Mechanistic links between systemic hypertension and open angle glaucoma

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Running Head: Links between hypertension and glaucoma

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Abstract

Systemic hypertension or hypertension is a very common chronic age-related disease worldwide. It is typically characterized by a sustained elevation of blood pressure, particularly when the systolic blood pressure and/or diastolic blood pressure are of more than 140 mmHg and 90 mmHg, respectively. If hypertension is not well controlled, it may lead to an increased risk of stroke and heart attack. It has been shown that hypertension is linked with various ocular diseases, including cataract, diabetic retinopathy, age-related macular degeneration, and glaucoma. Glaucoma is the leading cause of irreversible blindness worldwide. Primary open angle glaucoma is the most common form of the disease and is usually characterized by an increase in intraocular pressure (IOP). This condition, together with normal tension glaucoma, constitutes open angle glaucoma. Systemic hypertension has been identified as a risk factor for open angle glaucoma. It is speculated that blood pressure is involved in the pathogenesis of open angle glaucoma by altering IOP or ocular blood flow, or both. Recent evidence has shown that both extremely high and low blood pressure are associated with increased risk of open angle glaucoma. Additional pathogenic mechanisms, including increased inflammation likely to be involved in the development and progression of these two diseases, are discussed.

Introduction

Systemic hypertension (also known as hypertension) is a very common disease affecting more than 1.3 billion people worldwide.[1] Hypertension is commonly characterized by a high blood pressure in the systemic arteries with systolic blood pressure equal to or not lower than 140 mmHg and/or diastolic blood pressure not lower than 90 mmHg, respectively.[2] Hypertension has been associated with various age-related systemic chronic diseases, including diabetes[3] and osteoarthritis.[4] For example, it has been reported that hypertension and diabetes share common pathogenic mechanisms regarding increased insulin resistance, systemic inflammation, and oxidative stress.[3] Similarly, hypertension has been considered as a risk factor for various ocular diseases, including hypertension retinopathy,[5] diabetic retinopathy,[6] age-related macular degeneration,[7] cataract,[8] and glaucoma.[9] Hypertensive retinopathy is believed to be a direct ocular manifestation of hypertension. During the course of disease progression, there are clinical signs, including increased retinal arterial narrowing and intima thickening, breakdown of the blood-retinal barrier, retinal hemorrhages, and hard exudates. Papilledema may result from raised intracranial pressure, which is part of hypertension complications, in severe cases.[5] Diabetic retinopathy is shown to be exacerbated by hypertension because of the damages in vascular endothelium.[6] In addition, it has been shown that neovascular AMD is associated with moderate to severe hypertension especially with antihypertension treatment while non-neovascular age-related macular degeneration shows no association.[7] This is possibly related to hypertension-induced vascular changes, such as focal arteriolar narrowing.[10] Hypertension has also been suggested to associate with cataract development via increased inflammation and vascular endothelial dysfunction.[8]

Glaucoma is the leading cause of irreversible blindness worldwide. It is typically characterized by an optic neuropathy, leading to progressive visual field loss, and ultimately blindness.[11] Glaucoma is a complicated eye disease and has been associated

with elevated IOP.[12] Glaucoma can be classified into primary open angle glaucoma, normal tension glaucoma, primary angle-closure glaucoma, and acute angle closure glaucoma. Primary open angle glaucoma is the most common form of glaucoma and is characterized by an elevated IOP with a wide-open anterior chamber angle. Normal tension glaucoma is similar to primary open angle glaucoma, except that the level of IOP is comparable to that of healthy individuals. Because of the similarity between primary open angle glaucoma and normal tension glaucoma, they may be grouped together as open angle glaucoma. In contrast, primary angle-closure glaucoma is characterized by chronic IOP elevation accompanied by peripheral anterior synechiae, whilst acute angle closure glaucoma is caused by acute obstruction of anterior chamber angle, causing a sudden increase in IOP.[13] Two major theories have been proposed for the pathogenesis of open angle glaucoma, based on either mechanical or vascular aspects.[14,15] The mechanical theory suggests that the increased IOP compresses the laminar cribrosa, thereby damaging the axons and retinal ganglion cells. The vascular theory advocates that there is an insufficient blood supply to the optic nerve, causing ischemic-induced retinal damage. These theories are likely to be inter-related, as neither of these mechanisms alone can fully account for the variations in glaucomatous damage observed.

The association between Hypertension and Open Angle Glaucoma

The association between hypertension and open angle glaucoma remains controversial. Many studies have demonstrated a positive or negative relationship between hypertension and open angle glaucoma (**Table 1**). In one of the largest studies in recent years, Asefa et al. reported the odds ratios of glaucoma (without IOP adjustment) are 1.03, 1.01, and 1.03 per 10 mmHg increase in systolic blood pressure, diastolic blood pressure, and mean arterial pressure, respectively, suggesting that the risk of open angle glaucoma increases with blood pressure elevation.[9] In the Blue Mountains Eye Study,

without IOP adjustment, each 10 mmHg increase in systolic blood pressure results in an increase of 10% in open angle glaucoma prevalence, and each 10 mmHg increase in systolic blood pressure, diastolic blood pressure, or mean arterial pressure leads to a 20-30% increase in the prevalence of ocular hypertension.[16] A meta-analysis also indicated that hypertensive patients have an approximately 1.2-fold higher risk of developing open angle glaucoma than healthy individuals and that the risk was higher for primary open angle glaucoma than normal tension glaucoma.[17] This was consistent with other studies showing a positive association between hypertension and primary open angle glaucoma.[18-20] Despite the evidence of a positive correlation between hypertension and open angle glaucoma, other studies have demonstrated a negative association.[21,22] A longitudinal study showed that hypertension is protective against open angle glaucoma by reducing the risk by up to 50% during a 4-year follow-up period.[21] Perasalo et al. reported that patients with systolic blood pressure of >160 mmHg have better visual functions compared with those with systolic blood pressure <120 mmHg.[22] In the same study, patients with systolic blood pressure <120 mmHg had a 2-fold increase in risk to be visually impaired compared with those having a higher systolic blood pressure.[22] Tielsch et al. showed that for hypertensive patients younger than 60 years of age, hypertension is negatively correlated with glaucoma.[23] The odds ratio of primary open angle glaucoma to hypertension increases with the age of the patients. For hypertensive patients older than 69, their risk of developing primary open angle glaucoma is higher than normotensive people.[23] The exact reason for these discrepancies among different studies are not entirely clear, it could be due, at least in part, to the variations in criteria adopted in these studies including 1) age of subjects; 2) whether hypertension is present at baseline; 3) duration of hypertension; and 4) use of antihypertension medications.

Hypertension and Glaucomatous changes in the retina

In human, hypertension is associated with reduced retinal capillary density[24] and increased retinal arterial and venous narrowing,[25] significantly reduced thickness of the macular and ganglion cell complex but no change in the retinal nerve fiber layer thickness.[26] In contrast, Xu et al. observed that retinal nerve fiber layer thickness is reduced in hypertensive patients,[27] and Lim et al. showed that both the macular and retinal nerve fiber layer are thinner in patients with hypertension for more than five years.[28] It was notable that IOP measurements were not conducted in some of these studies. Akay et al.[26] and Lim et al.,[28] whose studies include IOP measurement, did not observe any significant IOP difference between the hypertension and control groups. These results suggest that hypertension-induced retinal thinning, when noted, may possibly be mediated, at least in part, by IOP-independent mechanisms.

In animal studies, arterial narrowing of the retinal blood vessels has been found in spontaneously hypertensive rats with systemic hypertension.[29] In addition, reduced outer nuclear layer thickness, but not inner nuclear and ganglion cell layers, are observed in spontaneously hypertensive rats at 10 and 40 weeks, as compared with control Wistar Kyoto rats.[29] Sicard et al. showed that the b-wave rather than the a-wave in the electroretinogram is reduced in 11-weeks old spontaneously hypertensive rats, indicating that bipolar cells, rather than photoreceptors, are selectively impaired in spontaneously hypertensive rats.[30] Another study showed that both retinal ganglion cells and photoreceptors are damaged in 42 weeks old spontaneously hypertensive rats.[31] However, as none of these studies measured the IOP, it remains unclear whether these retinal changes in spontaneously hypertensive rats are triggered by IOP-dependent mechanisms. It was previously shown that spontaneously hypertensive rats had a lower IOP as compared to controls at nine months.[32] However, a later study showed that IOP was significantly higher in spontaneously hypertensive rats compared with Wistar Kyoto rats at 13 weeks.[33] The precise relationship between the time-

dependent IOP changes with respect to retinal changes in hypertension has yet to be determined and it is possible that the age of these spontaneously hypertensive rats animals may be a compounding factor.

Relationship among Hypertension, Intraocular Pressure and Ocular Perfusion Pressure – concept of Autoregulation

Primary open angle glaucoma is shown to be more closely related to hypertension than normal tension glaucoma, raising the possibility that blood pressure may increase the risk of primary open angle glaucoma by elevating IOP.[17] It has been proposed that hypertensive patients are more likely to have higher IOP.[34] The prevalence of ocular hypertension is found to be 4.2% in people without hypertension, which is increased to 8.1% in those with treated, but poorly controlled hypertension and 8.2% in those with untreated hypertension.[16] A longitudinal study observed that for normotensive subjects, the mean change in IOP over a 9-year period was +0.22 mmHg. In contrast, for those with hypertension at baseline, the mean change in IOP was +0.49 mmHg, significantly higher than normotensives.[35] Similar studies have reported a positive correlation between blood pressure and IOP.[18,36,37] Despite these findings, a meta-analysis showed that each 10 mmHg increase in systolic blood pressure was associated with a 0.26 mmHg increase in IOP, and each 10 mmHg increase in diastolic blood pressure was associated with a 0.34 mmHg IOP elevation.[38] These findings suggested that, even though the blood pressure-dependent IOP elevation was statistically significant, clinically it may only be subtle.

In contrast, the blood supply to an organ is generally regulated by the perfusion pressure. The perfusion pressure is defined as the difference between arterial and venous pressure. The higher the perfusion pressure, the greater the blood flow to the organ and the less likely the organ becomes ischemic. In most cases, the pressure outside the vein is considered to be atmospheric,[39] as shown in **Figure 1a**. Nevertheless, under certain

circumstances, the tissue outside the vein could exert pressure on the vein. For example, whilst standing, there is blood pooling in the veins of the lower limbs due to gravity. To facilitate blood return to the heart, the skeletal muscle contracts, enhancing blood circulation in the presence of one-way venous valves.[40] In the eye, the IOP exerts pressure on the retina. Since there are no venous valves to control the direction of blood flow in ocular veins, the compression caused by IOP would hinder rather than enhance ocular circulation. It is suggested that venous pressure in the eye is roughly equivalent to the IOP. As shown in **Figure 1b**, the arterial pressure pushes the blood to flow downstream against the venous pressure, and the pressure in the veins before leaving the eye slightly exceeds the IOP under normal conditions.[41] In the eye, the ocular perfusion pressure is the difference between arterial pressure and IOP. In principle, the higher the ocular perfusion pressure, the higher the ocular blood flow to the tissue.[42] However, under physiological conditions, there is a lack of a linear relationship between ocular perfusion pressure and ocular blood flow.[43] This is attributed to the ability of maintaining a relatively constant ocular blood flow despite fluctuating ocular perfusion pressure, which is known as autoregulation.[42] Autoregulation is a complicated process and refers to the intrinsic property of organs to maintain a constant blood flow in response to changes in perfusion pressure. It is controlled by both myogenic and metabolic mechanisms. Since the retina has no autonomic innervation, the blood supply to the inner retina is regulated by local vascular mechanisms. In the myogenic mechanism, the smooth muscle cells in the blood vessels contract when being stretched. This process is possibly mediated by activating voltage-gated Ca^{2+} channels, resulting in an increased vascular resistance due to vasoconstriction.[44] Metabolic mechanisms refer to the regulation of retinal blood flow in response to changes in metabolic demand.[44] The increased retinal blood flow during flickering light stimulation is believed to be a result of metabolic autoregulation.[45] When the retinal neurons are activated by flickering light, the consumption of oxygen and glucose is increased. The metabolic mechanism is likely mediated by neurovascular coupling in the retina, in which Müller cells play a crucial role in the communication between retinal neurons

and blood vessels.[45]

Potential mechanisms underlying the positive correlation between Blood Pressure and Intraocular Pressure

Despite the fact that there is only a small but significant positive relationship between blood pressure and IOP observed clinically, the mechanisms responsible for the positive link between blood pressure and IOP have been studied extensively.[18,36,37] There are several hypotheses to account for the positive relationship between blood pressure and IOP. First, it could be attributable to increased systemic sympathetic activity. Excessive activation of the sympathetic nervous system has been implicated as a primary precursor of hypertension.[46] Stimulation of cervical sympathetic ganglions has been reported to reduce the cross-sectional area of Schlemm's canal and increase the outflow resistance and IOP in rats.[47] Second, increased blood pressure could lead to a higher perfusion pressure in the ciliary arteries, potentially increasing the rate of aqueous humor secretion and, thus, IOP.[48] Although ultrafiltration was shown not to be the major mechanism of aqueous humor secretion,[49,50] the ciliary blood flow was found to exhibit a linear relationship with aqueous humor inflow when the blood flow rate was below a critical level of perfusion.[51] Above that level, aqueous humor inflow remained relatively constant and was independent of ciliary blood flow.[51] Third, the Renin-Angiotensin system may present a common pathway through which blood pressure and IOP are regulated. Renin-Angiotensin system plays an essential role in the pathophysiology of hypertension. It consists of dozens of angiotensin peptides, among which two axes of Renin-Angiotensin system cascades have been extensively studied, namely Angiotensin Converting Enzyme 1, Angiotensin II, and Angiotensin Type 1 Receptor axis (ACE1-Angiotensin II-ATR1) and Angiotensin Converting Enzyme 2, Angiotensin (1-7), and Mas Receptor axis (ACE2- Angiotensin (1-7)-Mas).[52] Over-activation of ACE1-Angiotensin II-ATR1 is believed to be detrimental to the

cardiovascular system and exacerbates hypertension, because it can induce vasoconstriction, increased secretion of aldosterone, and proliferation and increased collagen synthesis of vascular smooth muscle cells.[53] The ACE2- Angiotensin (1-7)-Mas axis has been found to exert opposite effects, as it can induce vasodilation, anti-fibrosis, and antiproliferation.[52] Local Renin-Angiotensin system has been identified in animal and human eyes. The location of Renin-Angiotensin system components in human ocular structures are listed in **Table 2**.[52] Accumulating evidence suggests that Renin-Angiotensin system plays an important role in the pathogenesis of glaucoma, at least in part, through its effects on IOP modulation.[54-58] It is likely that Angiotensin II increases IOP by acting as a secretagogue. The co-existence of hypertension and raised IOP is believed to be triggered by fluid transport mechanisms in the renal tubular epithelium and ciliary epithelium. Aldosterone stimulates fluid and Na^+ retention by the renal tubular epithelium. It was hypothesized that the ciliary epithelium acts as an 'inverted' epithelium producing aqueous humor through Na^+ transport, which could be stimulated by aldosterone.[54] However, other studies revealed that Cl^-, rather than Na^+ transport, is likely to be the major driving force of aqueous humor secretion.[59-61] In addition, administration of Angiotensin II increases the cytoplasmic Na^+ concentration by stimulating the Na^+-H^+ exchanger and inhibiting H^+-ATPase in rabbit non-pigmented ciliary epithelium (NPE).[62] This finding favors the notion of Na^+ reabsorption by the non-pigmented epithelial cells, arguing against an increased Na^+ secretion across the ciliary epithelium. Further studies are required to determine the precise mechanism by which aldosterone regulates aqueous humor secretion across the ciliary epithelium. Additionally, Angiotensin II was shown to stimulate transforming growth factor β1 (TGF-β1) gene expression.[55] In the trabecular meshwork, TGF-β increases the secretion of extracellular matrix-related factors, such as fibronectin and connective tissue growth factor.[56] It is likely that Angiotensin II influences extracellular matrix deposition and homeostasis by stimulating TGF-β, resulting in an increased outflow resistance and IOP. It is worth noting that oral administration of losartan and captopril reduces IOP in primary open angle glaucoma patients,[57,58] suggesting that

systemic Renin-Angiotensin system may potentially affect the regulation of IOP by influencing ocular Renin-Angiotensin system. This is consistent with the finding that the blood-retinal barrier was shown to be more permeable in spontaneously hypertensive rats compared with that in Wistar Kyoto rats,[63] indicating that a disrupted blood-retinal barrier resulting from hypertension may enhance the effects of circulating Renin-Angiotensin system on the eye.

Impaired ocular perfusion in Hypertension and Open Angle Glaucoma

Defective Autoregulation in Hypertension and Open Angle Glaucoma

Endothelial dysfunction and increased vascular resistance have been reported in hypertension,[64,65] suggesting that autoregulation may be impaired in hypertension. Endothelial dysfunction is characterized by a reduced dilatory response of the arteries due to low bioavailability of vasodilators, as well as increased vasoconstriction of the arteries. An imbalance in the production of vasoactive substances can lead to an impaired dilation of arteries because of reduced endothelium-dependent vasodilation.[66] The increased arterial resistance leads to a reduced blood flow. Decreased vasodilatory activity in chronic hypertension could reduce the blood supply to the eye and aggravate the progression of open angle glaucoma. A defective autoregulation regarding ocular perfusion has been proposed in open angle glaucoma patients.[67] The mean resistance index of both the central retinal artery and the short posterior retinal arteries has been shown to increase in open angle glaucoma patients.[68] The mean end-diastolic velocity of the central retinal artery and short posterior ciliary arteries was found to be lower in eyes with open angle glaucoma.[68] In primary open angle glaucoma patients, there are changes in blood flow to the optic nerve after nitric oxide synthase inhibitor is reduced, implying that primary open angle glaucoma patients may have lower nitric oxide bioavailability or sensitivity in their ocular vasculature.[64]

Since ocular perfusion pressure increases with blood pressure, a higher ocular perfusion pressure, as observed in hypertension, is expected to protect against the development of open angle glaucoma due to an increased ocular blood flow. However, this was not observed clinically. Grunwald et al. measured the ocular perfusion pressure and optic nerve blood flow in healthy subjects and open angle glaucoma patients with and without hypertension.[69] While the mean ocular perfusion pressure was higher in the open angle glaucoma patients with hypertension, the optic nerve blood flow was significantly lower than that in controls.[69] It has been suggested that the range of autoregulation is reduced and altered in patients with hypertension, potentially worsening ocular perfusion. It is reported that long-term hypertension impairs ocular perfusion by vascular remodeling.[70] Studies have also shown that a higher wall-to-lumen ratio is observed in the blood vessels of hypertensive patients,[71,72] potentially leading to a lower ocular blood flow.[73] Ritt et al. also reported a negative correlation between retinal capillary blood flow and retinal arteriolar wall-to-lumen ratio.[74] Similar findings have been reported in rats, in which there is a negative correlation between aortic wall-to-lumen ratio and retinal peak vasodilation.[70] In addition, the retinal blood vessels in rats with prolonged chronic hypertension showed reduced vasodilatory capacity when the mean arterial pressure was decreased, as compared to normotensive rats.[70] In addition, it has been demonstrated that for rats with acute blood pressure elevation, the high blood pressure protects retinal functions against IOP elevation. However, for rats with chronic hypertension lasting for 12 weeks, the increased blood pressure is not beneficial to the eyes.[70] These findings imply that long-standing hypertension may result in arterial wall thickening and lumen narrowing, greatly reducing ocular blood flow and supply of nutrients to the retina. The potential mechanistic pathways linking hypertension, impaired autoregulation, and open angle glaucoma are illustrated in **Figure 2**.

Low ocular perfusion pressure in Normal Tension Glaucoma

In comparison, there is ample evidence to demonstrate that normal tension glaucoma, in which the IOP is within normal limits, is closely related to low blood pressure.[75] This correlation possibly results from low ocular perfusion pressure when blood pressure is reduced, subsequently mediating ischemic optic nerve hypoperfusion.[76] It has been demonstrated that normal tension glaucoma patients with a reduced diastolic blood pressure usually have faster disease progression.[76] This finding is in good agreement with the vascular theory of open angle glaucoma which states that adequate blood pressure is crucial for maintaining the optimal blood supply to the retina. In addition, nocturnal blood pressure dipping, the physiological decrease in nocturnal blood pressure relative to daytime blood pressure, has been demonstrated to be greater in patients with normal tension glaucoma.[77] In addition, it has been shown that normal tension glaucoma patients display a lower nocturnal ocular perfusion pressure, indicating a defective autoregulatory mechanism in normal tension glaucoma patients.[78] Consistent with these findings, normal tension glaucoma patients who have a greater magnitude and longer duration of nocturnal diastolic blood pressure dip are reported to demonstrate more severe visual field defects and are more prone to developing parapapillary choroidal microvasculature dropout, an indicator of compromised optic nerve head perfusion.[79] These findings suggest that nocturnal blood pressure dipping likely elicits normal tension glaucoma by inducing optic nerve head ischemic damages, despite the normal IOP (**Figure 2**).

It is important to note that systemic antihypertension treatment could contribute to low ocular blood flow in hypertensive patients. Topouzis et al. observed that hypertensive patients with diastolic blood pressure lower than 90 mmHg due to antihypertension treatment showed increased optic cupping and cup/disc ratio, compared with hypertensive patients with higher diastolic blood pressure or healthy subjects with diastolic blood pressure lower than 90 mmHg, despite the fact that hypertensive patients with lower diastolic blood pressure had the lowest IOP.[80] This was supported by the

evidence that low diastolic ocular perfusion pressure due to antihypertension treatment was associated with increased risk of open angle glaucoma.[81] This result supports the notion that increased retinal damage could be triggered by ischemic insult rather than mechanical compression. It is believed that sustained hypertension leads to microvascular damage. With a compromised microvascular system, the critical blood pressure level for hypertensive patients to maintain adequate ocular blood flow may be elevated. For chronic hypertensive patients, their vascular bed may have adapted to a new equilibrium with the long-term higher blood pressure level, and a small reduction of blood pressure and, thus, ocular perfusion pressure from this level causes vascular imbalance and ischemia. Interestingly, hypertension is shown to be protective against glaucoma in young patients and aggravating glaucoma in older patients.[23] The exact reason for this difference is not clear. One possible reason is that younger patients may still have relatively normal vascular structures and functions. Therefore, a higher blood pressure may lead to an increased ocular perfusion pressure at early stage of hypertension. However, the compromised vascular bed with an altered autoregulation in prolonged hypertension outweighs the benefits of a high ocular perfusion pressure, rendering it more prone to ischemia.

Increased inflammation in Hypertension and Open Angle Glaucoma

Increased systemic inflammation has been observed in both hypertension and primary open angle glaucoma. It has been shown that mice lacking T and B cells have blunted hypertension during Angiotensin II infusion, while adoptive transfer of T cells restores hypertension response to Angiotensin II.[82] Increased serum pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), have been identified as independent risk factors for hypertension.[83] In untreated essential hypertensive patients, both serum IL-6 and TNF-α have been found to be positively correlated with pulse wave velocity, a measurement of arterial stiffness.[84] TNF-α exacerbates vascular

dysfunction by inducing vascular endothelial apoptosis.[85] It has been shown that IL-6 induces arterial wall collagen synthesis and stimulates fibrinogen production, subsequently reducing cardiac contractility and increasing left ventricular fibrosis and hypertrophy.[86] The plasma level of inflammatory cytokines, including TNF-α and IL-6, have been shown to be elevated in primary open angle glaucoma patients.[87,88]

It is believed that local inflammation plays an important role in the pathogenesis of glaucoma.[89] In the retina and optic nerve, resident glial cells, including astrocytes, Müller cells, and microglia, are able to mediate local inflammatory responses.[90] When stimulated by ischemic injury and increased IOP, the glial cells redistribute in the retina and optic nerve and produce neurotoxic cytokines.[91] Elevated levels of TNF-α and IL-6 expression have been reported in glaucomatous retinas.[92] In addition, IL-6 is found to increase in the aqueous humor of primary open angle glaucoma patients and is higher in those with more severe visual field defects.[93] It is believed that TNF-α binds to the TNF-α type 1 receptor in retinal ganglion cells, thereby inducing apoptosis through caspase-8 activation in glaucomatous eyes.[94] In addition to activation of glial cells and increased local cytokine production during IOP elevation, a transient IOP spike was found to trigger peripheral T cell infiltration into the retina in mice.[95,96] These infiltrated T cells, such as T helper 1 cells, could lead to the prolonged glaucomatous neurodegeneration following direct mechanical injury induced by the transient IOP spike. This observation further supports the role of local inflammation in primary open angle glaucoma.[90,95] Despite the evidence supporting the role of local inflammation in the pathogenesis of glaucomatous degeneration and the presence of increased systemic inflammation in primary open angle glaucoma patients, it has yet to be established whether the increased systemic and local inflammation are inter-related. It is likely that the local inflammatory response could be influenced by the systemic inflammatory level, particularly with a defective blood-retinal barrier. In spontaneously hypertensive rats, the permeability of the blood-retinal barrier is increased compared with that of Wistar Kyoto rats.[63] As a result, it is possible that increased systemic inflammation in

hypertension and a defective blood-retinal barrier predispose the eye to increased local inflammation and subsequent glaucomatous neurodegeneration.

Systemic and local oxidative stress, Hypertension and Primary Open Angle Glaucoma

Increased oxidative stress is believed to play an important role in the pathophysiology of both hypertension and open angle glaucoma. Reactive oxidative species (ROS) reduce nitric oxide bioavailability and stimulate hypertrophy of vascular smooth muscle cells.[97,98] 8-Hydroxy-2'-deoxyguanosine (8-OHdG), a biomarker of systemic oxidative stress, is increased in the urine of hypertensive patients with left ventricular hypertrophy. Urinary 8-OHdG is positively correlated with plasma TNF-α and IL-6, supporting a potential positive link between systemic inflammation and oxidative stress in hypertensive patients.[99] Oxidative damage is also involved in the pathogenesis of open angle glaucoma. Plasma and aqueous 8-OHdG levels are both higher in primary open angle glaucoma and pseudo-exfoliative glaucoma patients, whilst both aqueous and serum total antioxidant status are lower in these patients compared with controls.[100] In normal tension glaucoma patients, the urinary 8-OHdG level has been shown to be negatively correlated with retinal blood flow, which is a contributing factor to visual field defects.[101] It is suggested that increased ocular oxidative stress may trigger glaucomatous neurodegeneration by inducing apoptosis of retinal ganglion cells.[102] Increased oxidative stress also increases IOP. Cellular senescence mediated by oxidative stress plays an important role in the pathogenesis of primary open angle glaucoma. After exposure to H_2O_2, senescence-associated β-galactosidase (SA-β-Gal) activity is increased in cultured human trabecular meshwork cells, supporting the notion that trabecular meshwork senescence could be triggered by oxidative stress.[103] Increased SA-β-Gal activity has been identified in the aqueous outflow pathway of primary open angle glaucoma donor eyes. After oxidative stress stimulation, senescent

cells trigger an increased expression of pro-inflammatory cytokines and lead to apoptosis of the adjacent non-senescent cells.[104] The ROS-induced cell senescence may eventually influence trabecular meshwork cellularity and outflow resistance.

Conclusion

The association between hypertension and open angle glaucoma remains controversial and further well-controlled studies need to be conducted. However, there are some common pathogenic conditions, including altered autoregulation and increased inflammation, observed in these two diseases. While recent studies have gain much insight, it has yet to be established whether 1) these similarities involve the core mechanism and/or pathway; and 2) there is a causative relationship between these two diseases. Future studies should be focused on the longitudinal monitoring of morphological, structural, and functional changes over a prolonged period for a better understanding of disease development and progression, in order to unravel the precise relationship between hypertension and open angle glaucoma. In addition, of particular importance and urgency is the understanding of therapeutic agent(s) that affect blood pressure in patients with open angle glaucoma, especially in normal tension glaucoma. The blood pressure-lowering effect for hypertension treatment may potentially result in a significant reduction of ocular perfusion pressure (assuming that IOP is maintained at a relatively constant level). This would potentially lead to an increased risk of ocular ischemia, aggravating glaucomatous progression. When a clear relationship between hypertension and open angle glaucoma is established, the prevention and treatment of these diseases could be initiated in a timely manner.

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Authors (reference)	Study Design	No. of Subjects	Definition of Hypertension	Type of Glaucoma	Effect of Hypertension on risk of Glaucoma/Odds Ratio (95% Confidence Interval)	Adjusted Covariates	Does Hypertension increase Intraocular Pressure?
Peräsalo et al. 1990 (22)	Cross-sectional	208	N/A	Open angle glaucoma, regardless of intraocular pressure	Patients having systolic blood pressure > 160 mmHg present better visual acuity and less visual fields loss compared with patients having systolic blood pressure ≤ 120 mmHg Systolic blood pressure ≤ 120 mmHg is associated with visual impairment	N/A	Yes
Dielemans et al. 1995 (20)	Cross-sectional	4,187	Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg	Primary open angle glaucoma, normal tension glaucoma	2.33 (0.99-5.47) for primary open angle glaucoma and 0.77 (0.22-2.72) for normal tension glaucoma	Age, sex, BMI	Yes
Tielsch et al. 1995 (23)	Cross-sectional	5,308	Systolic blood pressure > 160 mmHg and/or	Primary open angle glaucoma, normal tension glaucoma	1.06 (0.60-1.87) for 70-79-year-old patients and 2.36	Race	Yes

			diastolic blood pressure > 95 mmHg, and/or use of antihypertensive medication		(0.79-7.04) for patients older than 80		
Bonomi et al. 2000 (18)	Cross-Sectional	4,297	Systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 95 mmHg, and/or use of antihypertensive medication	Primary open angle glaucoma, normal tension glaucoma	2.1 (1.2-3.6) for primary open angle glaucoma and 0.6 (0.2-1.4) for normal tension glaucoma	Age, sex	Yes
Leske et al. 2002 (21)	Cohort	2989	Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or use of antihypertensive medication	Open angle glaucoma, regardless of intraocular pressure	Patients with baseline hypertension have half the risk of developing open angle glaucoma in 4 years, with relative risk of 0.49 (0.29-0.85)	N/A	Not mentioned
Mitchell et al. 2004 (16)	Cross-Sectional	3,627	Systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg, and/or use of antihypertensive medication	Open angle glaucoma, regardless of intraocular pressure	1.56 (1.01-2.40)	Age, sex, maximum intraocular pressure of 2 eyes, glaucoma family history, myopia, current thyroxine use, pseudoexfoliation, and diabetes	Yes

Orzalesi et al. 2007 (19)	Case-control	3,852	N/A	Primary open angle glaucoma	Primary open angle glaucoma patients have higher systolic blood pressure, diastolic blood pressure and intraocular pressure	N/A	Not mentioned
Bae et al. 2014 (17)	Meta-Analysis	60,084	N/A	Primary open angle glaucoma, normal tension glaucoma	Hypertension increases the risk of open angle glaucoma, especially for primary open angle glaucoma patients	N/A	Yes
Asefa et al. 2020 (9)	Cohort	86,814	Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and/or use of antihypertensive medication	Not Specified, including self-reported glaucoma diagnosis, and/or use of intraocular pressure-lowering medication, and/or a history of glaucoma laser treatment, and/or glaucoma-specific complaints	1.25 (1.16-1.35)	Age, sex, BMI	Not mentioned

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720 **Table 1**. Studies on the association between hypertension and open angle glaucoma.

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Molecule(s) of Renin-Angiotensin system	**Ocular structures**
Renin	Retina
Angiotensin Converting Enzyme 1 (ACE1)	Retina, Ciliary body, Aqueous humor
Angiotensin Converting Enzyme 2 (ACE2)	Retina
Angiotensin Type 1 Receptor	Retina
Angiotensin Type 2 Receptor	Retina
Angiotensin II	Retina, Ciliary body, Aqueous humor
Angiotensin 1-7	Retina

726 **Table 2**. Location of Renin-Angiotensin system in human ocular tissues.

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Figure legends:

Figure 1. a) The perfusion pressure is equivalent to the difference between the arterial pressure and the venous pressure; b) The ocular perfusion pressure is the difference between the arterial pressure and the intraocular pressure (IOP), because the venous pressure is approximately equivalent to the IOP. (Red arrow: Arterial Pressure; Blue arrow: Venous Pressure; Purple arrow: Perfusion Pressure / Ocular Perfusion Pressure; Green arrow: IOP)

Figure 2. The potential mechanistic pathways linking hypertension and glaucoma.