

REVISIÓN

Ocular manifestations of hypertension

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Abstract Elevated blood pressure leads to a multitude of vascular changes in eye. The earliest ocular effect of hypertension comprises of retinal microvascular changes called hypertensive retinopathy which is associated with indicators of end-organ damage (e.g., left ventricular hypertrophy, renal impairment) and may herald future risk of clinical events such as stroke, congestive heart failure and cardiovascular mortality.

Hypertension is also a major risk factor for the development and progression of diabetic retinopathy and has been associated with other ocular diseases such as retinal artery and vein occlusion, retinal arteriolar emboli, retinal macroaneurysm, glaucoma and age-related macular degeneration. In the management of patients with hypertension, physicians must be aware of the entire spectrum of the association between blood pressure and the eye.

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Manifestaciones oculares de la hipertensión arterial

Resumen La tensión arterial elevada conduce a una multitud de cambios vasculares en el ojo. El efecto más temprano de la hipertensión ocular consiste en cambios microvasculares de la retina, denominados retinopatía hipertensiva, y que se asocia con indicadores de daño en el órgano diana (por ejemplo, hipertrofia ventricular izquierda, insuficiencia renal) y puede anunciar riesgos futuros de accidente cerebrovascular, insuficiencia cardíaca congestiva o mortalidad cardiovascular, por ejemplo.

La hipertensión es también un factor de riesgo importante para el desarrollo y la progresión de la retinopatía diabética y se ha asociado con otras enfermedades oculares, tales como la oclusión arterio-venosa de la retina, el embolismo en arteriolas retinianas, el macroaneurisma retiniano, el glaucoma y la degeneración macular relacionada con la edad. En el manejo de pacientes con hipertensión arterial, los médicos deben ser conscientes la amplia gama de asociaciones existentes entre la presión arterial y el ojo.

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Introduction

Hypertension has profound vascular and often silent multi-systemic effects. The eye is unique in the sense that it reflects the direct sequelae of elevated blood pressure as retinal microvasculature changes visualized as hypertensive retinopathy; associated with risk of systemic morbidity and mortality. However, hypertension also plays a pivotal role in the development of diabetic retinopathy, with blood pressure control leading to prevention of diabetic retinopathy progression. Several other eye diseases such as retinal vascular occlusion, retinal arteriolar emboli, retinal macroaneurysm, glaucoma and age-related macular degeneration may also be related to hypertension, but these associations are not as well known to physicians. This review will summarize the broad ocular effects of hypertension.

Hypertensive retinopathy

Clinical Features

Hypertensive retinopathy consists of a series of retinal microvascular signs that typically include retinal arteriolar narrowing, arterio-venous nicking, retinal haemorrhages, and microaneurysms as well as optic disc and macular oedema, in severe cases. These signs develop due to acute and chronic elevations in blood pressure.¹ The initial response is diffuse and localized vasoconstriction of the retinal arterioles with consequent arteriolar narrowing; reflecting autoregulatory vasoconstriction in an attempt to limit the blood received by the retinal capillary bed² (Fig. 1). Arteriolar narrowing being the defining sign of hypertensive retinopathy, is most commonly seen in the early phase of hypertensive retinopathy before the onset of sclerosis, and can be detected even in children with hypertension.³ If the blood pressure remains chronically elevated, there is compression of venules due to arteriolar structural changes, leading to arteriovenous nicking (AVN) (Fig. 2). Severe hypertension ultimately causes progression

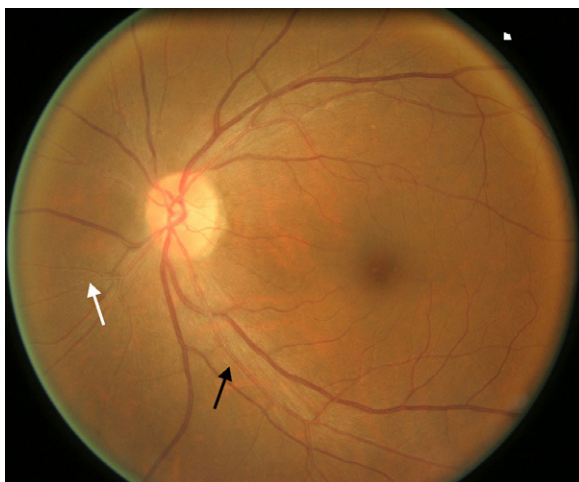


Figure 1 Generalized arteriolar narrowing (black arrow) and focal arteriolar attenuation (white arrow) with mild opacification of arterioles.

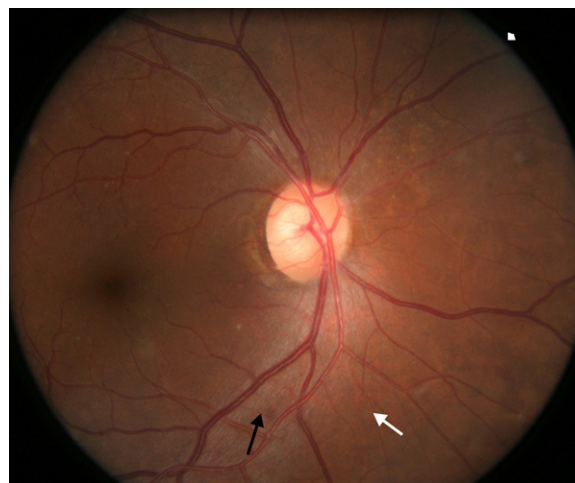


Figure 2 AVN (white arrow) with blot hemorrhage (black arrow) and generalized arteriolar narrowing: moderate retinopathy.

to an "exudative" stage in which flame-shaped retinal hemorrhages and cotton wool spots are observed (Fig. 3); and finally to a "malignant" stage with optic disc and macular edema.⁴

Chronic elevation of blood pressure can lead to hypertensive choroidopathy generally occurring in pliable vessels that are not sclerotic from long-standing hypertension. Acute elevations in blood pressure that overcome the compensatory response actually cause more damage to choroidal circulation due to its sympathetic innervation, as compared to retinal circulation.²

These stages of hypertensive retinopathy may not occur sequentially, and retinopathy signs reflecting the "exudative" stage (e.g., retinal haemorrhages) may be seen in eyes without the "arteriosclerotic" stage (e.g., AV nicking). In fact, hypertensive retinopathy signs are frequently seen in up to 10% of normotensive adults.⁵

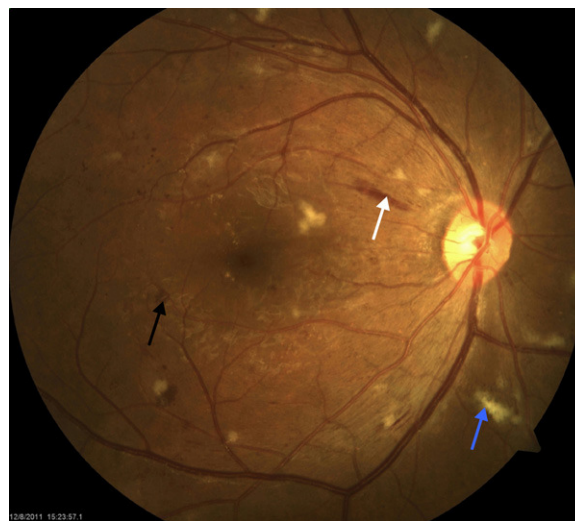


Figure 3 Flame shaped (white arrow), dot blot (black arrow) hemorrhages with cotton wool spots (blue arrow) and generalized arteriolar attenuation: Moderate retinopathy.

There are now new methods to measure and quantify sublethal hypertensive retinopathy changes from photographs.^{2,6} Studies based on semi-automated computerized analysis have shown that retinal arteriolar narrowing strongly correlates inversely with higher blood pressures, older age and negative history of hypercholesterolemia.⁷⁻⁹ Novel retinal vascular features such as branching angles, bifurcation, fractal dimension, tortuosity, vascular length-to-diameter ratio and wall-to-lumen ratio have shown to be related to hypertension and may provide additional information in predicting cardiovascular diseases.^{7,10-14} More specifically, increased curvature as reflected by a greater retinal venular tortuosity and wider retinal venular caliber have been linked with elevated blood pressure, younger age and smoking.^{7,9} Furthermore, smaller fractal dimension and smaller arteriolar branching asymmetry ratio are linked with uncontrolled hypertension.^{7,10}

It is important for physicians to be aware that some hypertensive retinal microvascular signs may also occur in other systemic and ocular conditions, such as diabetic retinopathy, radiation retinopathy, anemic/leukemic retinopathy, trauma, human immunodeficiency virus and other infections.² Thus, in an atypical situation, appropriate investigations may be necessary to rule out other important diseases which may masquerade as hypertensive retinopathy.¹⁵

Epidemiology

Population-based studies since 1990s^{30,5,16-24} indicate that many of the hypertensive retinopathy signs are commonly seen in 6 to 15% of non-diabetic adults aged ≥ 40 years.^{19,22}

Among hypertensive people, generalized arteriolar narrowing is seen in up to 25%, with focal arteriolar narrowing (FAN) and AVN found in 12%.⁵ Isolated retinal hemorrhages and/or microaneurysms are the most commonly observed signs (7-8%)⁵, with the presence of cotton wool spots being relatively uncommon (0.2%). The 10-year cumulative incidence of these retinopathy signs is 16%.²⁵

Racial variations in retinopathy prevalence show that highest rates of retinopathy are observed among Chinese (17.2%) and the lowest among white (11.9%) and black populations (13.9%). With respect to gender, higher incidence has been reported among men except for black populations.¹⁹ In Asian populations, Japanese²⁴ and Malays²² living in urban areas showed lower incidence of retinopathy (7.7% and 6% respectively) compared to rural Chinese populations (13.6%).²³

Association with Blood Pressure

The relationship between hypertensive retinopathy and severity of hypertension is well known;^{3,5,16-24,26} with frequency of generalized arteriolar narrowing (25.4% vs. 14.6%), FAN (12.1% vs. 6.2%) and AVN (12.3% vs. 6.1%) being significantly higher in hypertensive individuals⁵ especially those with elevated blood pressure (BP) despite medication, compared with those whose BP was controlled or those who were normotensive.¹⁶ The pattern of relationship between specific hypertensive retinopathy and hypertension may differ with duration and age. Generalized retinal arteriolar

narrowing and AVN are usually found in patients with chronic hypertension, and are independently associated with past blood pressure levels measured up to 10 years prior to the retinal assessment.²⁷ In contrast, FAN, retinal haemorrhages, microaneurysms and cotton wool spots indicate transitory blood pressure elevations.²⁸ Association between blood pressure and retinal microvascular signs is weaker with age, possibly reflecting greater sclerosis of retinal arterioles in older persons.²⁹

Smaller retinal arteriolar and larger venular calibers have been shown to precede clinical stage of hypertension²⁹ and are linked to 5-year risk of hypertension in normotensive people.³⁰⁻³²

It is estimated that each 10 mm Hg increase in mean arterial pressure is associated with a 3 μ m narrowing in mean retinal arteriolar diameter. Moreover, generalized arteriolar narrowing is linked with a twofold increase in the risk of incident hypertension.³³ This trend is noted even in extremely young children of 4 to 5 years of age in whom higher systolic BP is linked with narrower retinal arterioles and wider retinal venules.³⁴

Newer studies in children suggest that positive parental history of hypertension causes children to be heavier and have higher systolic BP with consequent adverse macrovascular and microvascular changes.³⁵

Prediction of Stroke and Heart Disease

Numerous studies have reported a strong link between hypertensive retinopathy and cerebrovascular disease.^{2,18,36} In one study, persons with hypertensive retinopathy were not only at an increased risk of developing incident stroke,³⁷ but also cognitive decline,³⁸ cerebral white matter lesions³⁶ and cerebral atrophy,³⁹ even after controlling for traditional risk factors. Additionally, generalized arteriolar narrowing and venular widening is associated with lacunar stroke, while retinopathy signs are linked to nonlacunar thrombotic and cardioembolic strokes.⁴⁰

Studies have also reported a relationship between hypertensive retinopathy signs and heart disease. Even mild retinopathy is a risk factor for cardiovascular mortality among men and women with and without hypertension.⁴¹ The risk of developing congestive heart failure is found to be doubled in patients with moderate hypertensive retinopathy as compared to those without retinopathy.⁴² Other studies have shown retinopathy to be strongly associated with coronary artery disease in elderly hypertensives,⁴³ and markers of subclinical or microvascular coronary disease,⁴⁴ especially in women with type 1 diabetes.⁴⁵ FAN and AVN are also related to left ventricular hypertrophy (LVH)^{46,47} Reversing LVH is being seen as an important therapeutic target of antihypertensive treatment; with angiotensin receptor antagonists and calcium antagonists being more effective in reversing LVH than beta-blockers, while the efficacy of diuretics is intermediate.^{48,49} Emerging evidence suggests that risk for coronary heart disease may be higher in women who were previously deemed "low risk" by traditional risk factors.^{50,51} Retinal arteriolar narrowing is also found to be closely linked to decreased myocardial blood flow and perfusion reserve.⁵²

Table 1 Classification of Hypertensive Retinopathy and Management Guidelines.

Retinopathy Grade	Description	Systemic Associations	Management
Mild	One or more of the following signs: Generalized arteriolar narrowing, focal arteriolar narrowing, arterio-venous nicking, arteriolar wall opacity (silver-wiring)	Weak associations with stroke, coronary heart disease and cardiovascular mortality	<ul style="list-style-type: none"> • Routine care • Closer monitoring of vascular risk
Moderate	Mild retinopathy with one or more of the following signs: Retinal hemorrhage (blot, dot or flame-shaped), microaneurysms, cotton wool spot, hard exudates	Strong association with stroke, congestive heart failure, renal dysfunction, and cardiovascular mortality	<ul style="list-style-type: none"> • Exclude diabetes • Closer monitoring of vascular risk • Possible indication for hypertension treatment and other risk factors
Malignant	Moderate retinopathy signs plus optic disc swelling and macular edema	Associated with mortality	<ul style="list-style-type: none"> • Urgent hypertension treatment

Classification and Clinical Management

Although there are detailed classifications by Marcus Gunn, Keith Wagner and Barker,² a simpler three-grade classification system has been proposed,⁵³ which overcomes the difficulty in clinically distinguishing early retinopathy grades (e.g., grade 1 from grade 2) noted in previous classification systems.^{2,54} A suggested management plan for patients with various retinopathy grades is shown in Table 1, based on this simple three-grade classification system for hypertensive retinopathy.⁵³

Patients with mild retinopathy signs will likely require routine care according to established guidelines. Patients with moderate retinopathy signs may benefit from further assessment of vascular risk (e.g., assessment of cholesterol levels) and, if clinically indicated, appropriate risk reduction therapy (e.g., cholesterol lowering agents). Patients with malignant retinopathy will need urgent anti-hypertensive management. Newer data suggests that BP control and use of cholesterol lowering agents may protect the retinal arterioles.⁹ Moreover, these preventive strategies, including healthy lifestyle and dietary habits, should be started early in life as implied by recent studies in children.³⁵

Finally, retinal assessment may be useful to study patients with white coat hypertension or masked hypertension, commonly seen in elderly women, with a prevalence of 12%–30%.⁵⁵ These patients are reported to represent an intermediate group between healthy people and sustained hypertensives with regards to target organ damage and cardiovascular risk. Detection of hypertensive retinopathy in subjects with white coat hypertension may indicate the need for antihypertensive therapy.²

Other ocular manifestations of hypertension

Diabetic Retinopathy

Diabetes and hypertension are both vascular risk factors with similar pathophysiological mechanisms. In the presence of

hypertension, persons with diabetes are more likely to have diabetic retinopathy (Fig. 4)⁵⁶

Various studies have identified hypertension as an important modifiable risk factor for diabetic retinopathy to the extent that every 10mmHg increase in systolic blood pressure is known to increase the risk of early and proliferative retinopathy by 10% and 15% respectively.⁵⁶ In fact, tighter blood pressure control is linked with reduction in microvascular disease and lower rates of progression to severe visual loss.^{56,57} Among the various anti-hypertensive treatment trials, recent data suggests that drugs targeting the renin-angiotensin system are more efficient in reducing the risk of diabetic retinopathy.^{58–61}

Retinal Vascular Occlusion

Hypertension is associated with retinal artery occlusion (RAO) and retinal vein occlusion (RVO). RAO presents with sudden, painless, dramatic visual impairment, has an

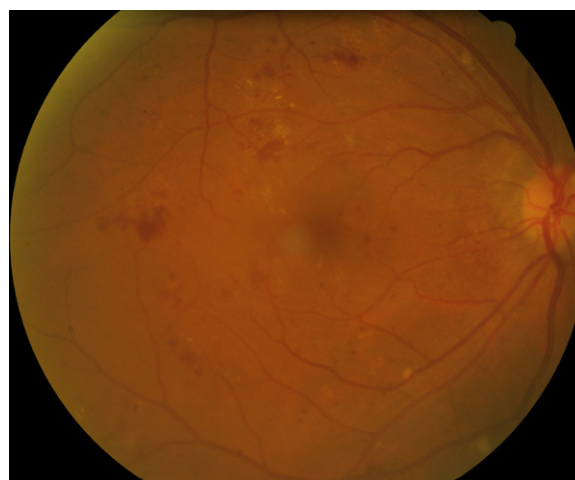


Figure 4 Concurrent moderate non-proliferative diabetic retinopathy with moderate hypertensive retinopathy.



Figure 5 Central RVO.

estimated incidence of 0.85/100 000 population,⁶² and occurs commonly among hypertensives.⁶³ Depending on which vessel is affected, the entire visual field (central retinal artery) or part of the visual field (branch retinal artery) may be affected. Retinal emboli may be visible in the retinal arterioles in up to 20% of central RAO and up to 70% of branch RAO.^{64,65}

Arterial hypertension, diabetes mellitus, hyperlipidemia, carotid and coronary artery disease, transient ischemic attack and tobacco smoking are the common risk factors for RAOs with systemic hypertension seen in more than 50% association of these patients.⁶⁶ Echocardiographic abnormalities have been documented in patients with RAO with 10% needing systemic management.⁶³

A thorough cardiovascular and cerebrovascular assessment, including carotid and cardiac imaging, is mandatory in patients with RAO. Central RAO is an ocular emergency, and efforts to restore ocular circulation and preserve vision include dislodgement of the embolus within 3 hours by digital massage of eyeball, paracentesis of anterior chamber fluid to lower intraocular pressure, and induction of vasodilatation by carbon dioxide rebreathing.⁶² However, success with these techniques is known to lead to visual improvement in only 15%.⁶²

RVO is a silent and painless vascular disease most commonly associated with hypertension with an estimated incidence of 1.6%.^{67,68} It generally presents with variable visual loss with fundal findings consisting of retinal vascular tortuosity, retinal hemorrhages (blot and flame shaped), cotton wool spots, optic disc swelling and macular edema. In a central retinal vein occlusion (CRVO), retinal hemorrhages will be found in all four quadrants of the fundus (Fig. 5), whilst these are restricted to either the superior or inferior fundal hemisphere in a hemiretinal vein occlusion. In a branch retinal vein occlusion (BRVO), hemorrhages are largely localized to the area drained by the occluded branch retinal vein. Decrease in vision is usually due to macular edema or ischemia (Fig. 6).



Figure 6 Inferonasal BRVO.

Various studies have reported the prevalence rates of BRVO ranging from 0.3% to 1.1%,⁶⁷ while CRVO is relatively rare with reported incidence of 0.1% to 0.5%;⁶⁹ with approximately 16 million people with RVO in at least one eye as per pooled analysis of population based studies.^{68,70} Recent study among the Japanese has shown a 9-year cumulative incidence of RVO to be 3.0%.⁷¹

Systemic hypertension is found to be the strongest independent risk factor associated with all types of RVO especially in the older (over 50 years) patients.^{67,68} Additional risk factors include diabetes, cigarette smoking and carotid artery disease as well as various hematological abnormalities (e.g., hyperhomocysteinaemia, anti-cardiolipin antibodies, protein S and C deficiencies, activated protein C resistance, and Factor V Leiden mutation).^{68,72,73} RVO has also been associated with stroke, coronary heart disease, cardiovascular mortality⁷⁰ and chronic kidney disease.⁷¹

The management of the RVO is closely linked to the underlying systemic disease and its management. Although there is no evidence that lowering of blood pressure would reduce the risk of complications associated with RVO, physicians should be more vigilant with the patients' treatment of hypertension after the occurrence of a RVO.

Retinal Arteriolar Emboli

Retinal arteriolar emboli are discrete plaque-like lesions lodged in the lumen of retinal arterioles which are pathologically heterogeneous and are transient.⁴ There are three types of emboli: calcific, cholesterol and platelet-fibrin. The carotid artery and the heart are the sources of embolism to the retinal arteries. In the carotid artery, plaque is the most common source. In the heart, sources of emboli are valvular lesions and tumors.^{66,74} Retinal emboli are usually asymptomatic and detected incidentally during eye examinations.⁷⁵

Data from various population based studies reveals that retinal arteriolar emboli can be detected in 1.3% to 1.4% of individuals above 40 years of age, with a 10-year incidence of 1.5% to 3.0%.⁷⁶ Hypertension, hypercholesterolemia, obesity, current smoking, increased fibrinogen

level and diabetes were significantly associated with incident emboli.^{63,75,76} Retinal vascular signs such as AVN, arteriolar wall opacification and RVO are documented to correlate considerably with presence of retinal emboli. Persons with hypertension at baseline are shown to be 2.5 times as likely to have prevalent emboli.⁷⁶

These migratory microemboli in retinal arterioles are a marker of incident stroke, cardiovascular disease and mortality^{75,77,78} as well as frank retinal artery occlusion,⁶⁶ which needs an emergency management.

Management of patients with retinal emboli should include a thorough systemic evaluation, concentrating on modifiable risk factors, such as the hypertension, dyslipidemia, smoking, obesity and diabetes. These patients may need carotid ultrasonography and Doppler, though it is suggested that 60-80% of people with asymptomatic retinal emboli do not have significant carotid stenosis.⁶⁶

Retinal Macroaneurysms

Retinal arterial macroaneurysms are acquired fusiform or saccular dilations of the retinal arterioles common in elderly women (60 – 80%) after the sixth decade of life with hypertension being a significant risk factor noted in upto 80% of patients.⁷⁹⁻⁸¹ Macroaneurysm maybe noted incidentally in asymptomatic patients, but can also present acutely with visual loss secondary to hemorrhage or exudation, with approximately one fifth of macroaneurysms being bilateral, and one in ten being multiple.⁸¹ Visual loss due to macroaneurysm may be the initial presentation of patients with uncontrolled hypertension.⁸⁰ Visual recovery typically occurs spontaneously with thrombosis of the macroaneurysm and resolution of the hemorrhage and exudates.⁸⁰ However, residual retinal damage from chronic macular edema and hard exudates deposition may lead to poor visual prognosis. Laser treatment could benefit selected cases where exudation threatens or involves the macula, which may lead to branch RAO.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss among elderly individuals worldwide with an estimated prevalence of 6.5%.^{82,83} Late AMD includes neovascular AMD (Fig. 7) and geographic atrophy; of which neovascular AMD accounts for 90% of blindness.⁸⁴

Mild-to-moderate association between hypertension and AMD^{84,85} has been supported by various prospective cohorts⁸⁶⁻⁹¹ and cross-sectional studies,⁹²⁻⁹⁶ with some case control studies^{97,98} demonstrating a statistically significant association.⁸⁴ Underlying atherosclerotic process has been implicated in AMD development secondary to hypertension by affecting the flow and permeability of choroidal vessels, though the definite mechanism remains unclear.^{84,85} Specific retinopathy signs like retinal arteriolar wall opacification,⁹⁹ dilated retinal arteriolar caliber,¹⁰⁰ AVN and FAN¹⁰¹ are linked with AMD. However, there is no convincing evidence in the literature that illustrates reduced risk for AMD development in subjects taking antihypertensive medication.⁸⁵

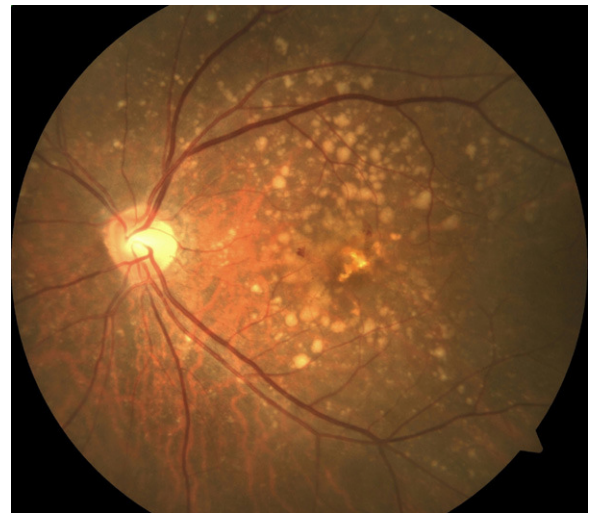


Figure 7 Neovascular Age-related macular degeneration.

Other risk factors associated with AMD include smoking, obesity, diabetes, cardiovascular disease, increased serum lipids, and inflammatory markers.⁸³⁻⁸⁵

Glaucoma

Glaucoma is characterized by multi-factorial and progressive optic neuropathy.^{102,103} It is a major cause of blindness globally with a prevalence of 60 million worldwide.¹⁰² While elevated intraocular pressure (IOP) is a major ocular risk factor,^{102,103} various systemic vascular factors like hypertension, diabetes, atherosclerosis, smoking and aging are also linked to glaucoma.¹⁰²

Relationship between hypertension and glaucoma is complex and conflicting.¹⁰⁴ A positive association exists between BP and IOP,^{105,106} but a similar and consistent relation between BP and open angle glaucoma (OAG) is not recognized.^{106,107} Current literature shows an inverse correlation between high BP and OAG incidence,¹⁰⁶ with hypotension increasing the risk for OAG.^{104,106,108} A strong positive association between SBP and IOP is described in cross-sectional studies but this relation is not supported by longitudinal population-based studies.^{104,106,107} However, the actual change in IOP with increasing BP is relatively small.^{106,107} Generalized retinal arteriolar narrowing has been found in patients with glaucomatous optic neuropathy.¹⁰²

The possible pathophysiological mechanisms causing IOP elevation are related to chronic microvascular damage and dysautoregulation induced by systemic hypertension with consequent optic nerve ischemia.^{102,104,108} Nocturnal circadian dipping in BP is known to cause reduced perfusion of the optic nerve, especially in individuals on anti-hypertensive medication.^{103,106,108} Low BP is also implicated in causing lower perfusion pressure which is an important vascular factor associated with a higher prevalence of OAG.^{104,106-108} Thus, treatment of hypertension in individuals who are either at risk of or already have glaucoma needs caution.^{104,106,107}

Conclusion

There are many eye conditions associated with hypertension that physicians should be aware of. Hypertensive retinopathy can predict target organ damage prior to clinical symptoms. Thus, an ocular assessment provides a noninvasive and useful tool for assessing vascular risk in persons with hypertension.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of Data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and /or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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