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LEARNING OBJECTIVES

Special Focus

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A review of glaucoma in patients with high blood pressure and arteriosclerosis including aspects such as badly controlled BP and fluctuations, vasospasms, cardiac arrhythmia and badly controlled lipid metabolism.

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A practical approach to glaucoma and systemic diseases such as autoimmune diseases, sleep apnea as well as drug administration.

TARGET AUDIENCE

This educational program is aimed at general ophthalmologists, ophthalmology residents and glaucoma specialists.

MAIN TOPIC:

"GLAUCOMA AND SYSTEMIC DISEASES"

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Special Focus:

The Glaucomatous Process: An Historical Perspective

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CORE CONCEPTS

The definition of glaucoma has evolved since ancient times to the present understanding of a group of characteristic optic neuropathies.

Manifest glaucoma has the two basic stages of optic nerve damage and progressive loss of visual field.

The glaucomatous process includes three pre-manifest stages (initial event, early ocular tissue alteration and pre-neuropathy event) and the two manifest stages.

All glaucomas have the five stages of the glaucomatous process, which is important to recognize in order to know how closely to follow each patient and when and how to treat.

Since all forms of glaucoma share the five stages of the glaucomatous process, it may be that primary and secondary divisions should be reconsidered in future classifications of the glaucomas.

1. Introduction and historical context

Glaucoma has been misunderstood for most of its history. Even the name is a misnomer.[1] When the ancient Hippocratic doctors chose the term glaucosis, referring to the greenish-blue colour of sea water, they were probably seeing in the pupil of their patients what we today would call a mature cataract. To further complicate matters, the Alexandrian doctors applied the term hypochysis to another blinding disorder, which was translated in Arab countries as "flowing down of water" and much later as the Latin word, "waterfall" or cataracta. The latter would have been a more appropriate term for what we know today as glaucoma, but the early physicians got the conditions reversed, and so "glaucoma" it is.

While the terminology for glaucoma and cataracts is less than precise, our distant predecessors did have a partial understanding of the natural history of the two groups of disorders. For example, it was observed in the first century CE that "all glaucomas are incurable, while hypochymas [cataracts] are usually, but not always, curable"[1] (the "cure," of course, being the ancient operation of couching). And yet, beyond the fact that they were incurable, little else would be known about the glaucomas for the next thousand years.

Although an association with firmness of the eye and glaucoma is found in some of the 10th-century Arabian writings, it was not until the 19th century that glaucoma was clearly recognized as a distinct group of ocular disorders, with elevated intraocular pressure (IOP) as a common denominator. And this is where the next misunderstanding began. While optic nerve damage was recognized as a cause of visual loss in glaucoma shortly after introduction of the ophthalmoscope in the mid 19th century, elevated IOP was believed to be the essential feature by which the glaucomas were defined.

The concept of glaucoma as a disorder of elevated IOP prevailed through the first half of the 20th century. In 1951, Sugar stated that "When the term glaucoma is used in the general sense, it is only a synonym for increased intraocular pressure and should be understood as such."[2] This understanding influenced not only the diagnosis of the glaucomas, but also the treatment, with many patients being treated who had only elevated IOP and others with true glaucoma being missed because their IOP never exceeded the statistical norm.

But, by the 1960s, observers were beginning to realize that elevated IOP, while still the most common risk factor for glaucomatous optic neuropathy, is not consistently associated with all cases of glaucoma and that the one common denominator in all patients who are destined (without proper treatment) to lose vision from glaucoma is the optic nerve damage. While this concept was generally accepted by the 1970s, it was not until 1992 that Van Buskirk and Cioffi articulated the now commonly accepted definition of glaucoma as "a characteristic optic neuropathy, which derives from various risk factors that include but are not limited to increased IOP"[3]

2. Modern staging systems and underlying events

So, when we assign the diagnosis of a glaucoma to our patient, we are implying that they demonstrate optic nerve head changes that are characteristic of glaucomatous optic neuropathy, with or without associated visual field loss. This manifest glaucoma might be thought of as having two stages – optic nerve damage and visual field loss – although sub-stages, including degrees of nerve damage[4] and field loss[5,6], have been proposed. And yet we know that there are many events or stages that precede manifest glaucoma.

Shields, Ritch and Krupin considered these pre-manifest glaucoma stages and proposed a five-stage system for what might be called the "glaucomatous process," which includes the pre-manifest and manifest stages.[7] For several years, Shields, Spaeth and colleagues debated the merits of the staging system and eventually proposed a slight modification.[8] Table 1 displays the five stages: Initial Event, Early Ocular Tissue Alteration, Pre-neuropathy Events, Optic Neuropathy and Functional Loss with Disability.

Initial Event. For every form of glau-

Table 1

Stages of the Glaucomatous Process

Stage	Description
1. Initial Event	Sets the glaucomatous process in motion (e.g. genetic mutation, ocular configuration, inflammation, retinal vascular disorder, ocular trauma)
2. Early Ocular Tissue Alteration	Tissue changes may be in aqueous outflow system, uveal tract, retinal ganglion cells, lamina cribrosa, ocular blood vessels
3. Pre-neuropathy Events	Forces created by the tissue alterations (e.g., a certain level of intraocular pressure, inherent weakening of optic nerve, altered ocular blood flow) with potential to lead to optic neuropathy
4. Optic Neuropathy	Progressive destruction of retinal ganglion cells and axons (established, or manifest, glaucoma)
5. Functional Loss with Disability	Documented loss of visual field, leading eventually (if not adequately treated) to functional impairment

coma, there is obviously some initial event that sets in motion the glaucomatous process. The event could be, for example, a gene mutation, a genetically-determined ocular configuration, an ocular inflammation, retinal vascular disorder, an ocular injury and many other ocular events, as well as any number of systemic disorders, such as cardiovascular disease, diabetes, inflammatory auto-immune disorders and infections, which could lead to the initial ocular event. Not every person with one of these events will go on to develop manifest glaucoma, but we need to understand the risk for progressing from this stage or the other pre-manifest stages into manifest glaucoma in order to know how closely to follow the patient and possibly even to intervene with treatment that is appropriate for each individual before the glaucoma becomes manifest.

Early Ocular Tissue Alteration. For those individuals who do progress to the second stage of the glaucomatous process, the initial event leads to alterations of various ocular tissues, which further increases the risk of glaucomatous optic neuropathy. These alterations may be in the aqueous outflow system, the uveal tract, the retinal ganglion cells, lamina cribrosa, ocular blood vessels or other ocular structures. The time between Stages 1 and 2 could be anywhere from decades, as in a gene mutation, to seconds, as in blunt trauma.

Pre-neuropathy Events. In this stage, the tissue alteration of Stage 2 has progressed far enough to initiate forces that may damage the optic nerve. The most common of these forces (or at least the most well-known) is a level of IOP that is high enough or unstable enough to cause nerve damage. Again, however, not all individuals with IOP above the statistical norm will develop glaucomatous optic neuropathy, nor will all patients with manifest glaucoma exhibit a pressure outside the norm. Other forces that may predispose to nerve damage include deformation of the lamina cribrosa from inherent "weakness" or altered "rigidity", altered ocular blood flow and/or other mechanisms.

Optic Neuropathy. The final two stages of the glaucomatous process represent manifest glaucoma - the common pathway of all the glaucomas. However, while glaucomatous optic neuropathy in general represents destruction of retinal ganglion cells and axons, the precise mechanism of the nerve damage and the resulting clinical appearance of the optic nerve head may differ according to the pre-neuropathy event that initiates the damage. For example, a form of high pressure glaucoma may have a different clinical appearance than one in which the IOP never exceeds the statistical norm, or a chronic form of glaucoma, in which elevated IOP causes gradual damage over time, may differ in appearance from an acute process with sudden pressure rise and rapid nerve damage.

Functional Loss with Disability. The fifth and final stage of the glaucomatous process, and the one for which all efforts to diagnose and treat are designed to avoid, is the progressive loss of vision that results from the optic neuropathy. While glaucomatous visual field loss mostly follows a characteristic pattern, there are subtle variations according to the mechanism(s) of the optic neuropathy.

Table 2

Glaucomatous Process in Neovascular Glaucoma

Stage	Description
1. Initial Event	Most often a retinal vascular disorder (e.g. central retinal vein occlusion, proliferative diabetic retinopathy), usually preceded by a systemic disorder
2. Early Ocular Tissue Alteration	Fibrovascular membrane in anterior chamber angle
3. Pre-neuropathy Event	Elevated intraocular pressure
4. Optic neuropathy	Progressive damage of optic nerve (manifest glaucoma)
5. Functional Loss with Disability	Progressive loss of visual field

3. Underlying processes in different forms of glaucoma

Tables 2-4 provide three examples of how the glaucomatous process, with its five basic stages, can be applied to various forms of glaucoma.

In neovascular glaucoma, the initial event (Stage 1) is most often a retinal vascular disorder, which is typically preceded by a systemic disorder such as arteriosclerosis or diabetes, leading to central retinal vein occlusion or proliferative diabetic retinopathy.

The initial event(s) leads to the formation of a fibrovascular membrane in the anterior chamber angle (Stage 2), which causes elevated IOP (Stage 3), which leads to the common pathway of optic neuropathy (Stage 4) and progressive visual field loss (Stage 5). (Table 2)

In pupil-block angle closure glaucoma, the initial event is a genetically determined ocular configuration with a shallow anterior chamber (Stage 1), which may, under certain conditions, lead to pupillary block and angle closure (Stage 2) with elevated IOP (Stage 3) and the common pathway of optic nerve damage and functional loss (Stages 4 and 5). (Table 3)

Table 3

Glaucomatous Process in Pupil-Block Angle Closure Glaucoma

Stage	Description
1. Initial Event	Genetically-determined shallow anterior chamber
2. Early Ocular Tissue Alteration	Pupillary block with appositional closure of anterior chamber angle (in response to various clinical conditions)
3. Pre-neuropathy Event	Elevated intraocular pressure
4. Optic Neuropathy	Progressive damage of optic nerve (manifest glaucoma)
5. Functional Loss with Disability	Progressive loss of visual field

The details of chronic (or primary) open angle glaucoma are less well understood, but the initial event is most likely a genetic mutation or polygenetic defect (Stage 1), which causes tissue alterations either in the trabecular meshwork or directly in the optic nerve (Stage 2). The former can impede aqueous outflow with elevated IOP, while the latter can increase the susceptibility of the optic nerve to damage either from normal levels of IOP or by pressure-independent mechanisms (Stages 3). Either event can lead to the common pathways of Stages 4 and 5. (Table 4)

4. Diagnosing glaucoma and assessing risk factors

Invoking the concept of the glaucomatous process does not change the current definition of glaucoma, which still requires the presence of the characteristic optic neuropathy. But it does help to emphasize that there is a complex process with multiple stages, including systemic disorders, that may lead to manifest glaucoma. It is important to recognize, as early as possible, when a patient is somewhere in the process and to understand the level of risk that each stage poses for progression to the next stage and ultimately to glaucomatous damage and visual loss. This not only guides the physician to know how closely the patient should be followed at all stages, but may signal when treatment is indicated, sometimes even before manifest glaucoma is present. For example, when elevated IOP, or ocular hypertension, (Stage 3) reaches a level at which the risk of progressing to the optic neuropathy (Stage 4) of chronic (or primary) open angle glaucoma is sufficiently high, medical or laser intervention may be justified to control the pressure. Or, when a retinal vascular disorder (Stage 1) has led to neovascularization of the iris and/or anterior chamber angle (Stage 2), treatment with pan retinal photocoagulation or injection of a vascular endothelial growth factor (VEGF) inhibitor may be indicated. There may even be a time when treatment is indicated at Stage 1, as in a patient with a genetically determined narrow anterior chamber angle, in which a laser iridotomy might be felt necessary to prevent progression to angle closure (Stage 2).

Table 4

Glaucomatous Process in Chronic (Primary) Open Angle Glaucoma

Stage	Description
1. Initial Event	Genetic mutation or polygenetic defect
2. Early Ocular Tissue Alteration	Changes in aqueous outflow system (with obstruction to aqueous outflow) or in optic nerve (retinal ganglion cells/axons, lamina cribrosa, ocular blood vessels, etc)
3. Pre-neuropathy Event	Elevated intraocular pressure (IOP) or inherent weakness of the optic nerve
4. Optic Neuropathy	Progressive damage of optic nerve (manifest glaucoma) either from elevated IOP or inherent weakness of optic nerve (in combination with a certain level of IOP or a pressure-independent mechanism)
5. Functional Loss with Disability	Progressive loss of visual field

5. Conclusion

The glaucomatous process applies to all forms of glaucoma, whether classified as primary or secondary. And this may be the next misunderstanding of glaucoma that should be addressed. Although it is presently a controversial issue among the experts, dividing glaucomas into primary and secondary forms seems to be a bit arbitrary, since they all share the same stages of the glaucomatous process. Future classifications may be based more on the initial event, whether genetic or acquired, and the pathway that leads to glaucomatous optic neuropathy for each form of glaucoma. In any case, the concept of the glaucomatous process will hopefully provide a framework on which our understanding of the glaucomas will evolve, as we continue to gain a more complete knowledge of this complex group of disorders.

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What's New:

Glaucoma in patients with high blood pressure and arteriosclerosis

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CORE CONCEPTS

Chronic systemic diseases, such as arterial hypertension (aHTN), vascular dysregulation, cardiac arrhythmia and dyslipidemia may be modifiable risk factors for primary open-angle glaucoma (POAG).

Despite conflicting findings, most of the population-based glaucoma studies do describe an association between aHTN and POAG.

Arterial HTN is a common comorbidity in patients with POAG.

Sleep-time systemic hypotension is associated with progression of the disease and needs to be sought and avoided.

Blood pressure fluctuations and intraocular pressure (IOP) fluctuations cause fluctuations in ocular perfusion pressures, which in turn cause blood flow instability and oxidative stress at the optic nerve head (ONH) compounded by the deficient autoregulation capacity associated with POAG.

Primary vascular dysregulation (PVD) is often associated with low blood pressure and vasospastic symptoms. Most of the symptoms result from an impaired autoregulation of blood supply. The condition is associated with a higher risk of normal pressure glaucoma (NPG).

Atrial fibrillation (AF) has been shown to increase the risk of developing NPG.

Hypercholesterolemia might be associated with POAG. Long-term statin use seems to be associated with a reduced incidence of POAG.

1. Introduction

Primary open-angle glaucoma (POAG) is a multifactorial optic neuropathy of unknown etiology with elevated intraocular pressure (IOP) and impairment of vascular supply to the optic nerve head (ONH) being the most important pathogenic factors. Chronic systemic diseases, such as arterial hypertension (aHTN), vascular dysregulation, cardiac arrhythmia and dyslipidemia may be risk factors for POAG.

2. Arterial hypertension

The findings of major epidemiological studies on POAG and the association with aHTN are quite inconsistent. However, a meta-analysis of eight population-based glaucoma studies on the prevalence of aHTN demonstrated a significant relationship with POAG (OR=1.67; 95%CI: 1.28-2.07) and concludes that aHTN is associated with POAG[1].

Several mechanisms could explain this association. Elevated blood pressure (BP) is associated with higher IOP[2]. In addition, aHTN may cause vascular insufficiency at the ONH by damaging microvasculature in the ONH, thereby reducing blood flow. Furthermore, aHTN impairs autoregulation of blood flow in the posterior ciliary artery circulation, which supplies the anterior ONH[3]. Moreover, antihypertensive treatment could induce hypotensive episodes, especially when asleep[4].

In a study examining 24-hour BP profiles of 314 white POAG patients (67.1±9.3 years) only 18% had normal 24-hour BP without medication, another 18% had normal 24-hour BP with antihypertensive medication and 64% had aHTN, with 26% not having any antihypertensive therapy at all and 38% being treated insufficiently[5] (Figure 1).

Arterial HTN is defined as a mean BP of ≥135 and/or ≥85 mmHg during daytime or when awake and a mean of ≥ 120 and/or ≥70 mmHg (systolic and diastolic respectively) during night-time or when asleep. There was no difference in the BP distribution between high pressure (HPG; 67.6±9.1 years) and normal pressure glaucoma (NPG; 66.8±9.4 years) patients (all p>0.5; Figure 2). Most of the NPG patients showed vasosclerotic changes rather than vasodysregulation. Arterial HTN is a very common comorbidity in glaucoma patients.

3. Nocturnal BP and glaucoma

Recent studies on diurnal BP have shown that a higher mean systolic BP (SBP) when asleep and a reduced sleep-time SBP decline are the most significant prognostic BP markers for risk of developing cardiovascular disease (CVD). Therefore, the goal of BP monitoring to prevent CVD is to detect abnormal sleep-time BP patterns and the goal of therapeutic interventions is to lower BP while asleep[6]. Currently there is intense discussion on whether a sole hypertension treatment prior to bedtime versus upon waking yields greater prevention against hypertension-associated morbidity and mortality [7, 8].

If antihypertensive treatment at night causes an extreme-dipper BP pattern (sleep-time mean BP decline ≥20%), and as a consequence nocturnal (more accurately sleep-time) hypotension, the optic nerve head blood flow (BF) may be reduced below a critical level over many hours. Sleep-time hypotension in glaucoma patients may be the final insult in a multifactorial situation[4] causing visual field progression despite good IOP control. An extreme-dipper BP pattern in the absence of sleep-time hypotension, however, is not associated with the severity of glaucoma[5] or an increased CVD risk. Therefore, it is advisable to use the term sleep-time hypotension rather than extreme-dipper. The "Dresden safety range" recommends a sleep-time mean arterial BP between 65 and 90 mmHg and a sleep-time mean arterial OPP from 50 to 75 mmHg[5].

Patients within this safety range have a slower progression compared with patients outside this range, as long as IOP is controlled. The J-curve phenomenon, already described in the internal medicine literature shows that there is a greater end organ damage at both extremes of the BP range. This agrees with the results of a recent meta-analysis[2] on the association of BP and POAG, which showed an increased risk for POAG with low and high BPs.

4. BP fluctuations and glaucoma

Systemic BP as well as IOP have circadian variations. Both parameters influence the ocular perfusion pressure (OPP), generally calculated as the difference between 2/3 of the mean arterial BP minus IOP values, in the assumption that the venous pressure equals IOP. This is correct for healthy eyes, but not for glaucoma, where the venous pressure often is much higher than the IOP[9]. Therefore, OPP is frequently underestimated even in glaucomatous eyes. BF autoregulation is the ability to keep BF stable despite changes in OPP. In glaucoma, autoregulation is impaired per se[10] and also by means of arteriosclerosis[3]. This supports the findings of the Early Manifest Glaucoma Trial, that an IOP reduction of even 1 mmHg slows down progression[11]. In the absence of a well-working autoregulation any IOP reduction enhances ocular BF and optic nerve perfusion. The same is true for a stabilized BP.

High 24-hour BP and IOP fluctuations cause fluctuation of ocular perfusion pressures, which cause BF instability and oxidative stress because of the lacking autoregulation capacity associated with POAG. Unstable OPP has been shown to be correlated with central visual field (VF) progression in NPG[12].

5. Vasospasm and primary vascular dysregulation

Primary vascular dysregulation (PVD) is often associated with low BP and vaso-spastic symptoms like cold hands and feet, migraine and tinnitus. Most of the symptoms result from an impaired autoregulation of blood supply. The condition is associated with a higher risk of NPG and an exaggerated sleep-time BP decline or extreme-dipping causing sleep-time hypotension[13]. Although this group of NPG patients requires special treatment efforts, it has to be emphasized again, that most of the NPG patients suffer from a vasosclerotically rather than a vasodysregulatively induced reduced ONH perfusion.

6. Cardiac arrhythmia, structural carotid changes

Studies on cardiac arrhythmias and a possible connection with POAG are rare. Atrial fibrillation (AF), one of the most common supraventricular arrhythmias, characterized by a completely irregular heart rate, has been shown to increase the risk of developing NPG[14]. The odds ratio of having NPG was > 5 times higher in the AF group compared with an age-matched control group with similar CVD (OR=5.25, 95% CI: 1.86-14.85)[14]. AF can induce transient ischemic episodes leading to an impaired ocular BF in the ONH. In another study, NPG patients with higher sympathetic activity causing higher autonomic dysfunction of the heart showed a faster rate of central VF progression[15]. Topical betablocker administration can cause bradycardia and may aggravate a cardiac conduction defect[16].

Hemodynamic relevant carotid artery stenosis was not associated with NPG, nor did patients with NPG have significant carotid artery stenosis[17].

7. Poorly controlled lipid metabolism

Kang et al[18] recognized a positive association between hypercholesterolemia and the incidence of POAG, as well as an inverse association between long-term statin use (≥5 years) and an increased incidence of POAG, when pooling data from three large, longitudinal cohort studies with a total of 136 782 participants. McGwin et al[19] also found that long-term use of oral statins is associated with a reduced risk of POAG. The biological basis for the reduced incidence of POAG with statin use could include increased nitric oxide production, facilitating trabecular outflow and thereby lowering IOP, increased BF to the optic nerve, and neuroprotective effects on the retinal ganglion cells. Moreover, hypercholesterolemia is a risk factor for arteriosclerosis, which in turn causes microvascular damage and impaired autoregulation with insufficient BF in the OHN as described above.

8. Conclusion

Although elevated IOP is the most prevalent risk factor and the only reliable therapeutic target in POAG, a number of systemic conditions, like aHTN, BP instability, PVD, atrial fibrillation and hyperlipidemia are associated with the disease, in the end causing a reduced oxygen and nutritional supply to the ONH in patients susceptible to POAG. These conditions are quite common in the elderly and in patients with POAG. BP fluctuations and sleep-time hypotension have been identified as important risk factors for progression of the disease as well as reduced ocular perfusion pressures, either caused by IOP increase or drop in BP.

Vascular risk factors are more clearly visible in patients with NPG, where IOP is low by definition. However, also patients with HPG often suffer from multiple vascular impairments. These should be addressed in particular when visual field deteriorates despite good IOP control, since they represent possibly modifiable risk factors.

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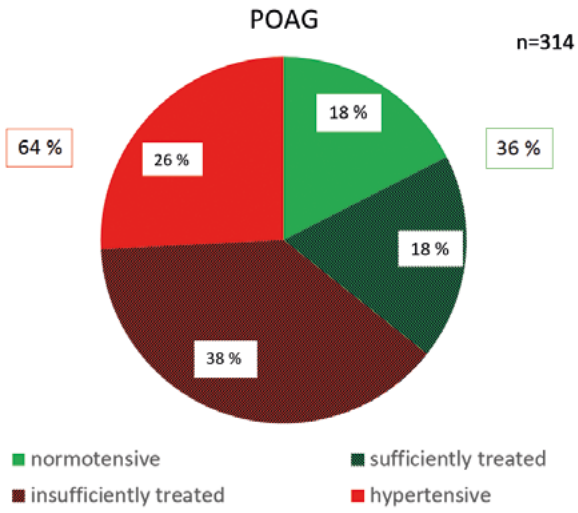

Figure 1: Distribution of 24-hour BPs in POAG patients (67.1±9.3 years)[5]. Arterial HTN being defined as a mean BP of ≥135 and/or ≥85 mmHg during daytime or while awake and of ≥120 and/or ≥70 mmHg at night-time or while asleep.

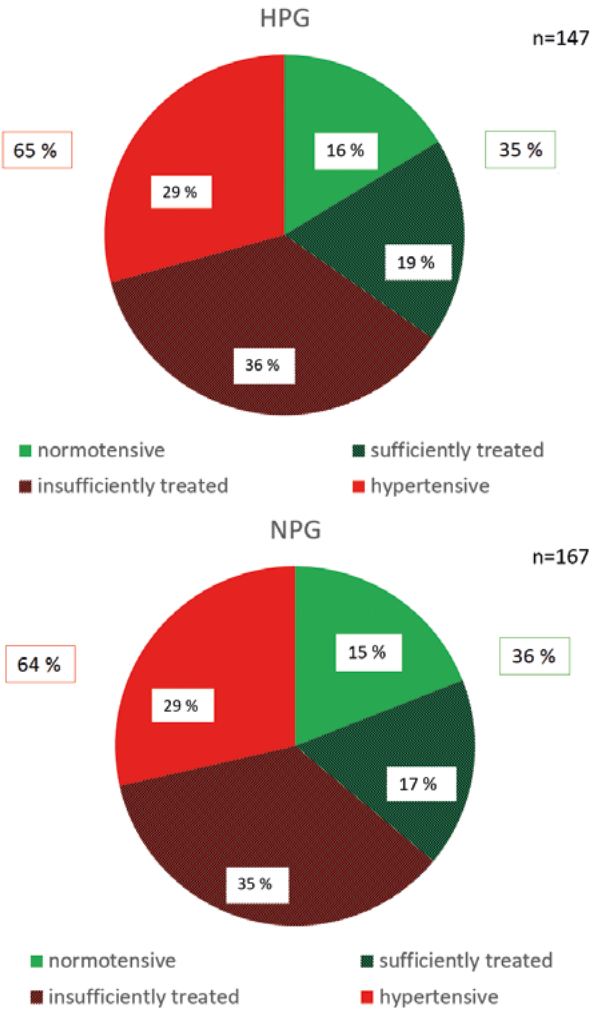

Figure 2: Distribution of 24-hour BPs in HPG (67.6±9.1 years) and NPG patients (66.8±9.4 years)[5]. Arterial HTN being defined as a mean BP of ≥135 and/or ≥85 mmHg during daytime or while awake and of ≥120 and/or ≥70 mmHg at night-time or while asleep.

Clinical Issues:

Glaucoma and Diabetes

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CORE CONCEPTS

Glaucoma and Diabetes have a complex relationship:

Primary open angle glaucoma is more common in people with diabetes.

Elevated glucose levels are partially neuroprotective for ischaemic and glaucomatous ganglion cells.

Diabetic vascular disease may cause ocular ischemia, and even secondary angle closure through neovascularisation of the iridocorneal angle.

Intravitreal injections for diabetic retinopathy or maculopathy can cause acute (usually transient) and chronic (often sustained) elevations in intraocular pressure (IOP) which can place glaucomatous stress on the optic nerve.

Long acting intravitreal steroids such as off-label triamcinolone as well as fluocinolone or dexamethasone implants can increase IOP through the steroid response

1. Introduction

The inter-relationship of diabetes and its treatment with glaucoma means that diabetes is not only important in contributing to the onset of glaucoma, but it also plays an important role in glaucoma progression and glaucoma morbidity in those already diagnosed with the disease.

2. Primary open angle glaucoma is more common in people with diabetes

Epidemiological studies have demonstrated that both ocular hypertension and open-angle glaucoma are about twice as common in people with diabetes[1]. There is no clear pathological process linking diabetes to primary open-angle glaucoma, notwithstanding the relationship with ocular hypertension. As glaucoma is an underdiagnosed disease, one explanation for these findings could be that people with diabetes are more likely to be referred to ophthalmologists who then detect the glaucoma. However, the Blue Mountains Eye Study reported that in about two thirds of cases, the glaucoma was diagnosed prior to the diabetes, suggesting a more complex inter-relationship between the two diseases.

3. Elevated blood sugar is partially neuroprotective for ischaemic and glaucomatous ganglion cells

One surprising finding from the Ocular Hypertension Treatment Study was the substantial protective effect of a prior diagnosis of diabetes on the risk of developing glaucoma in ocular hypertensives[2]. More recent research has shown that glucose is partially neuroprotective to retinal ganglion cells and can induce temporary visual recovery in patients with open-angle glaucoma[3].

4. Diabetic vascular disease can cause ocular ischemia, and secondary angle closure through neovascularisation of the iridocorneal angle

Epidemiological[1] and clinical[4] studies suggest that despite a beneficial effect from glucose, the pathophysiological harms of diabetes eventually outweigh those benefits and contributes to a primary open-angle form of glaucoma. When severe diabetic retinal ischemia induces the production of vascular endothelial growth factor (VEGF), diffusion and the conventional outflow pathway concentrate it at the trabecular meshwork, inducing the formation of neovascular and glial membranes which increase outflow resistance and elevate IOP[5]. Contraction of irido-corneal membranes draw the peripheral iris up over the trabecular meshwork, causing an often severe secondary angle-closure (and subsequent secondary angle-closure glaucoma), which is often associated with both an ischaemic and glaucomatous optic neuropathy.

5. Intravitreal injections for diabetes can cause acute (usually transient) and chronic (often sustained) elevations in IOP which can place glaucomatous stress on the optic nerve.

Intravitreal injection therapy with a VEGF blocking antibody is an increasingly common initial therapeutic modality for proliferative diabetic retinopathy. In many countries, these agents have also been approved for the treatment of diabetic macular oedema. While the benefit of the agents is usually great and often dramatic, any intravitreal injection transiently raises IOP, putting stress on the optic nerve[6]. Sustained IOP elevation after repeated intravitreal injections appear to occur relatively infrequently (3-10%) in patients without glaucoma. However, given the population prevalence of injections, this may be an important cause of new glaucoma cases. More concerning is a sustained elevation in IOP after repeated injections in patients with diagnosed glaucoma. This has been reported to be ten-fold higher at 33%[7].

6. Long acting intravitreal steroids such as off-label triamcinolone as well as fluocinolone and dexamethasone implants can cause a secondary IOP increase through the steroid response

In addition to the direct effects of repeated intravitreal injections on IOP control, corticosteroids can cause additional ocular hypertension and glaucoma morbidity via the steroid response. A metanalysis of studies of triamcinolone reported that about one third of subjects receiving a 4mg injection

had an IOP of greater than 21mmHg or an increase of 10mmHg or more. This prevalence rose with higher doses. For a 0.59mg Fluocinolone implant the proportion was about two-thirds, again with a higher prevalence at higher doses[8]. The reported data for dexamethasone implants is somewhat more variable, with a meta-analysis reporting IOPs increasing by at least 10mmHg or >21mmHg in about 10%9, but a later study reporting that a little over a quarter of subjects developed an IOP rise of over 10mmHg by 3 years[9].

7. Conclusions

Diabetes, its complications and treatment are all important risk factors for the development and progression of glaucoma (Figure 1). Diabetes is probably the most common disease that is associated with both primary and secondary as well as both open-angle and angle-closure forms of glaucoma.

Ophthalmologists managing or screening for diabetic eye disease need to pay particular attention to individual risks and signs of glaucoma and the specific glaucoma risks associated with various stages of the disease. For patients with pre-existing glaucoma, the impact of the stage of the diabetes and its attendant treatments is critical when formulating or revising a management plan and arranging follow-up.

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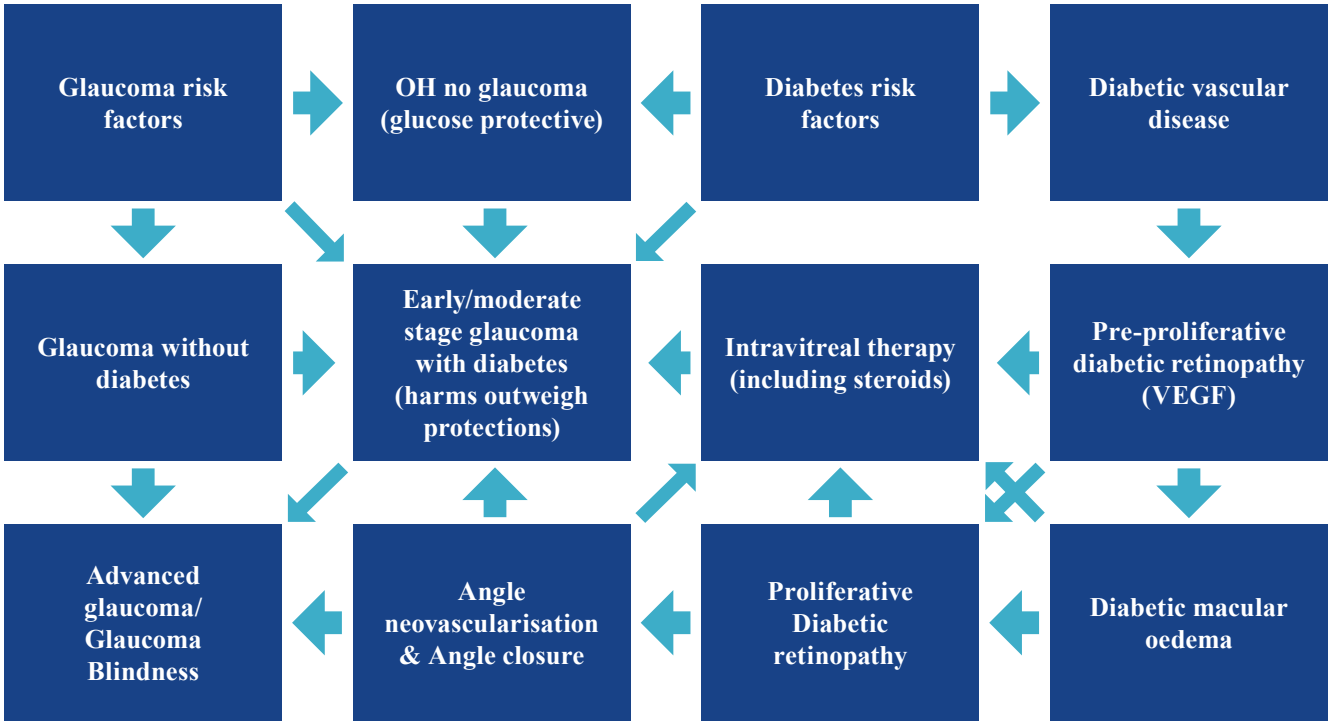

Figure 1: Pathways connecting Glaucoma and Diabetes (© Paul R. Healey 2020)

Practical Tips:

Glaucoma and systemic disease

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CORE CONCEPTS

Glaucoma may be associated with common systemic diseases

Spondylo-arthritis in adults and JIA (Juvenile Idiopathic Arthritis) in children are associated with inflammatory eye disease and glaucoma.

Acute and chronic ocular infections are associated with glaucoma

Sleep apnoea is associated with hypertension and raised IOP

Drugs, particularly corticosteroids, may precipitate glaucoma

1. Introduction

Ophthalmologists are often in a unique position to diagnose previously unrecognised systemic diseases (Table 1) or their complications when evaluating patients with raised intra-ocular pressure (IOP). These conditions include: inflammatory (including infections and autoimmune diseases), vascular and medication induced diseases.[1].

2. Inflammatory diseases

The most common systemic inflammatory diseases associated with glaucoma are the spondylo-arthropathies (SpA) which are associated with HLA-B27 and acute anterior uveitis. The SpAs are a spectrum of diseases that includes ankylosing spondylitis, psoriatic arthritis, reactive arthritis and inflammatory bowel disease. It is important to enquire about swollen joints, enthesitis (tendon insertion inflammation), nocturnal and early morning back pain and stiffness (Figure 1). Severe or frequently recurrent acute and chronic anterior uveitis can each be associated with increased IOP and secondary glaucoma. Up to 30% of children with juvenile idiopathic arthritis (JIA) develop anterior uveitis that is frequently complicated by glaucoma (Figure 2).[2] Other systemic inflammatory eye diseases such as: Behçet's disease, sarcoidosis and Vogt Koyanagi Harada Disease are also associated with glaucoma. Syndrome recognition is important to diagnose these diseases which are often associated with mucosal, skin, lymph node and neurological symptoms.

3. Infectious diseases

Infectious diseases involving the eye may also be associated with raised IOP. Viral anterior uveitis from Herpes Simplex Virus, Varicella Zoster Virus and CytoMegalo Virus is very frequently complicated by glaucoma.[3] Other infectious uveitides, including syphilis, toxoplasmosis, and herpetic retinitis are associated with glaucoma. These diseases may be display only subtle systemic signs, such as fever, small blisters or rash that are easily overlooked. The aim of management of raised IOP in patients with inflammatory eye disease is to identify and if possible treat the cause, control the uveitis and lower the IOP. IOP control often requires glaucoma surgery.

4. Congenital and high prevalence systemic diseases

There are a large number of familial and congenital diseases associated with glaucoma, including phacomatoses, such as Sturge-Weber syndrome, neurofibromatosis, and Marfan's syndrome. Syndrome recognition is important to assess the significance of skin and joint changes in such syndromes.

The Blue Mountains study showed a link between hypertension and raised IOP and glaucoma.[4] Glaucoma is also associated with diabetes, silent myocardial infarction, migraine, nocturnal hypotension and obstructive sleep apnoea. Sleep disorders are often overlooked as patients may present with fatigue, daytime sleepiness, morning headache, or their partners complain of snoring or witnessed apnoeas.[5] Vascular risk factors such as hypertension and obesity may also be indicators of the presence of obstructive sleep apnoea (OSA).

5. Medication related adverse events

Medication used for the treatment of systemic diseases should be considered when assessing patients with raised IOP. Around 30% of patients treated with topical, intraocular, peri-ocular and/or systemic corticosteroids develop elevated IOP within weeks of starting therapy that may progress to glaucomatous optic nerve damage. A large number of systemic medications can also increase IOP and cause glaucoma.[6] These are mainly the so-called "anti-drugs" and include: antidepressants, anticholinergics, antihistamines, anti-Parkinsonian medication, antipsychotics, antispasmodic and anaesthetic agents. Anti-hypertensive drugs that provoke nocturnal hypotension may be associated with glaucoma. Some drugs can precipitate acute angle closure crisis from primary or secondary angle closure, while others alter trabecular drainage or uveoscleral outflow. The drug history of a patient may also be a clue to the presence of a systemic disease.

6. Conclusion

Fortunately, the diagnosis of most systemic diseases and drugs associated with glaucoma can be readily detected by a careful history, including drug history, systems review and examination.

Table 1
Systemic diseases and glaucoma

Disease Mechanisms	Common conditions	Clues to presence of systemic Disease
Inflammation		
Infections	**Herpetic viral infection**	**Fever, rash, blisters, serology**
Immune	**SpA and JIA** **Sarcoidosis**	**Joint swelling, nocturnal back pain, enthesitis, psoriasis.** **Rash, lymphadenopathy and lung disease.**
Vascular	**Hypertension, migraine, ischaemic heart disease , diabetes and obesity.** **Sleep disorders**	**History of vascular risks factors. Snoring, headache, day time sleepiness, apnoeas**
Drug therapy	**Corticosteroids** **"Anti-drugs"**	**Drug history of treatment for systemic disease**

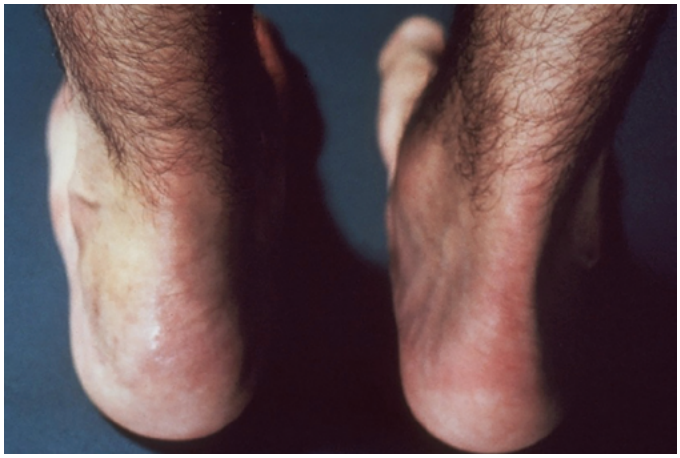

Figure 1: Patient with Archilles tendinitis in a patient with ankylosing spondylitis

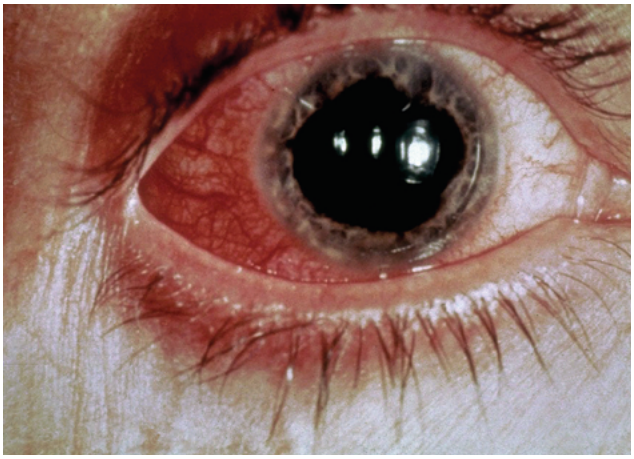

Figure 2: Patient with chronic anterior uveitis

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Recent months and years have seen significant advances in our understanding of glaucoma. Much has been learned, not only about damage mechanisms and pathogenesis, but also about diagnosis and management. Treatment options – both medical and surgical – continue to expand. This program will review this new knowledge with an emphasis on incorporating recent insights into day-to-day practice.

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