adequate IOP levels. In recent decades, the deficit in the ocular circulation of patients with this disease has been well established, which could explain the continuous progression in these cases [1]. Current scientific evidence has managed to demonstrate that there is an important association between systemic diseases with vascular compromise and ocular findings in patients with glaucomatous optic neuropathy. This correlation guides us to consider these diseases as a whole, it is about "a diseased eye in a diseased body." With the review of this topic, we intend to show more clearly the close relationship that exists between them and the importance that each professional dedicated to visual health always considers the evaluation of these aspects essential to act accordingly.

Growth

The diagnosis of POAG is based on the triad: IOP elevation, progressive degeneration of the optic nerve head, and visual field defects. However, up to 50% of patients with this disease have normal IOP, in these patients we speak of normal pressure glaucoma GPN. Currently there are several theories that help us understand the etiopathogenesis of NOG in these two types of glaucoma, these theories explain the different aspects of the production of this disease [4]. As more novel hypotheses we find: oxidative stress as a cause of axonal neurodegeneration of the optic nerve, although its relationship is not clear. Another theory is based on genetic alterations and changes in IOP, the variations of the latter determine modifications in the genetic expression of the astrocytes of the optic nerve [4]. The ionic stress generated in the head of the optic nerve by the different calcium gradient from the aqueous humor that can increase cell apoptosis and contribute to POAG is a hypothesis in development [4]. Within the classical theories, we find a mechanical theory that explains that the increase in IOP determines that the pressure gradient in the cribriform plate and in the axons of the ganglion cells generates deformation and mechanical stress, causing profound structural, functional and molecular alterations. On the other hand, vascular theory suggests that axonal loss in glaucoma is predominantly the result of ischemia. Thus, recent studies indicate that instability in optic nerve perfusion and reduced ocular blood flow (FSO) could greatly contribute to the development and/or progression of NOG. Elevated IOP is thought to compromise optic nerve head perfusion, causing ischemic damage, with consequent activation of programmed cell death (apoptosis) [4]. Another hypothesis suggests that reduced perfusion can lead to accumulation of excito-toxins, such as glutamate, causing toxicity and cell death. A phase of ischemia followed by restoration of normal blood supply (nocturnal or postural hypoperfusion) can cause damage with repercussions in the retinal ganglion cells with production of free radicals [1]. The blood flow of the optic nerve head depends on several factors such as: resistance to flow, blood pressure, intraocular pressure and viscosity of the blood. Defects of vascular autoregulation or a vaso-spastic circulation have been found more frequently in patients with glaucoma. Vasospasm produced intermittently by cold, stress, and smoking can interfere with self-regulation of the retina and optic nerve circulation [1,2]. In the vascular dysregulation syndrome, it is stated that local regulation cannot be carried out in relation to the needs of the organ or tissue. This may be due to endothelial cell damage caused by the rupture of an atheroma plaque or by mechanical irritation of a vessel. In addition to this, inflammation of the wall of a vessel can also alter the effective regulation. The systemic forms of dysregulation can be grouped into: Primary Vascular Dysregulation (PVD) and Secondary Vascular Dysregulation (DVS). In the context of glaucoma, PVD is the most important [4].

Primary Vascular Dysregulation PVD refers to a genetic predisposition to respond differently to a number of stimuli such as cold, mechanical stimuli, or emotional stress. Factors that are widely involved, but not exclusive to these, belong to the vascular system and have given the syndrome its name. On the other hand, because it is not caused by another disease, and has a hereditary component, it is recognized as primary. Vasospasm is a very prominent but not exclusive sign, which is why in the past this syndrome was known as the primary

vasospastic syndrome [1-3]. This syndrome occurs more in women than in men and in migraineurs, which indicates that sex hormones must play some role, it is more frequent in the Japanese population than in the Caucasian population and in academics than in the rest of the workers. Symptoms usually appear at puberty and lessen with age [4]. In clinical practice there are certain signs and symptoms that clearly point to PVD, these include: low blood pressure, especially in the very young and at night, cold in the extremities (in the hands and feet), reduced sensation of thirst, often a reduced body mass index, migraines frequently and an altered sensitivity to drugs (such as calcium antagonists or beta-blockers), because these subjects present an alteration in the expression of the proteins involved in their transportation. In general, the period of conciliation to sleep is longer, especially when they are cold and need to reach a good temperature in the feet as an essential requirement. They often have a very meticulous personality. It is known that certain subjects in stressful situations respond with redness or white spots on the chest or face. These individuals have a normal capacity to produce adenosine triphosphate (ATP), but in certain circumstances (sitting in a cold environment) they are not capable of producing as much ATP independent of heat, this being one of the reasons that explains the coldness of the skin and to reduce that heat loss, vasoconstriction occurs in their extremities. The ocular vessels are very similar to those of the skin, hence the measurement of blood flow in the capillaries of the nails can offer us indirect information on ocular vascular flow [4]. In daily clinical practice, some of these symptoms are not mentioned spontaneously by these patients in the consultation, but if they are asked they usually answer affirmatively. Some of them come to suffer orthostatic hypotension is the low reabsorption of sodium in the proximal tubule of the kidneys, this alteration depends mainly on endothelin [1] that has also been demonstrated in patients with PNG. Lack of rest at night is not only a consequence of PVD but also a manifestation of autonomic nervous system dysfunction [4]. The retinal vessels are stiffer and more irregular, and both neurovascular coupling and self-regulatory capacity are reduced, while retinal venous pressure often increases. The instability of ocular blood flow in these individuals with a limited range of self-regulation seems to predispose the optic disc structures to the risk of ischemia-reperfusion damage [3]. Reperfusion damage occurs by blood recirculation in a tissue after a period of ischemia. The absence of oxygen and nutrients from the blood to the tissue creates an environment in which the restoration of blood circulation ends up producing inflammation and oxidative stress damage rather than normal functional restoration. From an experimental point of view, this damage in the retina is caused when the blood circulation is reversibly blocked due to a marked increase in IOP and in a recurrent way. Mitochondria, which are abundant in the unmyelinated fibers of the head of the nerve Optical (due to high energy consumption) are increasingly damaged due to oxidative stress, which implies that energy production becomes insufficient, in this way the cellular compartments suffer and ends up causing accelerated aging [4]. The combination of DVP with a group of additional vascular and non-vascular signs and symptoms is also known as Flammer syndrome [5], the majority of subjects with this syndrome are healthy, however, they are at high risk of developing PNG [6].

Secondary vascular dysregulation

In this case it is a situation where dysregulation occurs as a consequence of another disease. The levels of vasoactive substances in the blood, particularly endothelin, rise, for example, in patients with Arthritis, synovial cells produce it, in Multiple Sclerosis lymphocytes as well as macrophages in patients with Acquired Immune Deficiency Syndrome. The consequence of endothelin elevations in the blood varies from one organ to another, in this way, being vasoactive substances, they only have access to smooth muscle and pericytes in those capillaries that are fenestrated (choroid). If the blood-retinal barrier is intact, the effect is minimal, but if it is impaired, endothelin leads to vasoconstriction and a significant reduction in ocular vascular flow occurs in the choroid. Endothelin can also diffuse within the optic nerve head [4]. Current scientific evidence has managed to demonstrate that there is an important association between systemic diseases with vascular compromise such as Migraine, Obstructive Sleep Apnea (OSA), Arterial Hypotension of different causes, Arterial Hypertension (HT), Cerebrovascular Disease (CVD), Ischemic Heart Disease and Diabetes Mellitus sharing vascular risk factors with glaucomatous optic neuropathy motivated by an interrelation of the pathophysiological mechanisms involved.

Migraine is considered a risk factor for glaucoma because its prevalence is higher in glaucomatous patients, especially those with normal pressure glaucoma. Migraine has traditionally been thought of as a vascular phenomenon, specifically caused by inadequate vasoconstriction of the cranial blood vessels. The throbbing headache associated with migraine appears to support this theory. Although the etiology of migraine is now thought to be a neural phenomenon, the vascular component still plays an important role in its pathophysiol-

ogy. The pathophysiology of migraine is complicated, and many details are still being investigated. The trigeminal-vascular system plays a central role in pain sensation. The cranial blood vessels are innervated by the ophthalmic branch of the trigeminal nerve. The vasoconstriction of these activates the afferent trigeminal nerves, leading to an activation of the trigeminal nucleus in the brain stem. The nucleus then commands the release of substances that cause vasodilation and increased vascular permeability in the cranial blood vessels. This causes the vessels to lose plasma, which can cause inflammation in the dura mater and consequently a perception of pain. Alternatively, activation of the trigeminal nucleus may be abnormally perceived by the brain, which can lead to pain [6]. The trigeminal vascular system is activated during migraines for two possible reasons. The first is that migraineurs may have an inherently unstable trigeminal vascular system due to dysfunction of the brainstem or diencephalic nuclei. The second is a phenomenon called expansive cortical depression that can cause vasoconstriction in the cranial blood vessels. and thus activate the system [7]. The theory of expansive cortical depression postulates that a self-propagating wave of neuronal and glial depolarization spreading through the cortex causes the migraine aura. As the wave progresses, neurons in the cortex become inactive, requiring less blood flow to meet their metabolic demands. This triggers the constriction of the cranial vessels and triggers the trigeminal vascular system [7]. Vasospasm has been associated with several eye diseases, such as corneal edema, occlusion of retinal arteries and veins, amaurosis fugax, and anterior ischemic optic neuropathy, and evidence indicates that it may also play a role in the etiology of glaucoma [7]. The pathogenesis of vasospasm may be related to a disturbance of endothelial-derived vasoactive factors. Patients suffering from migraine or Raynaud's disease, (both caused by vasospastic disorders), have an elevated plasma endothelin-1 level. It has also been shown to be elevated in patients with normal pressure glaucoma [6,7]. Numerous data show that the prevalence of migraine is significantly higher in subjects with GPN than in POAG subjects and normal subjects. This was first demonstrated by Phelps., *et al.* [8] and many subsequent studies have confirmed their results. Migraine patients, in general, suffer more frequently from DVP and vice versa. However, there are people with DVP who have never had migraines, and with migraines who have not had symptoms of DVP. If a patient with PVD suffers from migraines, the possibility of having migraine auras is higher. These can present in the form of visual symptoms, cold hands or in rare cases in the form of transient paralysis. A migraine attack can be triggered by emotional, physical stress, or even orgasm. Vasospasm leads to the production of visual symptoms that are normally localized in the visual area of the cortex and rarely in the retina. Spasms, however, can occur in some vessels such as the middle basilar artery [7].

Obstructive sleep apnea OSA is a chronic condition characterized by frequent episodes of collapse of the upper respiratory tract during sleep causing disturbances in the normal respiratory pattern, disturbances of gas exchange, increased effort of ventilation, peaks in systolic pressure and abrupt awakenings. This cycle is characterized by periods of hypoxia, hypercapnia, and negative intrathoracic pressure [6]. Studies have revealed increased sympathetic neural activity and increased catecholamine sensitivity related to cyclical hypoxemia, hypercapnia, arousals, tonic activation, and abnormal control of chemoreflexes [7]. OSA significantly disrupts sleep quality and causes daytime fatigue and lethargy. Over the course of months and years, these repeated awakenings and periods of hypoxemia lead to impoverished neuro-cognitive performance and organ dysfunction. Although several patient characteristics, including neck circumference, habitual snoring, hypertension, choking, and nocturnal panting, have been used to model for estimating a patient's chances of suffering from OSA, the best method to diagnose OSA. OSA is nocturnal polysomnography [6,7]. Men are three times more likely to suffer from it than women; however, the sex difference diminishes after menopause. The prevalence increases with age, doubling and even tripling in patients 65 years of age or older compared to those between 30 and 64 [7]. A very clear relationship has been found in patients with OSA, especially in the case of GTN patients. It is believed that the glaucomatous damage would be due to altered perfusion of the optic nerve secondary to prolonged and repeated periods of apnea or, alternatively, due to the induction of HTN or arteriosclerosis due to this syndrome, 7.2% of patients with obstructive sleep apnea may have POAG and 2.8%, GTN [4]. Patients with OSA may have defective endothelium-dependent vasodilation secondary to endothelial damage from apnea-induced hypoxia. A second explanation that has been suggested is a phenomenon called theft. Hypercapnia induces dilation of the cerebral arteries, reduces brain resistance, and increases cerebral blood flow. In glaucoma patients with abnormal self-regulation, such dilation may redirect blood flow away from the optic nerve head [7]. At the San Ignacio University Hospital in Bogotá D.C. The first study was carried out in Colombia that examined the prevalence of PNG in patients submitted to a polysomnographic study, where a frequency of 2.7% association between PNG and OSA was found, a figure

that is similar to that reported in the literature [9]. Circadian fluctuations in IOP have been studied for many years; But only recently have researchers discovered that blood pressure, ocular perfusion pressure, and ocular blood flow also fluctuate throughout the day. Several studies have indicated that fluctuations in perfusion pressure may be more significant than absolute changes in it [6]. In normal eyes, the nocturnal IOP peaks at the end of the night, just before waking up. When you go from standing to lying down, the blood supply to the eye is redistributed. This results in an increase in orbital venous pressure and consequently an increase in IOP. In healthy subjects, the lying position also causes an increase in pressure in the ophthalmic artery that exceeds the increase in IOP [7].

Systemic Arterial Hypotension Within an ophthalmological examination it is common that blood pressure measurement is not performed routinely; however, it is advisable to calculate the diastolic perfusion pressure. This can offer valuable information about the progress of this condition. Studies have been found in which there is an inversely proportional relationship between diastolic perfusion pressure and primary open-angle glaucoma. The critical value of the diastolic perfusion pressure is between 50 and 70 mmHg, below these values it is believed that the progression of glaucoma is significantly increased [10]. Systemic hypotension has been shown to impair the autoregulatory response to IOP fluctuations. This may contribute to the fact that hypotensive patients have a greater excavation of the optic nerve head [6]. Some studies have found that arterial hypotension combined with intraocular hypertension is a much more important risk factor than hypertension itself. It is generally accepted that extremes of blood pressure affect optic nerve blood perfusion, so hypertension is only one of the mechanisms involved in optic nerve damage [10]. There is growing evidence to support the notion that nocturnal hypotension increases the risk of POAG. Secondary to a reduction in sympathetic activity, blood pressure drops during sleep, and the most marked decrease usually occurs between 2 and 4 am, these levels are normally between 10% and 20% below the daytime average, and a transitory peak follows in the early hours of the morning. The fact that this reduction in blood pressure occurs at times when the IOP may rise causes significant reductions in blood pressure. ocular perfusion pressure and corresponding ocular circulation, causing chronic mild ischemia and optic nerve damage if self-regulatory mechanisms are insufficient to maintain blood flow above the critical level [7]. Patients with progressive glaucoma tend to have lower blood pressure at night than patients with stable glaucoma. In a prospective longitudinal cohort study, cumulative nocturnal hypotension predicted visual field loss. They demonstrated that when the mean nocturnal arterial pressure during sleep was 10 mmHg below the mean daytime arterial pressure, it was a significant predictor of the global progression of fieldimetric damage by multivariate analysis ($P < 0.02$) [11]. Patients who experience large fluctuations in blood pressure. Blood pressure at night may have a higher risk of glaucomatous progression compared to individuals whose blood pressure fluctuates within normal limits [7]. Because systemic hypertension is usually treated with oral antihypertensive medication, it is necessary to distinguish the effect of systemic antihypertensive medication from systemic hypertension itself. The use of antihypertensive drugs is considered one of the main factors contributing to the prevalence of hypotension postural, although other studies have not been able to find a significant causal association. The relationship between orthostatic hypotension and circadian variability of blood pressure has been investigated. There is some evidence showing that structural changes can be induced by taking systemic antihypertensive drugs [12].

Systemic arterial hypertension Systemic hypertension causes damage to target organs such as the vasculature, heart, brain, and kidneys. Complex biochemical, hormonal, and hemodynamic mechanisms are involved in pathogenesis. In the initial stage of hypertension, blood flow may increase in line with the increase in blood pressure. However, as irreversible vessel wall damage and endothelial hypertrophy progress, blood flow eventually decreases. This disease compromises vessel function more significantly in older people, thus they have a much higher risk of cardiovascular complications and a narrow range of self-regulation [12]. There are studies that report that POAG has a frequency 3 to 10 times higher in patients over 80 years of age than in patients between 40 and 50 years of age [13]. HT is a very important risk factor for the development of glaucoma in especially in elderly patients. This indicates that the damage it causes to the eye varies with age, in young patients, in fact, it can become a protective factor against glaucoma, since in this age group there are still no changes in the microvasculature that can cause hurt; on the contrary, in the elderly, angiosclerosis favors the ischemia of tissues such as the head of the optic nerve [14]. The association between HT and glaucoma has been studied extensively. There is evidence that it interferes with the self-regulation of the posterior ciliary circulation, which is already compromised in glaucoma. A group of researchers

support the theory that high blood pressure affects the progression and incidence of glaucoma and others claim that the important thing would be the perfusion pressure [14]. The association between both diseases was stronger in cross-sectional studies compared to longitudinal case-control studies, supporting the role of increased HT in IOP elevation and possibly in the development of glaucoma. HT may contribute to an increase in IOP through overproduction or alteration of the outflow of aqueous humor [14]. The study by Caprioli and Colemn [15], where they studied more than 3,000 patients, showed that there are significant changes in intraocular pressure in hypertensive patients. The pathophysiological mechanism underlying the relationship between HT and IOP is not fully understood. One proposed theory is that elevated systemic pressure increases the aqueous humor filtration fraction secondary to elevated ciliary artery pressure, causing a small but sustained increase in IOP. Other explanations for these findings include the common mechanisms that may account for increases in both systemic pressure and IOP, such as generalized sympathetic tone, plasma corticosteroids, or sclerotic changes that occur in both the vasculature and the outflow channels. of the eye [6,7]. In an article from an ophthalmology clinic in Germany, they concluded that hypertension is the most common cause of systemic disease associated with glaucoma; Because it affects ocular perfusion, there is especially dysfunction of the capillary endothelium, altering the retinal self-regulation mechanisms. They advise the periodic review of arterial hypertensive patients with the ophthalmologist [16]. It is important to consider that although there is a positive correlation between both pressures, the systemic and the ocular, the correlation between the increase in systemic pressure and the development of POAG is small. The probability ratio (odds ratio) for the development of the latter is related to the increase per 10 mmHg in systolic blood pressure or diastolic blood pressure, fluctuating between 1.08 and 1.12 and 1.00 to 1.09, respectively. This relationship is inherently difficult to study due to the different criteria by which studies define hypertension. Despite these limitations, several studies have found that hypertensive individuals have a 50% to 100% higher risk of developing GAA than individuals with normal IOP [7].

Cerebrovascular disease Carotid atheromatosis and ischemic strokes are more prevalent in glaucoma patients. Systemic atherosclerosis and optic nerve vessel sclerosis can compromise blood flow in the optic nerve head as has been demonstrated in multiple dynamic ocular perfusion studies with Doppler Ultrasound [2]. The association of glaucoma with stroke is particularly significant. This could be explained because in both diseases there are factors that could be confounding, such as age and HT, which are the factors most frequently associated with cerebrovascular disease. The relationship between glaucoma and carotid atheromatosis has been demonstrated, which could support the common aetiopathogenesis of both processes that justifies the clinical association found.2 The association between PNG and CVD is closer than in POAG, thus half of the patients with PNG according to certain studies have a history of CVD. It has also been shown that cerebrovascular diseases are more directly associated with NPG than with subjects without glaucoma [3]. Silent Cerebral Infarction (ICS) is caused by vascular occlusion and is discovered by chance on an MRI or CT scan, with no detectable neurological signs in apparently healthy patients. In people older than 60 years there is a prevalence of ICS of 10.7%, while in symptomatic patients the prevalence is between 10 and 38% [4]. In a study that included 94 patients with PNG, ICS was present in 34% of them and in another study of 20 patients with PNG, ischemic changes of small cerebral vessels were found on MRI, compared to controls. These changes would indicate a vascular component in the GPN. Migraine and nocturnal hypoxia due to OSA appeared associated with ICS and both are associated with PNG [4].

Ischemic heart disease Arterial stiffness or loss of its elasticity is one of the main signs of vascular aging. The increase in this has been recognized as an independent risk factor for cardiovascular diseases [17]. Some scientists have investigated the association between arterial stiffness and glaucoma. However, its role in the pathogenesis of glaucoma is still controversial. A cross-sectional study comparing POAG patients and age- and sex-matched controls showed that there was no difference in heart rate and pulse pressure between glaucoma patients and control subjects. However, both the common carotid artery compliance coefficient and baroreflex sensitivity were reduced in POAG patients, and vessel wall stiffness was greater in POAG patients than in controls using the follow-up system. of the wall by ultrasound [18]. In the study carried out by Jau., *et al.* in which 4032 patients with POAG were included, it was shown that these patients had a higher risk of suffering a cardiovascular accident (CVA) throughout the 5-year follow-up than the control group. After adjusting for age, gender, geographic location, and comorbidities (HTN, Diabetes Mellitus, Dyslipidemia, and coronary heart disease), they concluded that POAG continues to be an important predictor for the development of stroke [19]. Lin HC., *et al.* found longer hospital stays and higher

mortality in subjects with POAG [20]. These results are corroborated in the Barbados Eye Study, where they also found statistically significant associations between presenting cardiovascular mortality and POAG treated with Timolol (P = 0.04). The two studies previously described to avoid bias collected and verified their data to demonstrate interactions of any medication [19].

Mellitus diabetes DM is an endocrine-metabolic syndrome that presents with vascular and neurological complications. Different studies have described the relationship between it and glaucoma, but other studies deny this relationship [4]. Starting in the 1960s, a controversy began that continues today. It has been proven that both diseases, in the same subject, have a multigenic component, but to date studies do not support the existence of a common genetic component [4]. The presence of POAG increases in patients with type 2 DM, and also increases with its evolution time. The cause is not well understood, but it could be related to changes in the trabeculum [4]. There are factors in diabetes that can accelerate the onset or aggravate the characteristics of glaucoma, such as an increase in transforming growth factor B, an increase in this factor in the aqueous humor with the formation of glycoproteoglycans in the iridocorneal angle, as well as fibronectin deposits. favor POAG [3,4]. In the context of glaucoma, diabetes is generally considered a vascular risk factor due to the many and complex ways in which it disrupts blood vessels. In the eye, the vascular changes due to diabetes that contribute to retinopathy have been well documented, are the result of hyperglycemia, and include aberrant vascular flow, alterations in permeability, and inability to perfuse capillaries [7]. Initially, damage to the pericytes causes dysfunctional self-regulation of blood flow and contributes to the formation of microaneurysms. The deposition of materials in the extracellular matrix and the thickening of the basement membrane of the capillaries also play a role in defective self-regulation. In addition to these factors, leukostasis in retinal vessels can contribute to capillary non-perfusion, endothelial cell damage, as well as increased vascular permeability and angiogenesis. The ischemia that results from these occluded capillaries stimulates the release of angiogenic factors, including vascular endothelial growth factor. These factors cause neovascularization in the retina that can lead to devastating complications and also cause neovascular glaucoma due to neovascularization of the iris. Through similar mechanisms, including advanced glycation end products, chronic hyperglycemia causes vascular complications in other parts of the body, contributing to nephropathy, neuropathy, and cardiovascular disease [7].

There is a positive relationship between glycated hemoglobin levels and IOP in individuals with diabetic retinopathy (DR). Patients with higher levels of glucose in the aqueous humor increase the synthesis of fibronectin, which accumulates in the trabecular meshwork and offers greater resistance to the passage of aqueous humor, and consequently, greater elevation of IOP. It is confirmed that chronic hyperglycemia is associated with an increase in IOP in diabetics [21]. In 2003, a study in which 10,479 patients were followed for 8 years, found an increase in the prevalence of diabetes from 14 to 25%, and from 4.6 to 13.8% in the case of glaucoma in a group of older patients. This does not support the association between these entities [22]. Diabetics have higher IOP when performing applanation tonometry, since some corneal biomechanical parameters are affected in them. These include the resistance factor and the central corneal thickness. The values obtained when performing the tonometry must always be corrected. Many studies exclude IOP as a criterion, and find that there is no increased risk of glaucoma in diabetics [23] Lin HC [20] established an association between POAG and diabetic patients, glaucoma being 1.8 times more frequent in patients with DM than in control subjects. Those who support the relationship between both diseases point out that in diabetes the susceptibility of retinal cells (including ganglion cells) to apoptosis triggered by additional stress such as elevated IOP is increased. The metabolic lack of control of DM and elevated IOP, in a sustained way, affect the thickness of the nerve fiber layer of the retina, so these patients are more prone to suffer neuronal damage. In DR, there is an increase in glycation end products that justifies a greater sensitivity to neuronal damage in a situation of high IOP [23]. There are studies that support the hypothesis that POAG protects against DR. Elevated IOP is associated with less severe retinopathies. Williams., *et al.* Investigated the association between POAG, OHT and the elevated cup/disc radius with the progression of proliferative DR, and the results obtained demonstrate a protective effect of glaucoma on DR. The lower number of ganglion cells in glaucomatous retinas produces a lower retinal metabolism, and this a lower probability of PDR, or a beneficial effect on its progression [24]. Sato and Roy found that high glucose concentration results in upregulation of fibroconnective synthesis and its accumulation in bovine trabecular meshwork cells [25].

Conclusion

Advances in the understanding of the etiopathogenesis of glaucoma clearly allow it to be recognized as a multifactorial disease. It is not a disease confined to tshe eye; it is rather the manifestation at the ocular level of a systemic dysfunction. The traditional view of glaucoma as a disease caused by increased IOP is simplistic and incomplete. The complex interplay of vascular, genetic, immunological, and degenerative events continues to be studied. The commitment to expand the knowledge of the causes that originate glaucoma should be oriented towards the search for new therapies. Although the underlying relationship between risk factors is still unclear and evidence-based treatment is not yet based on vascular etiology, Doctors and researchers must always know the vascular origin of the pathogenesis of glaucoma.

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