European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2022; 26: 6424-6443

A literature review of hypertensive retinopathy: systemic correlations and new technologies

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Abstract. – OBJECTIVE: Hypertensive retinopathy (HR) is the most common ocular manifestation of systemic arterial hypertension. This paper aims to summarize the current knowledge of HR, reviewing its classical features, such as epidemiology, pathophysiology, clinical manifestations, classifications, management and the most significant systemic correlations. We also provide an update on the latest advances in new technologies focusing on novel instrumental classifications.

MATERIALS AND METHODS: A literature search was performed to identify articles regarding HR listed in Embase, PubMed, Medline (Ovid) and Scopus database up to 1 December 2021. The reference lists of the analyzed articles were also considered a source of literature information. The following keywords were used in various combinations: hypertensive retinopathy, hypertension and eye, hypertensive retinopathy and systemic correlations, optical coherence tomography (OCT) and hypertensive retinopathy, optical coherence tomography angiography (OCTA) and hypertensive retinopathy, adaptive optics (AO) and hypertensive retinopathy. The authors analyzed all English articles found using the aforementioned keywords. All the publications were thoroughly reviewed to create a detailed overview of this issue.

RESULTS: HR signs have a significative association with cardiovascular, cerebrovascular and other systemic diseases. Patients with arteriosclerotic changes and, at the same time, severe HR, are at increased risk for coronary disease, peripheral vascular disease, stroke and dementia. HR is even now diagnosed and classified by its clinical appearance on a fundoscopic exam that is limited by interobserver variability. New technologies, like OCT, OCTA, AO and artificial intelligence may be used to develop a new instrumental classification that could become an objective and quantitative method for the evaluation of this disease. They could be useful to evaluate the subclinical retinal microvascular changes due to hypertension that may reflect the involvement of other vital organs.

CONCLUSIONS: The eye is the only organ in the human body where changes in the blood vessels due to systemic hypertension can be studied in vivo. All doctors should be familiar with this disease because it has been largely demonstrated that signs of HR are correlated to patient's health and mortality.

Researchers should develop a new common, standardized, and objective method to assess hypertensive retinal changes; new technologies may have a significant role in this field. This review takes most of the literature published so far, including the OCTA studies in order to stimulate new points of reference to standardize parameters and new diagnostic markers of this disease.

Key Words:
Hypertensive retinopathy, Hypertension, OCT, OCTA, Adaptive optics.

Abbreviations

Hypertensive Retinopathy (HR), World Health Organization (WHO), Hyperten-sion-mediated organ damage (HMOD), Optical Coherence Tomography (OCT), Optical Coherence Tomography Angiography (OCTA), Adaptive optics (AO), Mean Platelet Volume (MPV), Vascular Endothelial Growth Factor (VEGF), Pigment Epithelium Derived Factor (PEDF), Ischemia Modified Albumin (IMA), Renin–Angiotensin–Aldosterone System (RAAS), Prorenin/Renin Receptor ((P)RR), Angiotensin II Type I Receptor (AT1R), Angiotensin II (Ang II), SubFoveal Choroidal Thickness (SFCT), Arteries to Vein ratio (A/Vr), Keith-Wagener-Barker classification (KWB), Central Retinal Artery Diameter (CRAD), Central Macular Thickness (CMT), Retinal Nerve Fiber Layer (RNFL), Inner Plexiform–Ganglion Cell Com-

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plex (IP-GCC), Paracentral Acute Middle Maculopathy (PAMM), Deep Capillary Plexus (DCP), Subretinal Fluid (SRF), Vessel Density (VD), Foveal Avascular Zone (FAZ), Perfusion Density (PD), Parietal Thickness (PT), Inner Diameter (ID), Outer Diameter (OD), Wall Cross-Sectional Area (WCSA), Wall-to-Lumen Ratio (WLR), Flood Illumination Ophthalmoscopy (FIO), Scanning Laser Ophthalmoscopy (SLO), Cardio-Vascular Disease (CVD), Cardiovascular (CV), Apnea–Hypopnea Index (AHI), Central Retinal Arteriolar Equivalent (CRAE), Atherosclerosis Risk In Communities (ARIC), Magnetic Resonance Imaging (MRI), Extremely High High-Density Lipoprotein-Cholesterol (EH-HDL), Coronary Artery Disease (CAD), Left Atrium (LA), Real-Time three-Dimensional Echocardiography (RT3DE), Carotid Intima-Media Thickness (CIMT), Aortic Arch Calcification (AAC), Chronic Kidney Disease (CKD), estimated Glomerular Filtration Rate (eGFR), Serum Uric Acid (SUA), Preeclampsia (PE), Glial Fibrillary Acidic Protein (GFAP), Cytotoxic Necrotizing Factor 1 (CNF1), Ubiquitin Carboxy-terminal Hydrolase L1 (UCHL1).

Introduction

Systemic arterial hypertension is a major public health problem and a treatable risk factor for different systemic conditions responsible for serious morbidity and mortality. World Health Organization (WHO), in the adult population, defines hypertension as a systolic pressure greater than 140 mmHg and/or a diastolic pressure greater than 90 mmHg (both measured on two different days). The WHO estimates that 1.13 billion people worldwide have hypertension and fewer than 1 in 5 people with hypertension have it under control. With advances in medical technology, the life expectancy continues to extend, and the number of patients with high blood pressure has increased.

Hypertension is a well-known risk factor for other diseases, called hypertension-mediated organ damage (HMOD), such as stroke, disability, myocardial infarction, heart failure, kidney failure and early death[1]. Hypertension affects the eyes through a series of pathophysiological modifications that can damage the retinal, choroidal, and optic nerve circulations causing respectively retinopathy, choroidopathy, and optic neuropathy.

The most common ocular manifestation of high blood pressure is hypertensive retinopathy (HR). In 1898 Marcus Gunn first documented the retinal vascular abnormalities associated with hypertension[2], Wong and Mitchell[3] defined HR as "retinal microvascular signs that develop in response to raised blood pressure".

The eye is the only organ in the human body where it's possible to detect vascular changes due to high blood pressure *in vivo*. This literature review aims to summarize the current knowledge of HR, examining its classical features and the most significant systemic correlations, and provide an update on the latest advances in new technologies focusing on novel instrumental classifications.

Materials and Methods

A literature search was performed to identify articles regarding retinal changes in HR listed in Embase, PubMed, Medline (Ovid) and Scopus database up to 1 December 2021. The authors did not use other databases. The reference lists of the analyzed articles were also considered a source of literature information. The authors did not attempt to search for unpublished articles.

The following keywords were used in various combinations: hypertensive retinopathy, hypertension and eye, hypertensive retinopathy and systemic correlations, optical coherence tomography (OCT) and hypertensive retinopathy, optical coherence tomography angiography (OCTA) and hypertensive retinopathy, adaptive optics (AO) and hypertensive retinopathy. The authors analyzed all English articles found using the aforementioned keywords. The authors did not contact other study authors to expand on unpublished information or to obtain additional data. All the publications were thoroughly reviewed to create a detailed overview of this issue.

Epidemiology

The epidemiology of HR is difficult to establish because vascular retinal changes are often masked by the presence of other retinal vascular diseases such as diabetes. As studied by Erden et al[5], the degree and duration of hypertension increase the incidence of HR. In their study the rate of retinal vascular changes in hypertensive outpatients was 66.3%.

In the Cardiovascular Health Study, a population of 2050 people aged from 69 to 97 years without diabetes was found to have 8.3% prevalence of retinopathy, 9.6% of focal arteriolar narrowing, and 7.7% of arteriovenous nicking and all retinal lesions were associated with systemic hypertension[6].

Data from Beaver Dam Eye Study, which evaluated patients with systemic hypertension in non-diabetic population over 5 years period, showed that the incidence of retinal vascular

changes was about 15%; in particular, 6% showed retinopathy, 9.9% arteriolar narrowing, and 6.5% arteriovenous nicking[7]. Also, Yu et al[8] reported similar findings of these changes in a population of 3654 people aged 49 years or older and demonstrated a direct correlation between age and hypertension severity. Differently from Erden et al[5] study, this work did not find a correlation with the duration of systemic hypertension.

Pathophysiology

Retinal microvascular signs of HR may be caused by an acute increase in systemic blood pressure or by chronic elevated hypertension. HR has been associated with endothelial cell dysfunction[9], low-grade systemic inflammation[10] and oxidative stress[11]. The pathophysiology of HR can be divided into three phases of histologic damage[12].

In the first phase or "vasoconstrictive phase", the initial response to elevated blood pressure is constituted by localized vasospasm and vasoconstriction of the retinal arterioles; this vasospasm is due to the local autoregulatory mechanisms to optimize blood flow. These events are seen clinically as generalized or focal narrowing of retinal arteries and can be revealed by the decrease in the normal arteries to vein ratio. Elevated blood pressure over time leads to structural changes in the vessel wall such as endothelial damage, intimal thickening, media-wall hyperplasia, and hyaline degeneration. This phase, called "sclerotic phase", results in arteriovenous crossing change or nicking (a more severe form of arteriolar narrowing), and accentuation of focal or diffuse light reflex of vessel walls (described as copper or silver wiring). Arteriovenous nicking occurs when a thickened arteriole crosses the venule where the vessels have their common adventitial sheath.

The "exudative phase" is seen in patients with severe systemic hypertension. This late phase leads to disruption of the blood-retina barrier causing blood exudation (haemorrhages) in the superficial or inner retinal layers (respectively flame-shaped and dot-blot haemorrhages) or exudation of lipids seen as hard exudates. This subsequently causes cotton-wool spots which are signs of retinal-nerve-fiber layer ischemia. In this phase microaneurysms can be a common finding.

Finally, very severe and long-standing systemic hypertension can lead to a condition called "malignant hypertension" characterized by elevated intracranial pressure which causes optic nerve ischemia and optic disc swelling (papilledema).

Mean Platelet Volume

The increased platelet activity may have a pivotal role in the not fully understood pathophysiological mechanism of HR. Increased mean platelet volume (MPV) is associated with essential hypertensive subjects, indicating it might be a contributing factor to increased risk of developing microvascular complications[13,14]. Elevated levels of MPV have a significant linear relationship with the grade of HR[15,16]. Furthermore, Yazici et al[17] established that MPV values were significantly higher in the prehypertensive group than in the control group.

MPV reflects platelet activity[18]: platelets normally circulate in a disc-shaped state (a quiescent form) but, when activated, they transform into a sphere shape, increasing in size. This change may accelerate the formation of thrombus and arterial contractions resulting in vascular dysfunction of susceptible organs, such as the retina[19].

Hypoxia

Some authors consider that increased blood pressure on its own can not fully clarify the development of retinal alterations, therefore oxidative stress can play an additional pathogenetic mechanism. In support of this hy-pothesis, Pavlovschi et al[21] evaluated changes in the level of Ischemia Modified Albumin (IMA) in the serum of patients with HR. IMA is a nonspecific marker of tissue ischemia and oxidative stress induced by ische-mia/reperfusion damage. They showed that the IMA values manifested a positive correlation with HR severity. Vascular Endothelial Growth Factor (VEGF) and Pigment Epithelium Derived Factor (PEDF) could also play a role in the pathogenesis of HR because they are important mediators of vascular permeability and angiogenesis and can be an expression for hypoxia conditions or lack of perfusion[20].

Renin-Angiotensin-Aldosterone System (RAAS)

RAAS can also play a role in the pathophysiology of HR. This assumption is based on the fact that different components of RASS are expressed in the human eye[22-24]. In particular, it is well established that prorenin/renin receptor ((P)RR) and angiotensin II type I receptor (AT1R) have an active role in eye diseases such as diabetic retinopathy and age-related macular degeneration. (P)RR-location in the retinal vasculature may indicate that this receptor is involved in the modulation of ocular angiogenesis[25,26]. Besides,

angiotensin II (Ang II) promotes the expression of VEGF by activating AT1R[27,28], an action blocked by angiotensin II receptor antagonists; this supports the idea that RAAS hyperactivity is a significant stimulator of neuronal, glial and vascular dysfunction in retinopathies like HR[29].

Subfoveal Choroidal Thickness (SFCT)

Pathophysiologic studies showed a positive correlation between SFCT and HR[30]. The autoregulatory power of the retinal circulation is absent in choroidal vasculature, and with the increase in blood pressure, ischemia and injury can occur. This process has several stages: first of all, choroidal arterioles would constrict, leading to ischemia of the choriocapillaris and retinal pigment epithelium, then, chronic constriction is characterized by extreme shrinkage and closure of the choroidal capillaries, which may reduce the SFCT. If high blood pressure persists, the choroid could get into the chronic reparative stage[31]. The occluded choroidal arteries, arterioles, and choriocapillaris are recanalized and the reparative choroidal vessels are depleted of Na–K-ATPase activity, high sodium content promotes water retention with simultaneous increase of the choroidal thickness[32]. This could explain why SFCT of patients with HR was significantly thicker than hypertensive patients without HR or normal people. Furthermore, SFCT was significantly associated with HR stage. Since grade of HR was related to the choroidal thickness, it may reveal that hypertension associated choroidal thickening was a risk factor for the development or progression of HR[33]. (See the OCT chapter).

Clinical Features

The signs of HR include: constricted and tortuous arterioles; generalized or focal vessels narrowing; decrease in the normal arteries to vein ratio (normal A/Vr is 2:3); arteriovenous crossing change or nicking (Salus's sign: deflection of retinal vein as it crosses the arteriole; Gunn's sign: tapering of the retinal vein on either side of the arteriovenous crossing; Bonnet's sign: banking of the retinal vein distal to the arteriovenous crossing); accentuation of focal or diffuse light reflex of vessel walls (copper or silver wiring); microaneurysms; retinal haemorrhages (flame-shaped and dot-blot); hard exudates and cotton wool spots (soft exudates).

Malignant hypertension can lead to optic neuropathy. The signs are flame-shaped haemorrhages at the disc margin, optic disk swelling (papilledema), congested retinal veins and macular exudates with macular star sign. Hypertension can also cause choroidopathy, more frequently in younger patients with malignant hypertension.

Diagnosis

HR diagnosis is based on a fundoscopic exam in patients with assessed hypertension, that shows the typical retinal signs described above. Besides the clinical observation, retinal imaging such as wide-field colour fundus photography is useful to complete the diagnosis and to monitor the HR progression.

Diabetic retinopathy is the most important differential diagnosis for HR with diffuse retinal haemorrhages, cotton wool spots, and hard exudates. Other diseases with similar retinal haemorrhages are radiation retinopathy, retinal vein occlusion, ocular ischemic syndrome, and blood dyscrasias. Conditions with optic disc edema also include diabetic papillopathy, anterior ischemic optic neuropathy, and neuroretinitis.

HR Classifications

The first classification of HR was the Keith-Wagener-Barker (KWB) classification proposed in 1939[34].

- Grade 1: generalized constriction and tortuosity of retinal arterioles;
- Grade 2: focal narrowing of retinal arterioles + AV nicking;
- Grade 3: Grade 2 retinopathy + flame-shaped haemorrhages, cotton-wool spots and hard exudates;
- Grade 4: Grade 3 retinopathy + retinal edema or/and papilledema.

In 1953 Scheie et al[35] summarized the ocular signs of hypertension through the Scheie Classification:

- Grade 0: No changes;
- Grade 1: Barely detectable arterial narrowing;
- Grade 2: Obvious arterial narrowing with focal irregularities;
- Grade 3: Grade 2 + retinal haemorrhagess, exudates, cotton wool spots or retinal edema;
- Grade 4: Grade 3 plus papilledema.

Scheie even classified the signs of chronic arteriosclerotic hypertension through the aspect of arteriolar light reflex:

- Stage 1: Widening of the arteriolar light reflex;
- Stage 2: Stage 1 + arteriovenous crossing sign;
- Stage 3: Copper wiring of arterioles (copper colored arteriolar light reflex);
- Stage 4: Silver wiring of arterioles (silver colored arteriolar light reflex).

In 1996 Dodson et al[36] proposed a simplified classification composed of only 2 stages: non-malignant (generalized or focal arterial narrowing, AV nicking) and malignant hypertension (haemorrhages, exudates with or without papilledema).

In 2004 Wong and Mitchell[12] (Figure 1) published a new classification where the worsening stages of retinopathy were more strongly associated with systemic issues:

- None: no detectable signs;
- Mild: one or more of the following: generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity of arteriolar wall ("copper wiring");
- Moderate: one or more of the following: retinal haemorrhages (blot, dot, or flame-shaped), microaneurysm, cotton-wool spots, hard exudates or a combination of these signs;
- Severe: moderate retinopathy + swelling of the optic disc.

New Technologies

OCT

OCT is a non-invasive diagnostic technique that renders a cross sectional view of the retina. It can be used for the diagnosis and monitoring of HR, and it is also useful as an objective measurement of retinal vessel lumen diameters and wall thicknesses[37].

In the study by Schuster et al[38] hypertensive vasculopathy has been analyzed through OCT scans and the results demonstrated a significant relationship between mean arterial blood pressure and A/Vr.

Feng et al[39] found that OCT could be useful for measuring the diameters of retinal vessels in the chronic stage of HR because it is a specific and reproducible technique. Besides, they showed that the central retinal artery diameter (CRAD) and the A/Vr in the hypertensive group were smaller than in the control group.

Numerous articles analyzed central macular thickness (CMT) and retinal nerve fiber layer (RNFL) thickness with OCT in patients with HR: Lee et al[40] studied patients with HR grade IV and followed them for more than one year. At first, the mean CMT and RNFL thickness in the HR group were significantly greater than those of the normotensive group, probably because of the macular and optic disc swelling determined by elevated blood pressure. After one year of antihypertensive

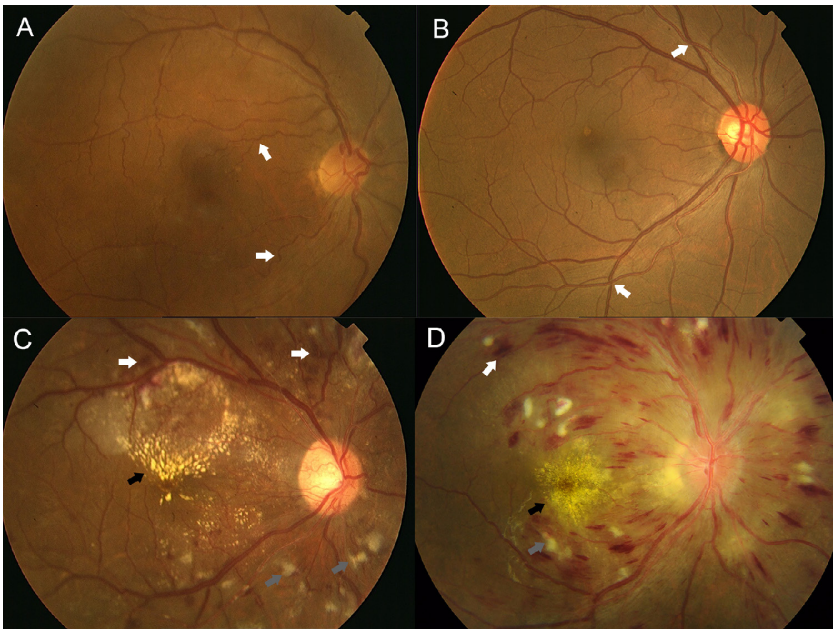

Figure 1. HR in different stages according to Wong and Mitchell classification. (Reproduced with permission from Hypertensive Retinopathy and the Risk of Stroke Among Hypertensive Adults in China, published by Invest. Ophthalmol. Vis. Sci., 2021). Illustrations **A** and **B** show two cases of mild HR: A shows generalized retinal arteriolar narrowing and arteriovenous tortuosity (w*hite arrows*); **B** shows focal narrowing with "copper wiring" of the arterioles and AV nicking (white arrows); Illustration **C** shows moderate HR: retinal haemorrhages (white arrows), exudates (*black arrow*) and cotton-wool spots (*grey arrows*); Illustration **D** shows a case of malignant HR: swelling of the optic disk with multiple retinal haemorrhages (*white arrow*), exudates (*black arrow*), cotton-wool spots (*grey arrow*).

treatment, the blood pressures returned to normal values and the signs of severe HR disappeared and the mean RNFL thickness and CMT were significantly lower than those of the control group except the temporal sector. The authors supposed that the papillomacular bundle of this region is less vulnerable to vasculopathy[41,42].

To explain this change in RNFL thickness and CMT, it is possible to hypothesize that there is a retinal ischemia after the edematous phase that causes permanent structural changes. In support of that, long-term changes in patients with cotton–wool spots in ischemic lesions have been studied by Gomez et al[43], and they show that even after the resolution of cotton–wool spots, there were significant changes in retinal layers, including the RNFL thinning. Koh et al[44] underlined the presence of localized RNFL defects after the appearance of retinal cotton–wool spots caused by vascular abnormalities.

In literature there is evidence that thinner SFCT is correlated to different systemic and ocular conditions, like older age, female gender, longer axial length, thinner lens, lower anterior chamber, high corneal curvature and lower best corrected visual acuity[33,45-49]. SFCT in HR was analyzed in various studies with different results: Simsek et al[50] found that hypertensive patients with HR had lower SFCT, CMT, Inner Plexiform–Ganglion Cell Complex (IP-GCC) and peripapillary RNFL thicknesses compared to patients without HR and the control group.

In Wei et al[49] and Shao et al[33] studies, SFCT was significantly directly related to the stage of HR. On the con-trary, SFCT was not significantly related to diastolic blood pressure, history and years of hypertension. Indeed, regarding hypertension without ocular involvement, Gök et al[51] examined a group of 116 patients with systemic hypertension and a group of 116 healthy controls and showed that there was no significant correlation between the mean SFCT and systemic hypertension. On the other hand, in a comparative cross-sectional study by Waghamare et al[52], they demonstrated that choroidal thickness was significantly lower in the hypertensive group as compared to the control group. The study group comprised 68 eyes of 34 adult individuals who were diagnosed with essential hypertension.

Paracentral Acute Middle Maculopathy (PAMM) was described by Sarraf et al[53] as an idiopathic isolated alteration of a retinal microcirculation at the level of the deep capillary plexus (DCP). This alteration has been described in several retinal vascular diseases such as retinal artery or venous occlusions, diabetic retinopathy and HR[54]. The association between hypertension and HR is reasonable because hypertension is one of the most important risk factors for retinal occlusions[55].

OCT Classification

A new classification, based on OCT features like subretinal fluid (SRF) has been proposed by Ahn et al[56]; their study found a significant correlation between OCT classification, KWB grading system and best-corrected visual acuity. HR is classified as mild-moderate retinopathy, malignant retinopathy without SRF and malignant retinopathy with SRF (Table I).

OCT Angiography

OCTA is another method still under study for HR. It allows the rapid and noninvasive assessment of the retinal capillary network and retinal blood flow. Several studies report retinal vascular changes in patients with systemic hypertension without clinical signs of HR.

Hua et al[57] studied 57 chronic hypertensive patients without HR and 40 healthy controls with OCTA. These patients were divided into three groups based on the history of arterial hypertension (>10 years of systemic hypertension, 5-10 years of systemic hypertension and patients without systemic hypertension). The results showed superficial plexus Vessel Density (VD), Foveal Avascular Zone (FAZ) area, capillary density, and inner retinal thickness changed significantly in the hypertensive groups.

In a study by Lim et al[58] the inner retinal layers of patients with a long story of hypertension were significantly thinner than those of normal controls. Besides, in these patients also VD and Perfusion Density (PD) were significantly decreased. They had, in addition, an enlargement of FAZ. They suggested that losses in the IP-GCC and peripapillary RNFL in hypertensive patients may be related to retinal microcirculation.

Shin et al[59] used OCTA imaging in a cross-sectional study and found that in patients with systemic hypertension, the peripapillary VD and PD in superficial capillary plexus were correlated with the RNFL and IP-GCC thicknesses, even without a correlation with HR.

In November 2021 Tan et al[60] conducted a meta-analysis about OCTA in patients with systemic hypertension without HR *vs.* control group: participants with systemic hyper-tension had significantly lower Superficial VD, lower Deep VD and

Table I. OCT and OCTA classifications of HR. (Reproduced with permission from Ahn et al. "Retinal and Choroidal Changes with Severe Hypertension and Their Association With Visual Outcome", IOVS 2014, and Liu et al. "Morphological changes in and quantitative analysis of macular retinal microvasculature by optical coherence tomography angiography in hypertensive retinopathy", Hypertens Res, 2021).

Classification	Category/stage	Funduscopic findings	OCT features	OCTA features
Ahn et al[58] (OCT)	mild to moderate malignant without SRF malignant with SRF	KWB grade 1, 2, 3 KWB grade 4 KWB grade 4	with/without SRF without SRF with SRF	
Liu et al[65] (OCTA)	1	KWB grade 1		No detectable signs or only focal capillary sparsity
	2	KWB grade 2		Focal capillary sparsity, scattered microangioma-like alterations and focal macular arch ring defect or a combination of these signs
	3	KWB grade 3		Signs of stage 2 retinopathy plus focal capillary disorder and nonperfusion or a combination of these signs

KWB: Keith-Wagener-Barker classification; SRF: subretinal fluid.

larger superficial FAZ. This suggests that OCTA can provide information about pre-clinical microvascular changes from systemic hypertension and this could be used to avoid subsequent long-term retinal damage in hypertensive patients. Concerning patients with HR, OCTA can improve disease staging and clarify pathophysiology. For example, Peng et al[61], in an observational cross-sectional OCTA study, consisting of 199 right eyes from 169 nondiabetic, hypertensive patients with HR, observed a neurovascular impairment with reduction of macular VD and peri-papillary RNFL thickness. Takayama et al[62] proposed to use of OCTA measurement of foveal choriocapillaris for evaluating the progression of systemic hypertension. They analyzed 206 eyes with HR and found a strong relationship between foveal VD and KWB grade. These results, for the first time, suggest that OCTA might surrogate the KWB classification for the evaluation of systemic hypertension in clinical practice.

OCTA Classification

The research by Liu et al[63] compared the morphological features of macular retinal microvasculature in 100 HR patients and 66 healthy controls using OCTA. The pathological signs pointed out in HR were the following: focal capillary shortage and non-perfusion in the superficial and deep vascular plexus, scattered microangioma-like alterations, and focal macular arch ring defects (Figure 2).

Finally, it has been evidenced that deep vessel density decreased with progressive stages of HR, so it could be a sensible indicator to monitor HR.

In this study 3 stages of HR without macular edema based on OCTA signs are proposed (Table I):

- stage 1 (only focal capillary sparsity), taking the place of KWB grade I;
- stage 2 (focal capillary sparsity and scattered microangioma-like alterations), taking the place of KWB grade II;
- stage 3 (focal capillary sparsity, scattered microangioma-like alterations, focal capillary disorder, and nonperfusion areas), taking the place of KWB grade III.

Adaptive Optics (AO)

AO camera is a new and accurate optoelectronic method, which can provide a non-invasive quantitative and qualitative microvascular morphometry of the different anatomical components of the retina at a near-histological scale.

The applicability of the AO technique has been tested in systemic hypertension: it can evaluate the retinal microcirculation and assess the effects of blood pressure and antihypertensive treatments on the anatomy of retinal arterioles[64].

The most important vascular biomarkers are the parietal thickness (PT), inner diameter (ID), outer diameter (OD), wall cross-sectional ar-

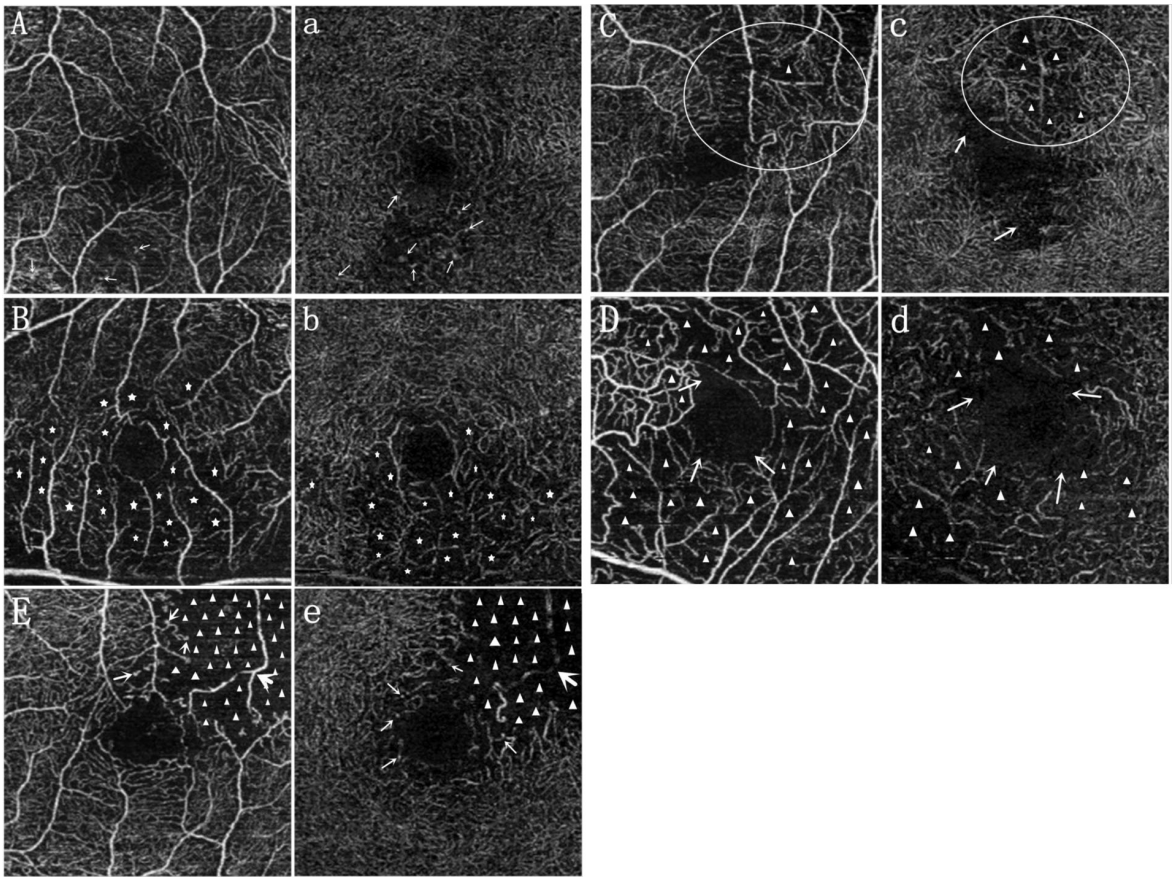

Figure 2. OCTA 3x3 mm scans in HR subjects with superficial and deep retinal capillary changes. In panels **A** and a, the arrows indicate, respectively, a few focal scattered microangioma-like alteration in the superficial and deep retinal capillary plexus below the fovea, in grade KWB II. In panels B and b, the pentagrams indicate, respectively, extensively scattered foci of local retinal capillaries in the superficial vascular plexus and deep capillary plexus around and below the macula arch ring, in KWB grade III. In **C** and c, the ellipses indicate, respectively, the superficial and deep retinal capillary angiograms in KWB grade III. Above the central fovea of the superficial and deep retinal vessel networks ellipses indicate focal retinal capillary disorder and triangles indicated scattered foci; the upper and lower parts of the deep arch ring are damaged (*arrows).* **D** and d indicate, respectively, that the superficial and deep macular arch rings are destroyed (*arrows)* in KWB grade III, with scattered focal retinal capillary ischemic areas (triangles). **E** and e indicate, respectively, the large retinal capillary nonperfusion areas (triangles) above the temporal fovea of the superficial and deep retinal capillaries with residual vascular tortuosity and dilatation (thick arrows) and sparse microangioma-like alterations (fine *arrows*), in KWB grade III. (Reproduced with permission from Liu et al[63] "Morphological changes in and quantitative analysis of macular retinal microvasculature by optical coherence tomography angiography in hypertensive retinopathy", Hypertens Res, 2021).

ea (WCSA) and wall-to-lumen ratio (WLR). In numerous studies in literature PT, ID, OD, WCSA and WRL in hypertensive patients had been demonstrated to be significantly different when compared to healthy controls[64-66].

As an example, Gallo et al[67] in a large population study (1,500 patients) identified a cut-off for ID<78 μm and WLR>0.31 that may indicate masked hypertension and help to discriminate between hypertensive and normotensive subjects.

Mehta et al[65] reported a significant difference in WCSA and WLR values between hypertensive and control groups. A recent systematic review of AO flood illumination ophthalmoscopy (FIO) and AO scanning laser ophthalmoscopy (SLO) by Bakker et al[68] well summarized all the numerous works on these biomarkers and the result of the meta-analysis for hypertensive patients showed that WLR, PT, and ID were significantly different when compared to healthy controls. The authors underline the necessity of standardized reference protocols and software enabling large-scale extraction of morphometric parameters on a montage of AO images to improve the use of this technology in clinical studies.

AO may also contribute to a better understanding of the pathophysiology of HR. Koch et al[69] studied the wall thickness of retinal vessels in patients with HR and arteriovenous nicking and focal arteriolar narrowing using a flood-illumination AO retinal camera. They found four cases of venous nicking occurring at a site where an arteriole and a venule ran in parallel, without overlapping (Figure 3); there was a gap of 10-30 microns between the vessels. Authors suggested that physical contact between the artery and the vein is not a prerequisite for venous nicking.

Automated Systems and Artificial Intelligence

An important task in computer-assisted medical image analysis for the diagnosis of HR is automatic segmentation of retinal images. The manual detection of these retinal vessels is a time-consuming process that can be automated with the help of artificial intelligence with deep learning. Deep learning technology can be the way to achieve accurate vessel segmentation and characterize subtle changes in the retinal vasculature[70].

New and old retinal vascular network parameters, such as fractal dimension, tortuosity and branching can be quantified through advanced image processing techniques and machine learning tools[71,72].

Recently, Yin et al[73] proposed a multiple classifiers decision-combination scheme that is specifically set for A/V classification. Also, Akbar et al[74] presented an automated system that detects with satisfactory results the HR at various stages using A/V ratio and papilledema signs through fundus retinal images.

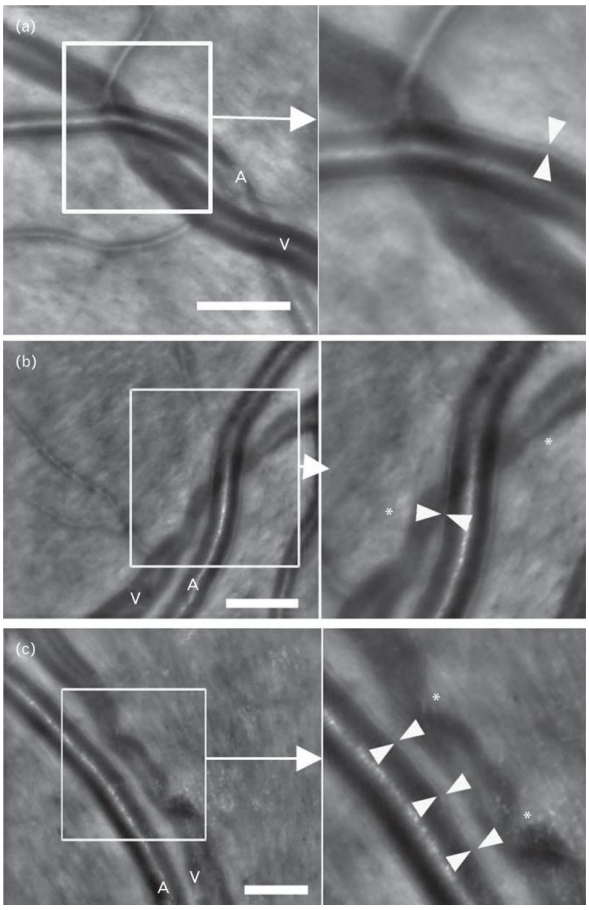

Figure 3. AO imaging of arteriovenous crossings. (Reproduced with permission from Koch et al[69] "Morphometric analysis of small arteries in the human retina using AO imaging relationship with blood pressure and focal vascular changes" J Hypertens, 2014). Arrowheads indicate the arteriolar wall. Right figures are magnifications of left figures. Illustration (**a**) shows a case of normal AV crossing. Illustration (**b**) shows a case of AV nicking; asterisks indicate the focal venous narrowings upstream and downstream of the AV overlap. Illustration (**c**) shows a case of venous nicking occurring nearly the arteriole without physical contact; there is a gap between the arteriolar wall and the vein.

Poplin et al[75] used deep-learning models on retinal imaging to predict cardiovascular risk factors, such as age, gender, smoking status, systolic blood pressure, and major adverse cardiovascular events.

HR and Systemic Correlations

The correlations between HR and systemic conditions are well known. Since the retina and other organs such as the brain and kidney share similar anatomical characteristics, studying retinal microcirculation allows us to value the health state of these organs[76].

The retinal microvascular changes in HR have a role in predicting the risk and mortality associated with cerebrovascular, cardiovascular, renal and gynaecological diseases[29,77-83].

Systemic hypertension can damage both the retinal, myocardial and renal circulation, and retinal fundoscopy can detect HMOD by a non-invasive method, in the same way as microalbuminuria and electrocardiography[84,85]. HR is independently associated with a higher risk of stroke and all-cause cardiovascular disease (CVD), regardless of blood pressure and other cardiovascular (CV) risk factors[84].

HR and its vascular manifestation were also correlated to Obstructive Sleep Apnea; in August 2021, Saeed et al[86] published a narrative review about this association. Fraser et al[87] demonstrated that Apnea–Hypopnea Index (AHI) > 40 doubles the risk of retinal vascular changes regardless of blood pressure measurement and Tong et al[88] concluded that there is a significant inverse association between AHI and A/Vr and central retinal arteriolar equivalent (CRAE) irrespective of mean arterial pressure.

Neurology

The retina has the same embryological origins as the brain, and their vasculatures share similar anatomic and physiologic properties: they share size (40-200 μm), structure (end arteries without anastomoses), vascular regulatory processes and the blood-retinal barrier is analogous to the blood-brain barrier[89]. Changes in retinal vessels could be similar to those in the brain and studying retinal signs may help in understanding the pathophysiology of cerebrovascular diseases. Since the retinal vasculature can be directly and noninvasively visualized *in vivo*, it can be seen as a surrogate for cerebral small vasculature. Furthermore, several major neurodegenerative disorders have their manifestations in the retina, for this reason authors called the eye the 'window' to the brain[90].

This concept is supported by epidemiological data that demonstrate with strong evidence the independent association between retinal microvascular abnormalities and cerebrovascular diseases, especially with stroke. The Atherosclerosis Risk In Communities (ARIC) study showed that retinal haemorrhages, microaneurysms and cotton wool spots were associated with two to four times the risk of developing a clinical stroke as compared to patients who did not have these signs, even when the analysis was controlled for other risk factors for stroke[91].

Also, the Cardiovascular Health Study showed a strong correlation between retinal haemorrhagess, microaneurysms, cotton-wool spots and clinical stroke[5].

In the Mitchell et al[92] and Wong et al[93] studies, HR was also strongly related to stroke mortality. Recently Chen et al[94] in a prospective study analyzed 9,753 Chinese hypertensive patients and pointed out a strong positive association between HR and the risk of the first stroke.

Since the vascular disease is an important cause of dementia and cognitive impairment in older people, several studies have investigated the association between retinal microvascular abnormalities and these diseases. In the ARIC, study signs of retinopathy were associated with reduced cognitive performance[95], cerebral white-matter lesions[96] and cerebral atrophy[97] defined with magnetic resonance imaging (MRI). Supporting that, also Baker et al[98] found a correlation between HR, retinal arteriolar wall signs and dementia. These studies reveal that correlations are strongest for more severe retinal microvascular abnormalities. On the contrary, they show a weaker correlation between signs of mild retinopathy and stroke, death from stroke, cognitive impairment, and cerebral changes on MRI.

The retinal abnormalities most strongly associated with stroke (retinal haemorrhages, microaneurysms, cotton-wool spots) are correlated with a breakdown of the blood–retina barrier. These findings may suggest that disruption of the blood–brain barrier may be an important phase in the development of cerebrovascular diseases[12,99,100].

Cardiology

High blood pressure is an important risk factor for the development and progression of CVD, including ischemic heart disease. Detecting early signs of organ damage caused by chronic hypertension is important for health professionals[101]. Traditionally, retinal vasculature assessment by

the fundus examination has been used to evaluate the state of the systemic microcirculation as a risk factor for CVD[102]. HR assessed by the KWB[34] and Scheie[103] classifications was found to be associated with cardiovascular mortality and events[79].

Nakajima et al[104] investigate the association between EH-HDL (extremely high high-density lipoprotein-cholesterol) and HR in a cross-sectional study of the general Japanese population. They found that EH-HDL≥110 mg/dL was associated with HR assessed by the KWB and Scheie classifications, and these associations were independent of sex, age and blood pressure. The authors propose that EH-HDL may indicate an atherosclerotic condition, possibly beyond blood pressure. In line with this concept, previous studies showed that associations of HR with cardiovascular events and mortality were independent of blood pressure[79,91,105]. The underlying mechanism is not yet fully understood, but uncommon high blood pressure not disclosed by typical measurements, such as paroxysmal and nocturnal hypertension and microartery hypertension play a key role[104]. Several studies have pointed out the association between HR and coronary damage.

The ARIC study found a 3-year incidence of cardiovascular accident risk in women and a 3-year incidence of cerebrovascular accident risk in patients with microvascular changes in the retina regardless of other baseline factors like diabetes, blood pressure or smoking[91,106].

Habib et al[107] investigated the relationship between worsening stages of HR and angiographic severity of coronary artery disease (CAD) assessed by Syntax Score. They found that patients with mild HR either had no CAD or mild CAD whereas patients with severe HR were more likely to have severe CAD on angiography.

Jibran et al[108] determined that HR is an independent risk factor for post-acute ST elevation myocardial infarction (STEMI) complications in successfully thrombolysed patients and increased the relative risk for complications by 3.17 times.

Kanar et al[109] investigated the relationship between left atrium (LA) volumes and retinal alterations through real-time three-dimensional echocardiography (RT3DE). They found that patients in the upper KWB category had higher values of LA volumes regarding RT3DE.

Zhang et al[110] explored the relationship between HR, diagnosed according to the KWB classification, and carotid intima—media thickness (CIMT), measured by carotid ultrasonography, in more than 12 thousand Chinese adults with a diagnosis of systemic hypertension. HR (grade 2 and higher) was significantly associated with an increase in CIMT in patients with high blood pressure.

HMOD start with vascular damage. Vascular calcification is a sign of vascular injury and aortic arch calcification (AAC) is one of the easily recognizable forms of vascular calcification. Adar et al[111] assumed that AAC predicts HR in patients with high blood pressure and found a significantly strong and positive correlation between HR and AAC grades.

Homocysteine level is an independent risk factor for HR as researched by Zhong et al[112]; they compared in the Chinese Han population 128 patients with HR and 128 control subjects. Each increase of 1 μmol/L of homocysteine concentration was significantly correlated with a 9% increased risk of HR (odds ratio [OR] = 1.09, 95% confidence interval [CI]: 1.07-1.55, $p < .05$).

Various studies showed a significant genetic contribution to retinal vascular caliber and its correlation with cardiovascular diseases[113-115].

Nephrology

Associations between more severe retinopathy and worse chronic kidney disease (CKD) levels have been demonstrated in several studies of CKD cohorts, especially in diabetic patients[81,116,117].

In the Chronic Renal Insufficiency Cohort (CRIC) study, the prevalence of retinopathy was 49% among CKD patients with diabetes despite 11% in those without diabetes. Furthermore, lower levels of estimated Glomerular Filtration Rate (eGFR) independently predict retinopathy severity among diabetic patients, but not among hypertensive patients[116].

In Africa, numerous studies reported the prevalence of HR among patients with systemic hypertension and other comorbidities like CKD[118-121]. Indeed, a recent study analyzed how retinopathy severity can be used as a marker of CKD severity in non-diabetic patients with hypertension and CKD. It found that more severe CKD, higher hypertension grades, as well as alcohol consumption, independently predicted the presence of more than mild HR in Tanzania patients[122].

Significant epidemiological evidence showed that serum uric acid (SUA) might be associated with hypertension[123] and that SUA elevation was a risk factor for hypertension disease[124]. The prevalence of hyperuricemia in hypertensive patients was around 20-50%[125,126]. Chen et al[127] demonstrated that SUA concentration was positively associated with odds of HR, every 1 mg/dl increase

in SUA concentration was associated with 6% higher odds of retinopathy. A hypothesis is that increase in SUA levels can lead to endothelial cell dysfunction and, via nitric oxide synthase, it can stimulate vascular smooth muscle cell proliferation, resulting in the development of atherosclerosis[124].

Gynaecology

Preeclampsia (PE) may alter the retinal vasculature producing retinopathy[128]. Thus, in eyes of women with PE, it is possible to find signs of HR[129].

Bakhda et al[130] studied 300 cases of pregnancy-induced hypertension: 20.33% of mild PE, 98.68% of severe PE and 97.62% of eclampsia showed vascular fundus changes. The incidence of preterm babies, intrauterine death, stillbirth and low birth weight infants was higher in mothers with fundus changes. The perinatal mortality was higher in patients having Grade II (33.85%), Grade III (54.29%), and Grade IV (100%) of HR. The authors suggest that similar vascular ischemic changes of HR occur in the placenta. Ramírez-Montero et al[29] proposed that PE can be a predisposing factor to faster development of retinal alterations induced by a second insult that could affect the cardiovascular system. They demonstrated that VEGF and PEDF are modified during PE and could have a role in retinopathy; they also suggest possible participation of (P)RR and AT1R.

Management

Treatment for HR is primarily focused on decreasing systemic blood pressure. To reduce ocular and systemic damage and prevent complications it is important to collaborate with the patient's primary care doctor. The main limitation in HR management, observed by Van den Born et al[131], is that fundoscopic evaluation is limited by interobserver variability. Retinal photography can be a potentially sensitive, precise and more objective method to assess retinal microvascular signs and an additional value in the management of hypertensive patients[131,132].

Funduscopic examination should be performed in every patient with a suspected hypertensive emergency because anamnesis alone is not sufficient to rule out retinopathy. In a retrospective study by Nijskens et al[133], mean blood pressure in patients with a suspected hypertensive emergency was significantly higher in patients with reti-nopathy, but retinopathy was also seen in patients with lower blood pressure. The authors concluded that iden-tification of patients with retinopathy grade III/IV can facilitate the selection of those who need to control blood pressure with intravenous medication.

The 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend that fundoscopy should be performed in patients with KWB grade 2 or 3 hypertension or hypertensive patients with diabetes, in whom significant retinopathy is more likely, while in patients at early stages, signs of HR have less predictive value and are limited by intraobserver and interobserver reproducibility[134].

A study by Biesenbach et al[135] in 1994 had already demonstrated that fundoscopy and eye examination in the evaluation of hypertension improve the indication for systemic therapy. Indeed, diagnosing HR could help select patients with hypertension who need a more aggressive treatment[84].

Grosso et al[102] recommended the use of a supplemental risk assessment flowchart that may allow primary care physicians to further guide their treatment (Figure 4). In the presence of borderline or inconsistent hypertension, the ophthalmologist's retinal evaluation and hypertensive grading could be of use and may assist the primary care physician in determining if additional antihypertensive therapy should be initiated or if stricter lifestyle modification is sufficient.

For hypertensive patients with KWB grade 1 or 2 ophthalmological referrals may be considered for patients with diabetes or visual symptoms. In the presence of moderate retinal signs, ophthalmologists may refer people for further cardiac evaluation to improve the cerebrovascular risk stratification and pharmacological treatment may be warranted. The presence of retinopathy may be an indication for more aggressive intervention on associated cardiovascular risk factors and co-morbidities and has an important practical impact on treatment decisions and for a close follow up. For all KWB grade 3 hypertensive patients there are compelling indications for an ophthalmological referral to evaluate and treat retinal vascular complications. In case of malignant retinopathy, the patient needs urgent hypertension treatment.

Studies have explored intravitreal antibody treatment against vascular endothelial growth factors for acute HR and they showed a reduction in macular edema and retinal haemorrhagess[136-138]. Moreover, another study showed prompt recovery of malignant HR in patients after administration of bevacizumab[139]. However, the use of these agents has not been widespread or accepted yet.

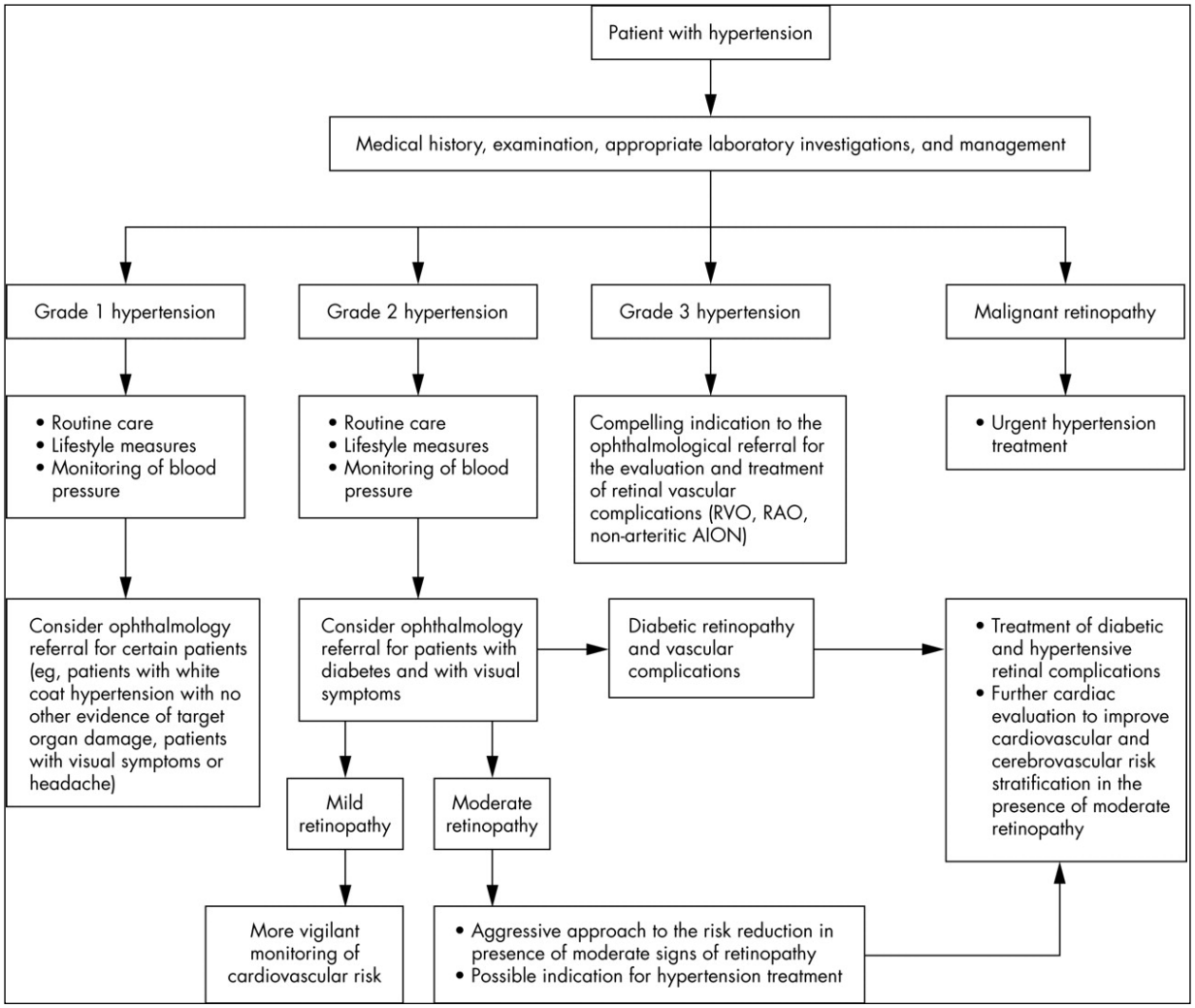

Figure 4. Flow chart: supplemental risk assessment by retinal examination. (Reproduced with permission from Grosso et al[102] "Hypertensive retinopathy revisited: some answers, more questions", Br J Ophthalmol, 2005).

Alternative Therapeutic Strategies

Target therapy represents a new therapeutic frontier for medicine and ophthalmology. By analyzing in detail the pathophysiological, molecular and biological mechanisms, it is possible to find new targets for therapeutic strategies.

Inflammation and immunoproteasome are associated with retinal diseases, in particular some subunits of proteasome seem to have a key role in the pathogenesis of Ang II-induced retinopathy. Li et al[140] studied the overexpression of the catalytic subunit β2i of the immunoproteasome and its contribution to Ang II-induced retinopathy in mice. Wang et al[141] found that immunoproteasome catalytic subunit β5i promoted Ang II-induced retinopathy.

Confirming the role of neuroinflammatory processes in HR, the retinal damage due to high blood pressure is correlated to increased expression of Glial Fibrillary Acidic Protein (GFAP). Proteins belonging to the Rho GTPase family are involved in the activation of Müller glia and the progression of photoreceptor degeneration; Matteucci et al[142] observed that topical administration of a Rho GTPase modulator, the Cytotoxic Necrotizing Factor 1 (CNF1), improves electrophysiological, behavioural visual performances and leads to a reduction of Rac1 activity and retinal GFAP expression in aged spontaneously hypertensive rats.

The enzyme ubiquitin carboxy-terminal hydrolase L1 (UCHL1), which has been reported to be associated with hypertension and cardiovascu-

lar disease, is also involved in retinopathy and a study in hypertensive rats by Liu et al[143] suggests that UCHL1 may be used as a potential therapeutic target for treating HR.

Conclusions

The retina is a sensorineural tissue that can be affected by high blood pressure[144]. Systemic hypertension remains a major public health problem with numerous multisystemic effects. The eye is the only organ in the human body where changes in the blood vessels due to systemic hypertension can be studied *in vivo*. These alterations have a significative association with cardiovascular, cerebrovascular and other systemic diseases. Patients with arteriosclerotic changes and, at the same time, severe HR, are at increased risk for coronary disease, peripheral vascular disease, stroke and dementia.

The ophthalmologist should be familiar with the symptoms and signs of HR as it has short-term and long-term correlations to the patient's clinical status and mortality. Eye care specialists should work in coordination with the primary care physician or, in cases of malignant retinopathy, with an emergency department. Furthermore, screening for HR might differentiate patients who need more intensive treatment and those who do not.

Since HR may be associated with other ocular diseases and is often asymptomatic, screening with a fundoscopic examination in patients with conditions such as retinal vascular occlusions, diabetic retinopathy and ischemic optic neuropathy will be useful[145,146].

Actual classifications and diagnosis of HR are limited by interobserver variability, therefore researchers should develop a standardized photographic classification for HR signs, like ETDRS classification for diabetic retinopathy.

New technologies, like OCT, OCTA, AO and artificial intelligence may be used to develop a new instrumental classification that could become an objective and quantitative method for the evaluation of this important disease. They could be useful to evaluate the subclinical retinal microvascular changes due to hypertension that may reflect the involvement of other vital organs.

There are several articles in the literature on HR, but it is important to underline how few reviews are available and the absence of a Cochrane meta-analysis. This review takes most of the literature published so far, including the OCTA studies in order to stimulate new points of reference to standardize parameters and new diagnostic markers of the disease.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Funding

This research received no external funding.

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References

1) Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension 2020; 75: 285-292.
2) Walsh JB. Hypertensive retinopathy. Description, classification, and prognosis. Ophthalmology 1982; 89: 1127-1131.
3) Wong TY, Mitchell P. The eye in hypertension. Lancet 2007; 369: 425-435.
4) Bhargava M, Ikram MK, Wong TY. How does hypertension affect your eyes? J Hum Hypertens 2012; 26: 71-83.
5) Erden S, Bicakci E. Hypertensive retinopathy: incidence, risk factors, and comorbidities. Clin Exp Hypertens 2012; 34: 397-401.
6) Wong TY, Klein R, Sharrett AR, Manolio TA, Hubbard LD, Marino EK, Kuller L, Burke G, Tracy RP, Polak JF, Gottdiener JS, Siscovick DS. The prevalence and risk factors of retinal microvascular abnormalities in older persons: The Cardiovascular Health Study. Ophthalmology 2003; 110: 658-666.
7) Klein R, Klein BE, Moss SE. The relation of systemic hypertension to changes in the retinal vasculature: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc 1997; 95: 329-348; discussion 348-350.
8) Yu T, Mitchell P, Berry G, Li W, Wang JJ. Retinopathy in older persons without diabetes and its relationship to hypertension. Arch Ophthalmol 1998; 116: 83-89.
9) Karaca M, Coban E, Ozdem S, Unal M, Salim O, Yucel O. The association between endothelial dysfunction and hypertensive retinopathy in essential hypertension. Med Sci Monit 2014; 20: 78-82.
10) Coban E, Nizam I, Topal C, Akar Y. The association of low-grade systemic inflammation with hypertensive retinopathy. Clin Exp Hypertens 2010; 32: 528-531.

11) Coban E, Alkan E, Altuntas S, Akar Y. Serum ferritin levels correlate with hypertensive retinopathy. Med Sci Monit 2010; 16: CR92-95.
12) Wong TY, Mitchell P. Hypertensive retinopathy. N Engl J Med 2004; 351: 2310-2317.
13) Coban E, Yazicioglu G, Berkant Avci A, Akcit F. The mean platelet volume in patients with essential and white coat hypertension. Platelets 2005; 16: 435-438.
14) Gang L, Yanyan Z, Zhongwei Z, Juan D. Association between mean platelet volume and hypertension incidence. Hypertens Res 2017; 40: 779-784.
15) Coban E, Adanir H, Bilgin D. The association of mean platelet volume levels with hypertensive retinopathy. Platelets 2008; 19: 115-118.
16) Bhatti AB, Ali F, Satti SA. Relationship of Hypertensive Retinopathy with Mean Platelet Volume Among Hypertensive Patients. Cureus 2015; 7: e422.
17) Yazici M, Kaya A, Kaya Y, Albayrak S, Cinemre H, Ozhan H. Lifestyle modification decreases the mean platelet volume in prehypertensive patients. Platelets 2009; 20: 58-63.
18) Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets 2002; 13: 301-306.
19) Jagroop IA, Clatworthy I, Lewin J, Mikhailidis DP. Shape change in human platelets: measurement with a channelyzer and visualisation by electron microscopy. Platelets 2000; 11: 28-32.
20) Penn JS, Madan A, Caldwell RB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 2008; 27: 331-371.
21) Pavlovschi E, Pantea V, Borovic D, Tagadiuc O. Study of ischemia modified albumin (IMA) as a biomarker in hypertensive retinopathy. Med Pharm Rep 2021; 94: 185-190.
22) Wilkinson-Berka JL, Miller AG, Binger KJ. Prorenin and the (pro)renin receptor: recent advances and implications for retinal development and disease. Curr Opin Nephrol Hypertens 2011; 20: 69-76.
23) Vaajanen A, Lakkisto P, Virtanen I, Kankuri E, Oksala O, Vapaatalo H, Tikkanen I. Angiotensin receptors in the eyes of arterial hypertensive rats. Acta Ophthalmol 2010; 88: 431-438.
24) Sarlos S, Rizkalla B, Moravski CJ, Cao Z, Cooper ME, Wilkinson-Berka JL. Retinal angiogenesis is mediated by an interaction between the angiotensin type 2 receptor, VEGF, and angiopoietin. Am J Pathol 2003; 163: 879-887.
25) Lambert G, Brichant JF, Hartstein G, Bonhomme V, Dewandre PY. Preeclampsia: an update. Acta Anaesthesiol Belg 2014; 65: 137-149.
26) Kanda A, Ishida S. (Pro)renin receptor: Involvement in diabetic retinopathy and development of molecular targeted therapy. J Diabetes Investig 2019; 10: 6-17.
27) Nakamura S, Tsuruma K, Shimazawa M, Hara H. Candesartan, an angiotensin II type 1 receptor antagonist, inhibits pathological retinal neovascularization by downregulating VEGF receptor-2 expression. Eur J Pharmacol 2012; 685: 8-14.
28) Haque R, Iuvone PM, He L, Hur EH, Chung Choi KS, Park D, Farrell AN, Ngo A, Gokhale S, Aseem M, Kumar B. Prorenin receptor (PRR)-mediated NADPH oxidase (Nox) signaling regulates VEGF synthesis under hyperglycemic condition in ARPE-19 cells. J Recept Signal Transduct Res 2017; 37: 560-568.
29) Ramirez-Montero C, Lima-Gomez V, Anguiano-Robledo L, Hernandez-Campos ME, Lopez-Sanchez P. Preeclampsia as predisposing factor for hypertensive retinopathy: Participation by the RAAS and angiogenic factors. Exp Eye Res 2020; 193: 107981.
30) Tso MO, Jampol LM. Pathophysiology of hypertensive retinopathy. Ophthalmology 1982; 89: 1132-1145.
31) Henderson AD, Bruce BB, Newman NJ, Biousse V. Hypertension-related eye abnormalities and the risk of stroke. Rev Neurol Dis 2011; 8: 1-9.
32) Amin MS, Reza E, Wang H, Leenen FH. Sodium transport in the choroid plexus and salt-sensitive hypertension. Hypertension 2009; 54: 860-867.
33) Shao L, Zhou LX, Xu L, Wei WB. The relationship between Subfoveal Choroidal Thickness and Hypertensive Retinopathy. Sci Rep 2021; 11: 5460.
34) Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. Am J Med Sci 1974; 268: 336-345.
35) Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. AMA Arch Ophthalmol 1953; 49: 117-138.
36) Dodson PM, Lip GY, Eames SM, Gibson JM, Beevers DG. Hypertensive retinopathy: a review of existing classification systems and a suggestion for a simplified grading system. J Hum Hypertens 1996; 10: 93-98.
37) Rim TH, Choi YS, Kim SS, Kang MJ, Oh J, Park S, Byeon SH. Retinal vessel structure measurement using spectral-domain optical coherence tomography. Eye (Lond) 2016; 30: 111-119.
38) Schuster AK, Fischer JE, Vossmerbaeumer C, Vossmerbaeumer U. Optical coherence tomography-based retinal vessel analysis for the evaluation of hypertensive vasculopathy. Acta Ophthalmol 2015; 93: e148-153.
39) Feng X, Wang H, Kong Y, Zhang J, He J, Zhang B, Zhang J, Qi H, Wang Y. Diagnosis of chronic stage of hypertensive retinopathy based on spectral domain optical coherence tomography. J Clin Hypertens (Greenwich) 2020; 22: 1247-1252.
40) Lee HM, Lee WH, Kim KN, Jo YJ, Kim JY. Changes in thickness of central macula and retinal nerve fibre layer in severe hypertensive retinopathy: a 1-year longitudinal study. Acta Ophthalmol 2018; 96: e386-e392.
41) Pavlidis M, Stupp T, Hummeke M, Thanos S. Morphometric examination of human and monkey retinal ganglion cells within the papillomacular area. Retina 2006; 26: 445-453.
42) Rao A, Mukherjee S, Padhy D. Optic nerve head characteristics in eyes with papillomacular bundle

defects in glaucoma. Int Ophthalmol 2015; 35: 819-826.

43) Gomez ML, Mojana F, Bartsch DU, Freeman WR. Imaging of long-term retinal damage after resolved cotton wool spots. Ophthalmology 2009; 116: 2407-2414.

44) Koh JW, Park KH, Kim MS, Kim JM. Localized retinal nerve fiber layer defects associated with cotton wool spots. Jpn J Ophthalmol 2010; 54: 296-299.

45) Ikuno Y, Tano Y. Retinal and choroidal biometry in highly myopic eyes with spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci 2009; 50: 3876-3880.

46) Fujiwara T, Imamura Y, Margolis R, Slakter JS, Spaide RF. Enhanced depth imaging optical coherence tomography of the choroid in highly myopic eyes. Am J Ophthalmol 2009; 148: 445-450.

47) Povazay B, Hermann B, Hofer B, Kajic V, Simpson E, Bridgford T, Drexler W. Wide-field optical coherence tomography of the choroid in vivo. Invest Ophthalmol Vis Sci 2009; 50: 1856-1863.

48) Yasuno Y, Miura M, Kawana K, Makita S, Sato M, Okamoto F, Yamanari M, Iwasaki T, Yatagai T, Oshika T. Visualization of sub-retinal pigment epithelium morphologies of exudative macular diseases by high-penetration optical coherence tomography. Invest Ophthalmol Vis Sci 2009; 50: 405-413.

49) Wei WB, Xu L, Jonas JB, Shao L, Du KF, Wang S, Chen CX, Xu J, Wang YX, Zhou JQ, You QS. Subfoveal choroidal thickness: the Beijing Eye Study. Ophthalmology 2013; 120: 175-180.

50) Simsek EE, Kanar HS, Kanar BG, Cetin H, Arsan A, Tigen MK. Can ocular OCT findings be as a predictor for end-organ damage in systemic hypertension? Clin Exp Hypertens 2020; 42: 733-737.

51) Gok M, Karabas VL, Emre E, Aksar AT, Aslan MS, Ural D. Evaluation of choroidal thickness via enhanced depth-imaging optical coherence tomography in patients with systemic hypertension. Indian J Ophthalmol 2015; 63: 239-243.

52) Waghamare SR, Mittal S, Pathania M, Samanta R, Kumawat D, Gupta N, Mittal SK. Comparison of choroidal thickness in systemic hypertensive subjects with healthy individuals by spectral domain optical coherence tomography. Indian J Ophthalmol 2021; 69: 1183-1188.

53) Sarraf D, Rahimy E, Fawzi AA, Sohn E, Barbazetto I, Zacks DN, Mittra RA, Klancnik JM, Jr., Mrejen S, Goldberg NR, Beardsley R, Sorenson JA, Freund KB. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. JAMA Ophthalmol 2013; 131: 1275-1287.

54) Burnasheva MA, Maltsev DS, Kulikov AN, Sherbakova KA, Barsukov AV. Association of Chronic Paracentral Acute Middle Maculopathy Lesions with Hypertension. Ophthalmol Retina 2020; 4: 504-509.

55) Moura-Coelho N, Gaspar T, Ferreira JT, Dutra-Medeiros M, Cunha JP. Paracentral acute middle maculopathy-review of the literature. Graefes Arch Clin Exp Ophthalmol 2020; 258: 2583-2596.

56) Ahn SJ, Woo SJ, Park KH. Retinal and choroidal changes with severe hypertension and their association with visual outcome. Invest Ophthalmol Vis Sci 2014; 55: 7775-7785.

57) Hua D, Xu Y, Zeng X, Yang N, Jiang M, Zhang X, Yang J, He T, Xing Y. Use of optical coherence tomography angiography for assessment of microvascular changes in the macula and optic nerve head in hypertensive patients without hypertensive retinopathy. Microvasc Res 2020; 129: 103969.

58) Lim HB, Lee MW, Park JH, Kim K, Jo YJ, Kim JY. Changes in Ganglion Cell-Inner Plexiform Layer Thickness and Retinal Microvasculature in Hypertension: An Optical Coherence Tomography Angiography Study. Am J Ophthalmol 2019; 199: 167-176.

59) Shin YI, Nam KY, Lee WH, Ryu CK, Lim HB, Jo YJ, Kim JY. Peripapillary microvascular changes in patients with systemic hypertension: An optical coherence tomography angiography study. Sci Rep 2020; 10: 6541.

60) Peng Q, Hu Y, Huang M, Wu Y, Zhong P, Dong X, Wu Q, Liu B, Li C, Xie J, Kuang Y, Yu D, Yu H, Yang X. Retinal Neurovascular Impairment in Patients with Essential Hypertension: An Optical Coherence Tomography Angiography Study. Invest Ophthalmol Vis Sci 2020; 61: 42.

61) Takayama K, Kaneko H, Ito Y, Kataoka K, Iwase T, Yasuma T, Matsuura T, Tsunekawa T, Shimizu H, Suzumura A, Ra E, Akahori T, Terasaki H. Novel Classification of Early-stage Systemic Hypertensive Changes in Human Retina Based on OCTA Measurement of Choriocapillaris. Sci Rep 2018; 8: 15163.

62) Tan W, Yao X, Le TT, Tan ACS, Cheung CY, Chin CWL, Schmetterer L, Chua J. The Application of Optical Coherence Tomography Angiography in Systemic Hypertension: A Meta-Analysis. Front Med (Lausanne) 2021; 8: 778330.

63) Liu Y, Li J, Pan J, Wang Y, Mao G, Jiang Z. Morphological changes in and quantitative analysis of macular retinal microvasculature by optical coherence tomography angiography in hypertensive retinopathy. Hypertens Res 2021; 44: 325-336.

64) Rosenbaum D, Mattina A, Koch E, Rossant F, Gallo A, Kachenoura N, Paques M, Redheuil A, Girerd X. Effects of age, blood pressure and antihypertensive treatments on retinal arterioles remodeling assessed by adaptive optics. J Hypertens 2016; 34: 1115-1122.

65) Mehta RA, Akkali MC, Jayadev C, Anuj A, Yadav NK. Morphometric analysis of retinal arterioles in control and hypertensive population using adaptive optics imaging. Indian J Ophthalmol 2019; 67: 1673-1677.

66) Meixner E, Michelson G. Measurement of retinal wall-to-lumen ratio by adaptive optics retinal camera: a clinical research. Graefes Arch Clin Exp Ophthalmol 2015; 253: 1985-1995.

67) Gallo A, Mattina A, Rosenbaum D, Koch E, Paques M, Girerd X. Retinal arteriolar remodeling

evaluated with adaptive optics camera: Relationship with blood pressure levels. Ann Cardiol Angeiol (Paris) 2016; 65: 203-207.

68) Bakker E, Dikland FA, van Bakel R, Andrade De Jesus D, Sanchez Brea L, Klein S, van Walsum T, Rossant F, Farias DC, Grieve K, Paques M. Adaptive optics ophthalmoscopy: a systematic review of vascular biomarkers. Surv Ophthalmol 2022; 67: 369-387.

69) Koch E, Rosenbaum D, Brolly A, Sahel JA, Chaumet-Riffaud P, Girerd X, Rossant F, Paques M. Morphometric analysis of small arteries in the human retina using adaptive optics imaging: relationship with blood pressure and focal vascular changes. J Hypertens 2014; 32: 890-898.

70) Liew G, Wang JJ, Mitchell P, Wong TY. Retinal vascular imaging: a new tool in microvascular disease research. Circ Cardiovasc Imaging 2008; 1: 156-161.

71) Cheung CY, Tay WT, Mitchell P, Wang JJ, Hsu W, Lee ML, Lau QP, Zhu AL, Klein R, Saw SM, Wong TY. Quantitative and qualitative retinal microvascular characteristics and blood pressure. J Hypertens 2011; 29: 1380-1391.

72) Thomas GN, Ong SY, Tham YC, Hsu W, Lee ML, Lau QP, Tay W, Alessi-Calandro J, Hodgson L, Kawasaki R, Wong TY, Cheung CY. Measurement of macular fractal dimension using a computer-assisted program. Invest Ophthalmol Vis Sci 2014; 55: 2237-2243.

73) Yin XX, Irshad S, Zhang Y. Artery/vein classification of retinal vessels using classifiers fusion. Health Inf Sci Syst 2019; 7: 26.

74) Akbar S, Akram MU, Sharif M, Tariq A, Yasin UU. Arteriovenous ratio and papilledema based hybrid decision support system for detection and grading of hypertensive retinopathy. Comput Methods Programs Biomed 2018; 154: 123-141.

75) Poplin R, Varadarajan AV, Blumer K, Liu Y, McConnell MV, Corrado GS, Peng L, Webster DR. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng 2018; 2: 158-164.

76) Cheung CY, Ikram MK, Sabanayagam C, Wong TY. Retinal microvasculature as a model to study the manifestations of hypertension. Hypertension 2012; 60: 1094-1103.

77) Ong YT, Wong TY, Klein R, Klein BE, Mitchell P, Sharrett AR, Couper DJ, Ikram MK. Hypertensive retinopathy and risk of stroke. Hypertension 2013; 62: 706-711.

78) Liew G, Wong TY, Mitchell P, Cheung N, Wang JJ. Retinopathy predicts coronary heart disease mortality. Heart 2009; 95: 391-394.

79) Sairenchi T, Iso H, Yamagishi K, Irie F, Okubo Y, Gunji J, Muto T, Ota H. Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: the Ibaraki Prefectural Health Study. Circulation 2011; 124: 2502-2511.

80) Thiagarajah R, Kandasamy R, Sellamuthu P. Hypertensive Retinopathy and the Risk of Hemorrhagic Stroke. J Korean Neurosurg Soc 2021; 64: 543-551.

81) Wong TY, Coresh J, Klein R, Muntner P, Couper DJ, Sharrett AR, Klein BE, Heiss G, Hubbard LD, Duncan BB. Retinal microvascular abnormalities and renal dysfunction: the atherosclerosis risk in communities study. J Am Soc Nephrol 2004; 15: 2469-2476.

82) Sabanayagam C, Shankar A, Klein BE, Lee KE, Muntner P, Nieto FJ, Tsai MY, Cruickshanks KJ, Schubert CR, Brazy PC, Coresh J, Klein R. Bidirectional association of retinal vessel diameters and estimated GFR decline: the Beaver Dam CKD Study. Am J Kidney Dis 2011; 57: 682-691.

83) Edwards MS, Wilson DB, Craven TE, Stafford J, Fried LF, Wong TY, Klein R, Burke GL, Hansen KJ. Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the Cardiovascular Health Study. Am J Kidney Dis 2005; 46: 214-224.

84) Kolman SA, van Sijl AM, van der Sluijs FA, van de Ree MA. Consideration of hypertensive retinopathy as an important end-organ damage in patients with hypertension. J Hum Hypertens 2017; 31: 121-125.

85) Muiesan ML, Salvetti M, Rizzoni D, Paini A, Agabiti-Rosei C, Aggiusti C, Agabiti Rosei E. Resistant hypertension and target organ damage. Hypertens Res 2013; 36: 485-491.

86) Al Saeed AA, AlShabib NS, Al Taisan AA, Kreary YA. Association of Retinal Vascular Manifestation and Obstructive Sleep Apnea (OSA): A Narrative Review. Clin Ophthalmol 2021; 15: 3315-3320.

87) Fraser CL, Bliwise DL, Newman NJ, Lamirel C, Collop NA, Rye DB, Trotti LM, Biousse V, Bruce BB. A prospective photographic study of the ocular fundus in obstructive sleep apnea. J Neuroophthalmol 2013; 33: 241-246.

88) Tong JY, Golzan M, Georgevsky D, Williamson JP, Graham SL, Farah CS, Fraser CL. Quantitative Retinal Vascular Changes in Obstructive Sleep Apnea. Am J Ophthalmol 2017; 182: 72-80.

89) Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 2005; 206: 319-348.

90) London A, Benhar I, Schwartz M. The retina as a window to the brain-from eye research to CNS disorders. Nat Rev Neurol 2013; 9: 44-53.

91) Wong TY, Klein R, Couper DJ, Cooper LS, Shahar E, Hubbard LD, Wofford MR, Sharrett AR. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet 2001; 358: 1134-1140.

92) Mitchell P, Wang JJ, Wong TY, Smith W, Klein R, Leeder SR. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology 2005; 65: 1005-1009.

93) Wong TY, Klein R, Nieto FJ, Klein BE, Sharrett AR, Meuer SM, Hubbard LD, Tielsch JM. Retinal

microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology 2003; 110: 933-940.

94) Chen X, Liu L, Liu M, Huang X, Meng Y, She H, Zhao L, Zhang J, Zhang Y, Gu X, Qin X, Zhang Y, Li J, Xu X, Wang B, Hou FF, Tang G, Liao R, Huo Y, Li J, Yang L. Hypertensive Retinopathy and the Risk of Stroke Among Hypertensive Adults in China. Invest Ophthalmol Vis Sci 2021; 62: 28.

95) Wong TY, Klein R, Sharrett AR, Nieto FJ, Boland LL, Couper DJ, Mosley TH, Klein BE, Hubbard LD, Szklo M. Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. Stroke 2002; 33: 1487-1492.

96) Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, Hubbard LD, Mosley TH, Study AIARiC. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA 2002; 288: 67-74.

97) Wong TY, Mosley TH, Jr., Klein R, Klein BE, Sharrett AR, Couper DJ, Hubbard LD, Atherosclerosis Risk in Communities S. Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology 2003; 61: 806-811.

98) Baker ML, Marino Larsen EK, Kuller LH, Klein R, Klein BE, Siscovick DS, Bernick C, Manolio TA, Wong TY. Retinal microvascular signs, cognitive function, and dementia in older persons: the Cardiovascular Health Study. Stroke 2007; 38: 2041-2047.

99) Cheung CY, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. Prog Retin Eye Res 2017; 57: 89-107.

100) Rim TH, Teo AWJ, Yang HHS, Cheung CY, Wong TY. Retinal Vascular Signs and Cerebrovascular Diseases. J Neuroophthalmol 2020; 40: 44-59.

101) Luo BP, Brown GC. Update on the ocular manifestations of systemic arterial hypertension. Curr Opin Ophthalmol 2004; 15: 203-210.

102) Grosso A. Detection and management of vascular hypertension. Compr Ophthalmol Update 2007; 8: 145-151.

103) Nokiba H, Takei T, Suto C, Nitta K. Association between Ophthalmological Changes and Cardiovascular Diseases in Patients with Chronic Kidney Disease Undergoing Hemodialysis. J Atheroscler Thromb 2015; 22: 1248-1254.

104) Nakajima K, Higuchi R, Mizusawa K, Nakamura T. Association between extremely high high-density lipoprotein-cholesterol and hypertensive retinopathy: results of a cross-sectional study from Kanagawa Investigation of Total Checkup Data from the National Database-6 (KITCHEN-6). BMJ Open 2021; 11: e043677.

105) Wong TY, Klein R, Sharrett AR, Schmidt MI, Pankow JS, Couper DJ, Klein BE, Hubbard LD, Duncan BB, Investigators A. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. JAMA 2002; 287: 2528-2533.

106) Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, Klein BE, Hubbard LD. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA 2002; 287: 1153-1159.

107) Habib SA, Jibran MS, Khan SB, Gul AM. Association Of Hypertensive Retinopathy With Angiographic Severity Of Coronary Artery Disease Determined By Syntax Score. J Ayub Med Coll Abbottabad 2019; 31: 189-191.

108) Jibran MS, Habib SA, Khan SB. Hypertensive Retinopathy: A Prognostic Factor for Morbidity and Mortality after Acute ST Elevation Myocardial Infarction. J Coll Physicians Surg Pak 2019; 29: 205-209.

109) Kanar BG, Kanar HS, Karatay A, Tigen K, Sonmez A. Assessment of left atrium and diastolic dysfunction in patients with hypertensive retinopathy: A real-time three-dimensional echocardiography-based study. Clin Exp Hypertens 2017; 39: 696-704.

110) Zhang W, Li J, Zhao L, Zhang J, She H, Meng Y, Peng Y, Shang K, Zhang Y, Gu X, Chen X, Zhang Y, Yang Y, Sun P, Qin X, Wang B, Xu X, Hou F, Tang G, Liao R, Lin T, Jiang C, Huo Y, Yang L. Positive relationship of hypertensive retinopathy with carotid intima--media thickness in hypertensive patients. J Hypertens 2020; 38: 2028-2035.

111) Adar A, Onalan O, Sevik O, Turgut Y, Cakan F. Could aortic arch calcification help in detection of hypertensive retinopathy? Blood Press Monit 2021; 26: 118-123.

112) Zhong ZL, Liu J. Association between Hyperhomocysteinemia and Hypertensive Retinopathy in a Chinese Han Population. Curr Eye Res 2021: 1-5.

113) Sun C, Zhu G, Wong TY, Hewitt AW, Ruddle JB, Hodgson L, Montgomery GW, Young TL, Hammond CJ, Craig JE, Martin NG, He M, Mackey DA. Quantitative genetic analysis of the retinal vascular caliber: the Australian Twins Eye Study. Hypertension 2009; 54: 788-795.

114) Jensen RA, Sim X, Smith AV, Li X, Jakobsdottir J, Cheng CY, Brody JA, Cotch MF, McKnight B, Klein R, Wang JJ, Kifley A, Harris TB, Launer LJ, Taylor KD, Klein BE, Raffel LJ, Li X, Ikram MA, Klaver CC, van der Lee SJ, Mutlu U, Hofman A, Uitterlinden AG, Liu C, Kraja AT, Consortium CE-CBP, Mitchell P, Gudnason V, Rotter JI, Boerwinkle E, van Duijn CM, Psaty BM, Wong TY. Novel Genetic Loci Associated With Retinal Microvascular Diameter. Circ Cardiovasc Genet 2016; 9: 45-54.

115) Veluchamy A, Ballerini L, Vitart V, Schraut KE, Kirin M, Campbell H, Joshi PK, Relan D, Harris S, Brown E, Vaidya SS, Dhillon B, Zhou K, Pearson ER, Hayward C, Polasek O, Deary IJ, MacGillivray T, Wilson JF, Trucco E, Palmer CNA, Doney ASF. Novel Genetic Locus Influencing Retinal Venular Tortuosity Is Also Associated With Risk of Coronary Artery Disease. Arterioscler Thromb Vasc Biol 2019; 39: 2542-2552.

116) Grunwald JE, Alexander J, Ying GS, Maguire M, Daniel E, Whittock-Martin R, Parker C, McWilliams K, Lo JC, Go A, Townsend R, Gadegbeku CA, Lash JP, Fink JC, Rahman M, Feldman H,

Kusek JW, Xie D, Jaar BG, Group CS. Retinopathy and chronic kidney disease in the Chronic Renal Insufficiency Cohort (CRIC) study. Arch Ophthalmol 2012; 130: 1136-1144.

117) Sabanayagam C, Shankar A, Koh D, Chia KS, Saw SM, Lim SC, Tai ES, Wong TY. Retinal microvascular caliber and chronic kidney disease in an Asian population. Am J Epidemiol 2009; 169: 625-632.

118) Geletu AH, Teferra AS, Sisay MM, Teshome DF. Incidence and predictors of chronic kidney diseases among type 2 diabetes mellitus patients at St. Paul's Hospital, Addis Ababa, Ethiopia. BMC Res Notes 2018; 11: 532.

119) Nwachukwu DC, Aneke EI, Obika LF, Nwachukwu NZ. Effects of aqueous extract of Hibiscus sabdariffa on the renin-angiotensin-aldosterone system of Nigerians with mild to moderate essential hypertension: A comparative study with lisinopril. Indian J Pharmacol 2015; 47: 540-545.

120) Omotoso AB, Kolo PM, Olanrewaju TO, Owoeye JF, Biliaminu SA, Olatunji VA. Relationship between retinopathy and renal abnormalities in black hypertensive patients. Clin Hypertens 2016; 22: 19.

121) Kabedi NN, Mwanza JC, Lepira FB, Kayembe TK, Kayembe DL. Hypertensive retinopathy and its association with cardiovascular, renal and cerebrovascular morbidity in Congolese patients. Cardiovasc J Afr 2014; 25: 228-232.

122) Chillo P, Ismail A, Sanyiwa A, Ruggajo P, Kamuhabwa A. Hypertensive retinopathy and associated factors among nondiabetic chronic kidney disease patients seen at a tertiary hospital in Tanzania: a cross-sectional study. Int J Nephrol Renovasc Dis 2019; 12: 79-86.

123) Yang T, Chu CH, Bai CH, You SL, Chou YC, Hwang LC, Chien KL, Su TC, Tseng CH, Sun CA. Uric acid concentration as a risk marker for blood pressure progression and incident hypertension: a Chinese cohort study. Metabolism 2012; 61: 1747-1755.

124) Mellen PB, Bleyer AJ, Erlinger TP, Evans GW, Nieto FJ, Wagenknecht LE, Wofford MR, Herrington DM. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. Hypertension 2006; 48: 1037-1042.

125) Edwards NL. The role of hyperuricemia in vascular disorders. Curr Opin Rheumatol 2009; 21: 132-137.

126) Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Engl J Med 1966; 275: 457-464.

127) Chen X, Meng Y, Li J, She H, Zhao L, Zhang J, Peng Y, Shang K, Zhang Y, Gu X, Yang W, Zhang Y, Li J, Qin X, Wang B, Xu X, Hou F, Tang G, Liao R, Huo Y, Yang L. Serum uric acid concentration is associated with hypertensive retinopathy in hypertensive chinese adults. BMC Ophthalmol 2017; 17: 83.

128) Kattah AG, Garovic VD. The management of hypertension in pregnancy. Adv Chronic Kidney Dis 2013; 20: 229-239.

129) Benschop L, Schalekamp-Timmermans S, Roeters van Lennep JE, Jaddoe VWV, Wong TY, Cheung CY, Steegers EAP, Ikram MK. Gestational hypertensive disorders and retinal microvasculature: the Generation R Study. BMC Med 2017; 15: 153.

130) Bakhda RN. Clinical study of fundus findings in pregnancy induced hypertension. J Family Med Prim Care 2016; 5: 424-429.

131) van den Born BJ, Hulsman CA, Hoekstra JB, Schlingemann RO, van Montfrans GA. Value of routine funduscopy in patients with hypertension: systematic review. BMJ 2005; 331: 73.

132) Wong TY. Is retinal photography useful in the measurement of stroke risk? Lancet Neurol 2004; 3: 179-183.

133) Nijskens CM, Veldkamp SR, Van Der Werf DJ, Boonstra AH, Ten Wolde M. Funduscopy: Yes or no? Hypertensive emergencies and retinopathy in the emergency care setting; a retrospective cohort study. J Clin Hypertens (Greenwich) 2021; 23: 166-171.

134) Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, Authors/Task Force M. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018; 36: 1953-2041.

135) Biesenbach G, Zazgornik J. High prevalence of hypertensive retinopathy and coronary heart disease in hypertensive patients with persistent microalbuminuria under short intensive antihypertensive therapy. Clin Nephrol 1994; 41: 211-218.

136) Harjasouliha A, Raiji V, Garcia Gonzalez JM. Review of hypertensive retinopathy. Dis Mon 2017; 63: 63-69.

137) Al-Halafi AM. Tremendous result of bevacizumab in malignant hypertensive retinopathy. Oman J Ophthalmol 2015; 8: 61-63.

138) Salman AG. Intravitreal bevacizumab in persistent retinopathy secondary to malignant hypertension. Saudi J Ophthalmol 2013; 27: 25-29.

139) Kim EY, Lew HM, Song JH. Effect of intravitreal bevacizumab (Avastin((R))) therapy in malignant hypertensive retinopathy: a report of two cases. J Ocul Pharmacol Ther 2012; 28: 318-322.

140) Li J, Wang S, Zhang YL, Bai J, Lin QY, Liu RS, Yu XH, Li HH. Immunoproteasome Subunit beta5i Promotes Ang II (Angiotensin II)-Induced Atrial Fibrillation by Targeting ATRAP (Ang II Type I Receptor-Associated Protein) Degradation in Mice. Hypertension 2019; 73: 92-101.

141) Wang S, Li J, Wang T, Bai J, Zhang YL, Lin QY, Li JM, Zhao Q, Guo SB, Li HH. Ablation of Immunoproteasome beta5i Subunit Suppresses Hypertensive Retinopathy by Blocking ATRAP Degradation in Mice. Mol Ther 2020; 28: 279-292.

142) Matteucci A, Ricceri L, Fabbri A, Fortuna A, Travaglione S, Guidotti M, Martinelli A, Villa M, Pricci F, Maroccia Z, Campana G, Malchiodi-Albedi F, Fiorentini C, Loizzo S. Eye Drop Instillation of the Rac1 Modulator CNF1 Attenuates Retinal Gliosis and Ameliorates Visual Performance in a Rat Model of Hypertensive Retinopathy. Neuroscience 2019; 411: 119-129.

143) Liu S, Wang C, Lu J, Dai G, Che H, He W. Long-term inhibition of UCHL1 decreases hypertension and retinopathy in spontaneously hypertensive rats. J Int Med Res 2021; 49: 3000605211020641.

144) Chatterjee S, Chattopadhyay S, Hope-Ross M, Lip PL. Hypertension and the eye: changing perspectives. J Hum Hypertens 2002; 16: 667-675.

145) Muramatsu C, Hatanaka Y, Iwase T, Hara T, Fujita H. Automated selection of major arteries and veins for measurement of arteriolar-to-venular diameter ratio on retinal fundus images. Comput Med Imaging Graph 2011; 35: 472-480.

146) Harbaoui B, Courand PY, Defforges A, Khettab F, Milon H, Girerd N, Lantelme P. Cumulative Effects of Several Target Organ Damages in Risk Assessment in Hypertension. Am J Hypertens 2016; 29: 234-244.