Controversies in the vascular theory of glaucomatous optic nerve degeneration

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Abstract

An understanding of the pathogenesis of glaucoma is one of the foundations in glaucoma management. A number of theories have been presented to explain glaucomatous neural degeneration. The vascular theory attempts to explain the causation of glaucoma on the basis of vasogenic factors and altered hemodynamics in the body; however, this theory remains controversial. There are proponents for and against the role played by vascular factors in the development of glaucomatous optic nerve degeneration. This review aims to analyze the various studies performed to provide evidence for and against the vascular theory of glaucoma. It also affirms the need to undertake further studies regarding the pathogenesis of glaucoma and integrate them into our management strategies. The literature search for this systemic analysis was performed using search engines, such as PubMed, The Virtual Library of the Ministry of Health Malaysia, Google Scholar, and ClinicalKey.

1. Introduction

Glaucoma is a broadly used term signifying a neurodegenerative disorder of ocular tissues. It is characterized by structural damage to the cellular components of the retina and axonal elements in the optic nerve. These changes are correspondingly reflected in functional parameters, such as the visual fields, electroretinograms, and others. There is a plethora of knowledge regarding the structure-function changes and their management in glaucoma; however, the pathophysiologic mechanisms responsible for the development and progression of glaucoma remain unclear.1,2

A number of theories have been presented over the years to explain the causation of glaucoma. Initially, the mechanical theory was put forward to explain the pathogenesis of glaucomatous optic nerve degeneration (GOND). It was hypothesized that GOND occurred due to the raised intraocular pressure (IOP) forcing the lamina cribrosa backward and squeezing the nerve fibers within its meshes to disturb axoplasmic flow. However, this theory is unable to explain those patients whose IOP is above the normal range (21 mmHg), but who do not develop GOND (ocular hypertension). The Ocular Hypertension Treatment Study also reported that >90% of individuals with high IOP failed to progress to glaucoma when followed over a 5-year period.3 Conversely, there is a sub-group of patients who develop changes characteristic of glaucoma, even though they have what is considered a statistically normal level of IOP (normal-tension glaucoma). It was also observed that some patients continue to progress, despite the lowering of IOP to an ideal target range.3 Thus, the mechanical theory fails to entirely explain the pathophysiologic concepts of GOND.

Subsequently, a number of other theories have been presented to describe the etiopathogenesis of GOND. These include the vascular, genetic, and biochemical theories.4 The vascular theory attempts to explain glaucoma causation on the basis of reduced perfusion pressure, faulty vascular autoregulation, or loss of neurovascular coupling.5 While some researchers advocate the vascular theory as the cause of GOND, others provide evidence against this. Therefore, this article reviews the opposing perspectives in favor of and against the vascular theory of GOND.

The importance of studying the various mechanisms of glaucoma pathogenesis cannot be overemphasized. Only greater insight into these basic concepts can refine our current practice of glaucoma management.
2. Evidence in favor of the vascular theory

2.1. History of the vascular theory

The earliest reference to a vascular etiology in the pathogenesis of glaucoma was attributed to von Jaeger in 1858, who argued that neuronal damage due to elevated IOP was mediated by ischemia and not compression of nerve fibers.2

Priestly Smith, Kummel, Magitot, Duke-Elder, and several others also contributed to the vascular theories of GOND.7,11 In 1922, Felix Lagrange12 claimed that glaucoma was just one manifestation of a deranged circulatory physiology affecting the entire body. He termed glaucomatous optic neuropathy a “sick eye in a sick body.”

In 1948, Dienstbier et al13 stated that, “the solution of the problem of pathogenesis of glaucoma has entered its final phase…. glaucoma is the expression of stasis in the venous system and the eye capillaries. It has its origin partly in organic vascular changes with a more or less marked spastic factor and partly in changes in function (vasoneurosis).”

In 1970, Hayreh14 defined glaucoma as, “a disease wherein the normal balance between the IOP and blood pressure in the choroidal vessels, supplying the optic disc and retrolaminar part of the optic nerve is disturbed. This results in vascular insufficiency in the optic disc and retrolaminar part of the optic nerve and hence in visual field defects and pathological changes in the optic disc and optic nerve.”

2.2. Ocular blood flow

One of the foundations of the vascular theory is ocular blood flow (OBF). It is theorized that faulty blood flow is an important contributor to GOND. Indeed, ocular circulation is an intricate system that supplies essential nutrients to a diverse group of ocular structures, such as the optic nerve, retina, and choroid. Concurrently, this vascular system is required to perform functions without interfering with image formation and transmission in the visual pathway. Therefore, OBF requires meticulous regulation and adapts to ever-changing metabolic requirements as stipulated by the varying visual functions. Additionally, OBF compensates for fluctuating perfusion pressures and maintains an optimal temperature around the eye. However, ocular circulation is not uniform, and considerable individual variation exists in the distribution of vascular flow in this region.5

Some researchers suggested that the decrease in OBF intrinsically does not lead to glaucoma. Instead, other characteristics, such as an alteration in the quality of blood supply to the optic nerve head (ONH) are implicated in GOND.16 Flammer et al17 suggested that an unstable, fluctuating OBF is the likely mechanism of glaucomatous damage. Fluctuating OBF leads to unstable oxygen supply, which, in turn, triggers oxidative stress. Deokule et al18 studied the correlation of blood flow with perimetric changes and reported that retrobulbar blood-flow velocities are reduced in advanced disease and correlate with standard automated perimetry (SAP) global indices in glaucoma patients. Changes in neuretinal rim blood flow in primary open-angle glaucoma (POAG) patients also correlate positively with mean deviation (MD) on SAP.18 Additionally, increasing parapapillary atrophy was reported in eyes with progressive glaucomatous changes, and is assumed to be related to hypoperfusion of the ONH.18

2.3. Ocular perfusion pressure

Ocular circulation is dependent upon a net pressure gradient that causes blood flow to the eye and is known as ocular perfusion pressure (OPP). This factor represents a relationship between two key dynamic biological parameters: blood pressure (BP) and IOP. In simplistic terms, OPP is defined by:

\[ \text{OPP} = \text{BP} - \text{IOP} \]  

(1)

From Eq. (1), a higher BP or a lower IOP results in a better OPP. Studies showed that low OPP is a risk factor for the prevalence, incidence, and progression of glaucoma.20 According to Flammer et al,12 the best predictor of progression of glaucomatous damage is fluctuation in OPP; however, underlying factors relating OPP and glaucoma have not been identified. It is yet to be determined whether low OPP is independent of the sum of the two risk factors, i.e., low BP/mean arterial pressure and high IOP.12,23

Increased systemic BP will correspondingly increase pressure in the anterior ciliary artery. This, in turn, leads to an increased ultrafiltration and, therefore, increased IOP. However, as per Eq. (1), a rise in BP should cause an increase in OPP. Epidemiological studies, quoted by He et al12 also suggested that systemic hypertension is a protective factor in glaucoma; however, glaucoma is frequently reported in both hypo- and hypertensive patients. Moreover, normal tension glaucoma (NTG) was commonly reported in patients with low BP. The Barbados Eye Study, the Proyecto VER Study, and the Egna-Neumarkt Study showed that low diastolic perfusion pressure (45–50 mmHg) is associated with a higher risk of developing glaucoma.23–25 The Los Angeles Latino Eye Study concluded that both low diastolic pressure and high systolic pressure are associated with an increased prevalence of open-angle glaucoma.26 Glaucoma is also seen in individuals who have large nocturnal dips in BP. Interestingly, the Baltimore Eye Survey demonstrated that systemic hypertension is protective against glaucoma in younger patients, but poses an increased risk in elderly patients.27 It is theorized that vascular sclerosis in old age reduces OBF, even in hypertensive patients, thereby increasing the risk of GOND.28

Studies have shown that alterations in ocular hemodynamics may play a significant role in the POAG pathogenesis. It was suggested that in glaucomatous eyes, OBF decreases, because apoptotic retinal ganglion cells (RGCs) require less oxygen and nutrients. Therefore, reduced OBF is assumed to be a secondary phenomenon resulting from the loss of RGCs. There are conflicting schools of thought, however, which infer a reduced OBF as the primary event that subsequently leads to ischemic death of RGCs. This process most likely involves some vascular factors.8,28,29

2.4. Biochemical factors and ocular blood flow

Ocular blood flow can be affected by a number of biochemical factors. The retina and ONH of glaucoma patients exhibit increased levels of hypoxia inducible factor 1α.17 This oxygen-regulated transcriptional activator can increase oxygen delivery or facilitate metabolic adaptation to hypoxia.29 Some of the circulating molecules that diffuse from the choroid into the ONH and retina include endothelins (ET), vascular endothelial growth factor, and matrix metalloproteinases (MMPs). These molecules weaken the blood-retina barrier and allow erythrocytes to escape from vessels, clinically appearing as splinter hemorrhages at the optic disc margin. Elevated ET-1 levels in glaucomatous patients are associated with oxidative stress as a causative factor. ET-1 reduces blood flow in posterior ciliary arteries, and high ET-1 levels are also associated with disease progression.30–32 Similarly, MMP-2 and MMP-9 are upregulated in the ONH of glaucoma patients, contributing to apoptosis.33

Ischemia causes oxidative stress, which is mediated by a group of cytotoxic byproducts known as reactive oxygen species (ROS), such as free radicals, superoxide, and lipid peroxides. ROS are constantly produced as a result of normal cellular metabolism and...
react with lipids, nucleic acids, and proteins. Additionally, ROS are implicated in tissue injury during ischemia and in secondary degeneration following reperfusion.4,31,34 Under normal conditions, ROS are neutralized by autoregulatory mechanisms; however, when the intrinsic antioxidant capacity of a cell is exceeded, excess ROS results in DNA damage and apoptosis.31

2.5. Systemic vascular abnormalities in glaucoma patients

Glaucoma patients may also suffer from systemic vascular disorders. For example, reduced blood flow was reported in other parts of the body, such as decreased levels of nail-fold capillary flow. Obviously, being so far from the ONH, this change cannot be a consequence of glaucomatous damage.4 Other indirect signs of altered blood flow reported in glaucoma patients include changes in conjunctival capillaries, increased prevalence of ONH hemorrhages, venous thrombosis, gliosis-like alterations, hearing problems, silent myocardial ischemia, and small ischemic lesions in the brain.35 These patients also demonstrate impaired systemic vascular regulation, including nocturnal hypotension, vasospasms and migraines, blood rheologic abnormalities, and disturbance of vasoactive compounds, such as ET-1.35 Therefore, glaucoma could represent a part of the spectrum of systemic vascular abnormalities.

2.6. Vascular dysregulation

Among other factors, glaucoma is also attributed to dysregulation of an autoregulatory mechanism present in the eye.30,35 Autoregulation is a physiological phenomenon, wherein vascular resistance changes dynamically and maintains blood flow at the level required by the local metabolic activity, despite changes in perfusion pressure. Metabolic, shear-dependent, and myogenic mechanisms all play a role in autoregulation.15,20 In the presence of hypoxia, autoregulation is activated in an attempt to sustain normal blood flow; however, failure of such mechanisms produces ischemia, subsequent cellular injury, and apoptosis.1 According to Hayreh,14 autoregulation can only operate within a critical range of perfusion pressure. Therefore, once perfusion pressure declines or surpasses a critical range, autoregulation breaks down.14

Faulty autoregulation or vascular dysregulation has been implicated in glaucoma pathogenesis. Vascular dysregulation can be primary or secondary, with secondary vascular dysregulation (SVD) observed in disorders, such as multiple sclerosis. Conversely, primary vascular dysregulation (PVD) occurs in otherwise healthy individuals and constitutes an inborn tendency to respond differently to a variety of stimuli, such as feeling cold and emotional or physical stress. It has an inclination for females, slim and professional individuals, and Asian individuals. Cold extremities are the leading symptom, while other features include reduced feeling of thirst, prolonged sleep-onset time, altered drug sensitivity, nocturnal hypotension, splinter hemorrhages, and reversible visual-field (VF) defects. Patients with PVD have a high risk of various eye diseases, but especially for glaucoma. In PVD, the adaptation to changes in OBF due to perfusion pressure is disturbed and appears to be the major link to glaucoma.1,31

2.7. OBF assessment

In recent years, researchers have strived to study OBF directly in order to further understand the mechanism of vasogenesis. The methods utilized to study OBF included fundus fluorescein angiography (FFA), Doppler imaging, scanning laser-Doppler flowmetry, oximetry, and laser-speckle flowgraphy.19 FFA demonstrated an increased incidence of ONH-filling defects near the superior and inferior poles of the disc, with good correlation with VF defects.1,35 Optical coherence-tomography angiography showed decreased ONH perfusion in a small group of patients having early glaucomatous defects.36 Hamard et al.37 demonstrated that patients with POAG and NTG have reduced optic nerve blood-flow velocity and increased aggregation of erythrocytes, and concluded that impairment of ONH perfusion was associated with these factors.37

In conclusion, several hypothetical and experimental studies showed that vascular factors play an important role in the initiation and progression of glaucoma. Reduced OBF could be a primary event in a susceptible individual, evident by the number of PVD and SVD disorders seen in glaucoma patients. Conversely, the reduced OBF may be secondary to compression of the blood vessels in a progressively distorted lamina cribrosa secondary to high IOP. The final effect of reduced OBF is regional hypoxia. In non-glaucomatous individuals, an autoregulatory mechanism may overcome these changes; however, failure of such a process leads to ischemia and catalyzes an apoptotic response in RGCs due to mediation of several factors.

3. Refuting the vascular theory of glaucomatous optic nerve degeneration

Although numerous articles substantiate the existence of a vascular mechanism leading to GOND, issues, such as inaccurate methodology, testing on non-primate animal models, and substandard evaluation of the parameters being examined, pose limitations. Additionally, some studies that assessed vasogenesis as a causative mechanism of glaucoma failed to achieve desired results. Cioffi3 highlighted: “many studies remain controversial, since the validity of the various hemodynamic measurements remain under investigation.” Therefore, it is imperative to critique such studies and seek an authentication of the vascular theory as a causative factor in the development of GOND.

3.1. OPP

An important factor discussed previously is OPP, which is regarded as the driving force for blood circulation in the eye and is dependent on BP and IOP. It is also credited with playing a major role in determining retinal function1; however, a number of studies showed that GOND may not be directly related to BP. Ernest et al7 discovered that changes in systemic BP did not result in alteration of oxygen tension at the ONH after reaching an initial period of equilibrium; indicating that BP affects neither OBF nor results in GOND. Some authors denied a strong association between BP and OBF. Weinstein et al38 reported that blood flow to the optic nerve remains stable across a wide range of blood pressures. Similarly, Graham et al.39 reported no significant difference between systemic BP or centrally-derived aortic BP between glaucoma patients and normal individuals. Thus, they refuted that glaucoma patients, especially those with NTG, have lower central BP levels.35 Hwang et al40 found no correlation between blood flow and structural changes in the ONH, and claimed that blood-flow reduction and structural loss were independent predictors of VF loss in glaucoma patients.40

Some studies demonstrated a positive correlation between systemic BP and glaucoma, while others found no correlation. These conflicting results suggested a complex link between BP and glaucoma. BP is also an imperfect surrogate of ocular perfusion. Eq. (1), mentioned previously, is a simplification of the actual equation:

\[ \text{OPP} = \text{MAP}_{\text{ophthalmic}} - \text{IOP} \]  

(2)

Because the mean ophthalmic artery pressure (MAP_{ophthalmic}) is not commonly measured in clinical practice, the mean brachial
arterial pressure (MAP_{brachial}) is substituted. This is an estimate, assuming that the MAP_{ophthalmic} and MAP_{brachial} (BP) are the same. However, these two vary in the presence of diseased vascular beds, and significant differences could potentially arise with positional change.\textsuperscript{1} In an experimental study, Hayreh et al\textsuperscript{11} induced arteriosclerosis (using a high-cholesterol diet) and systemic hypertension (by renal artery occlusion) in monkeys for several years. Subsequently, chronic IOP elevation was achieved by laser photocoagulation of the trabecular meshwork. It was astonishing that neither systemic hypertension nor arteriosclerosis was found to have a significant influence on the retinal and optic nerve changes induced by elevated IOP.\textsuperscript{1}

3.2. OBF

Various studies evaluated the relationship between OBF and IOP. Ernest\textsuperscript{61} found little change in blood flow until IOP was elevated to levels much greater than clinical relevancy. Similarly, Armaly and Araki\textsuperscript{26} also found that blood flow to the optic nerve was stable until IOP exceeded 50 mmHg. Sossi and Anderson\textsuperscript{43} reported that raised IOP did not decrease OBF, and Sperber and Bill\textsuperscript{44} utilized the 2-deoxyglucose technique to study OBF. This method gives an accurate representation of the nutritional status of the optic nerve, provides data over a long duration, and has high spatial resolution. According to their findings, OBF and metabolism in the optic nerve is unaltered, except at very high levels of IOP.\textsuperscript{44} Quigley et al\textsuperscript{4} also studied the effects of IOP on ONH blood flow using iodooantipyrine autoradiography, and reported that despite long-term increase in IOP, there was no relationship between increased IOP and decreased blood flow. Deokule et al\textsuperscript{18} reported a lack of correlation between the severity of VF loss (MD), described as a continuous variable, and parapapillary retinal blood-flow parameters.\textsuperscript{18}

Hayreh\textsuperscript{74}\textsuperscript{45} claimed that in patients diagnosed with POAG or NTG, VF defects were due to vascular disturbances in the anterior part of the optic nerve. Maumeeni contradicted this conclusion, mentioning: “There is no evidence in the physiologic experiments that have been done to date nor in the histologic studies performed on human eyes with glaucoma, to indicate that vascular alteration is the primary factor in axonal damage and visual field loss.”\textsuperscript{47} Hayreh\textsuperscript{46} also stated “... it is not possible to state definitely the reason for the characteristic distribution of the various nerve fiber bundle defects in glaucoma.” Therefore, any vascular theory should be able to prove an association between characteristic VF defects and OBF changes in glaucoma. Decreased OBF is also found in conditions other than glaucoma. For example, in multiple sclerosis, the marked reduction in OBF is due to high levels of circulating ET. However, a high proportion of patients with multiple sclerosis do not develop glaucoma, despite reduced OBF.\textsuperscript{5,25}

The ONH appearance in anterior ischemic optic neuropathy (AION) is an interesting phenomenon. AION due to arteriosclerosis leads to bland atrophy of the ONH, whereas AION due to giant-cell arteritis leads to ONH excavation comparable to GOND.\textsuperscript{25} Flammer and Mozaffarieh\textsuperscript{25} and Burgoyne et al\textsuperscript{1} mentioned that AION leads to a pale and atrophic ONH, while Hayreh\textsuperscript{14} demonstrated that in glaucoma, choroidal circulation is affected. Hence, these tests fail to measure blood flow in the vascular bed. Hayreh\textsuperscript{14} claimed: “We do not have a single clinical method which gives scientifically valid information on the in vivo blood flow in the optic nerve head.”\textsuperscript{14} Cull et al\textsuperscript{9} highlighted that studies on ONH blood flow in glaucoma have been cross-sectional, indicating that these results merely provide glimpses during the multiple stages of glaucoma. These methods do not provide concrete data regarding the continual evolvement of hemodynamic changes in the development of glaucoma.\textsuperscript{28}

3.3. The role of biochemical factors

Vascular endothelial cells are known to release endothelial agents, including prostanoids, nitric oxide, ETs, angiotensins, oxygen free radicals, and thromboxane A2. These agents are theorized to play an important role in GOND by regulating vascular tone. This homeostasis is attributed to a balance between the endothelial vasodilators (e.g., nitric oxide) and vasoconstrictors (e.g., ETs).\textsuperscript{14} However, increased ET-1 is also observed in other autoimmune diseases and Susac syndrome. Therefore, elevated ET-1 levels apparently have no significant association with glaucoma prevalence.\textsuperscript{29}

3.4. Weaknesses in methodology

Numerous studies assessing OBF were performed on animal models, including cat, sheep, and monkey eyes.\textsuperscript{1} Because the ocular anatomy of these mammals differ from those of humans, the conclusions from these studies cannot be automatically applied to humans. Hayreh\textsuperscript{15} stated that all methods evaluating ONH circulation have limitations. For example, laser techniques only focus on the optic disc surface. This structure is supplied by the central retinal artery, while Hayreh\textsuperscript{14} demonstrated that in glaucoma, choroidal circulation is affected. Hence, these tests fail to measure blood flow in the vascular bed. Hayreh\textsuperscript{14} claimed: “We do not have a single clinical method which gives scientifically valid information on the in vivo blood flow in the optic nerve head.”\textsuperscript{14} Cull et al\textsuperscript{9} highlighted that studies on ONH blood flow in glaucoma have been cross-sectional, indicating that these results merely provide glimpses during the multiple stages of glaucoma. These methods do not provide concrete data regarding the continual evolvement of hemodynamic changes in the development of glaucoma.\textsuperscript{28}

3.5. Systemic vascular disorders

As mentioned previously, glaucoma is commonly associated with a number of systemic vascular disorders. However, Graham et al\textsuperscript{19} refuted any link between glaucoma and migraines or Raynaud’s phenomenon.

3.6. Role of dysfunctional autoregulation

Dysfunctional autoregulation of OBF has been implicated in the pathogenesis of GOND. However, the part of the optic nerve that develops faulty autoregulation is still a matter of debate. Evans et al\textsuperscript{26} found the central retinal artery to have faulty autoregulation; however, Weinstein et al\textsuperscript{30} showed that autoregulation is equally effective for the prelaminar, laminar, and postlaminar segments of the optic nerve. However, it was noted that the distal optic nerve exhibited a higher vulnerability to arterial hypotension (“shock-induced optic neuropathy”). He debated that autoregulation is efficient in this region, and, therefore, a possibility of increased metabolic activity in the distal optic nerve causing glaucomatous damage is likely, even with small decrements in blood flow. He concluded: “Further studies are needed to clarify what role, if any, is played by ischemia in human glaucoma.”\textsuperscript{30}

There are many studies showing that the commonly presumed associations in glaucoma may not be causative factors associated with its pathogenesis. OPP, BP, OBF, and the methods employed to assess these associations suffer from systematic and statistical errors. Thus, the role played by vasogenesis in glaucoma inception and progression has yet to be established.

4. Conclusion

Because the mechanical theory was unable to explain many facets of GOND, the alternative vascular theory was proposed, and many experiments were performed to prove that parameters, such as ocular blood flow and perfusion pressure, are the deciding
factors in the causation of this condition we call glaucoma. However, we are currently aware that not all assumptions regarding the vascular theory hold true. Other mechanisms, including those associated with the biochemical and genetic theories, indicate that several other factors can lead to glaucoma. It is assumed that glaucoma is a multifactorial disorder, with multiple mechanisms active in the same patient. Therefore, further prospective, longitudinal, clinical, and epidemiological studies should be conducted to conclusively prove the role of vasogenesis in the causation of glaucoma, and ultimately use that fact of pathogenesis in better management of patients suffering from this condition in a more holistic manner.69

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