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), Hypertension-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-
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), Cardiovascular 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. 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, Wong and Mitchell 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., 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.

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. Also, Yu et al. 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. 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, low-grade systemic inflammation and oxidative stress. The pathophysiology of HR can be divided into three phases of histologic damage.

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 subsequent 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. Elevated levels of MPV have a significant linear relationship with the grade of HR. Furthermore, Yazici et al. established that MPV values were significantly higher in the prehypertensive group than in the control group.

MPV reflects platelet activity: 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.

**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 hypothesis, Pavlovsc et al. 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 ischemia/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.

**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. In particular, it is well established that prorenin/renin receptor ((P) RR) and angiotensin II type 1 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. Besides,
angiotensin II (Ang II) promotes the expression of VEGF by activating AT1R\textsuperscript{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\textsuperscript{29}.

**Subfoveal Choroidal Thickness (SFCT)**
Pathophysiologic studies showed a positive correlation between SFCT and HR\textsuperscript{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\textsuperscript{31}. The occluded choroidal arterioles, 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 haemorrhages, 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. 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 (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.

In the study by Schuster et al., 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. 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. 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 (white 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).
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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\cite{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\cite{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\cite{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\cite{33,45-49}. SFCT in HR was analyzed in various studies with different results: Simsek et al\cite{46} 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\cite{47} and Shao et al\cite{48} studies, SFCT was significantly directly related to the stage of HR. On the contray, SFCT was not significantly related to diastolic blood pressure, history and years of hypertension. Indeed, regarding hypertension without ocular involvement, Gök et al\cite{49} 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\cite{50}, 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\cite{51} 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\cite{52}. The association between hypertension and HR is reasonable because hypertension is one of the most important risk factors for retinal occlusions\cite{53}.

**OCT Classification**

A new classification, based on OCT features like subretinal fluid (SRF) has been proposed by Ahn et al\cite{54}; 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\cite{55} 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\cite{56} 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\cite{57} 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\cite{58} conducted a meta-analysis about OCTA in patients with systemic hypertension without HR vs. control group: participants with systemic hypertension had significantly lower Superficial VD, lower Deep VD and
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.


<table>
<thead>
<tr>
<th>Classification</th>
<th>Category/stage</th>
<th>Funduscopic findings</th>
<th>OCT features</th>
<th>OCTA features</th>
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<tbody>
<tr>
<td>Ahn et al. (OCT)</td>
<td>mild to moderate malignant without SRF malignant with SRF</td>
<td>KWB grade 1, 2, 3</td>
<td>with/without SRF</td>
<td>No detectable signs or only focal capillary sparsity</td>
</tr>
<tr>
<td>Liu et al. (OCTA)</td>
<td>1</td>
<td>KWB grade 1</td>
<td>Only focal capillary sparsity</td>
<td>Focal capillary sparsity, scattered microangioma-like alterations and focal macular arch ring defect or a combination of these signs</td>
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<td></td>
<td>2</td>
<td>KWB grade 2</td>
<td></td>
<td>Signs of stage 2 retinopathy plus focal capillary disorder and nonperfusion areas or a combination of these signs</td>
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<tr>
<td></td>
<td>3</td>
<td>KWB grade 3</td>
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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. 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 peripapillary RNFL thickness. Takayama et al. 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. 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.

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

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 controls64-66.

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 re-
AO may also contribute to a better understanding of the pathophysiology of HR. Koch et al. 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.

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.

Recently, Yin et al. proposed a multiple classifiers decision-combination scheme that is specifically set for A/V classification. Also, Akbar et al. 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. “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\textsuperscript{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\textsuperscript{76}.

The retinal microvascular changes in HR have a role in predicting the risk and mortality associated with cerebrovascular, cardiovascular, renal and gynaecological diseases\textsuperscript{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\textsuperscript{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\textsuperscript{84}.

HR and its vascular manifestation were also correlated to Obstructive Sleep Apnea; in August 2021, Saeed et al\textsuperscript{86} published a narrative review about this association. Fraser et al\textsuperscript{87} demonstrated that Apnea–Hypopnea Index (AHI) > 40 doubles the risk of retinal vascular changes regardless of blood pressure measurement and Tong et al\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{91}.

Also, the Cardiovascular Health Study showed a strong correlation between retinal haemorrhages, microaneurysms, cotton-wool spots and clinical stroke\textsuperscript{3}.

In the Mitchell et al\textsuperscript{92} and Wong et al\textsuperscript{93} studies, HR was also strongly related to stroke mortality. Recently Chen et al\textsuperscript{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\textsuperscript{95}, cerebral white-matter lesions\textsuperscript{86} and cerebral atrophy\textsuperscript{97} defined with magnetic resonance imaging (MRI). Supporting that, also Baker et al\textsuperscript{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\textsuperscript{42,99,100}.

**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\textsuperscript{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. HR assessed by the KWB and Scheie classifications was found to be associated with cardiovascular mortality and events.

Nakajima et al. investigated 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. 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.

Habib et al. 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. 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. 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. 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.

Homocysteine level is an independent risk factor for HR as researched by Zhong et al.; 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.

**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. 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.

In Africa, numerous studies reported the prevalence of HR among patients with systemic hypertension and other comorbidities like CKD. 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.

Significant epidemiological evidence showed that serum uric acid (SUA) might be associated with hypertension and that SUA elevation was a risk factor for hypertension disease. The prevalence of hyperuricemia in hypertensive patients was around 20-50%. Chen et al. 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\textsuperscript{124}.

**Gynaecology**

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

Bakhda et al\textsuperscript{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. Ramirez-Montero et al\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{133}, mean blood pressure in patients with a suspected hypertensive emergency was significantly higher in patients with retinopathy, 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\textsuperscript{134}.

A study by Biesenbach et al\textsuperscript{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\textsuperscript{134}.

Grosso et al\textsuperscript{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 haemorrhages\textsuperscript{136-138}. Moreover, another study showed prompt recovery of malignant HR in patients after administration of bevacizumab\textsuperscript{139}. However, the use of these agents has not been widespread or accepted yet.
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. studied the overexpression of the catalytic subunit β2i of the immunoproteasome and its contribution to Ang II-induced retinopathy in mice. Wang et al. 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. 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 cardiovascular risk, was also found to be correlated with retinal damage in hypertensive patients. Grosso et al. suggested that the screening of UCHL1 expression in the retina could be a useful tool for the early detection of hypertensive retinopathy.

**Figure 4.** Flow chart: supplemental risk assessment by retinal examination. (Reproduced with permission from Grosso et al. “Hypertensive retinopathy revisited: some answers, more questions”, Br J Ophthalmol, 2005).
Lar disease, is also involved in retinopathy and a study in hypertensive rats by Liu et al. 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. 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 significant 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.

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.

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