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THE OPHTHALMIC MANIFESTATIONS OF SYSTEMIC VASCULAR DISEASES: A LITERATURE REVIEW

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Abstract: Background: Systemic vascular diseases exert profound effects on the ocular circulation, reflecting the shared architecture of endothelial, neural, and metabolic regulation that connects the eye to the rest of the body. Retinal and choroidal microvasculature offer a unique opportunity to observe systemic pathophysiology in vivo, transforming ophthalmology into a window for vascular medicine. **Objective:** To synthesize the current literature on the ophthalmic manifestations of systemic vascular diseases, emphasizing pathophysiologic mechanisms, diagnostic technologies, and the prognostic value of ocular findings in systemic health. **Methods:** A narrative review was conducted using PubMed, Scopus, Embase, and Web of Science databases. Seventeen peer-reviewed articles published between 2012 and 2025 were selected for relevance, originality, and accessibility. The review integrates studies addressing hypertensive and atherosclerotic retinopathy, diabetic microangiopathy, autoimmune vasculopathies, ocular ischemic syndrome, and emerging imaging-based biomarkers. **Results:** Hypertension and atherosclerosis produce progressive arteriolar narrowing, endothelial dysfunction, and retinal ischemia, while diabetes induces pericyte loss, basement-membrane thickening, and neuroinflammation. Autoimmune disorders such as systemic lupus erythematosus and Behçet's disease provoke immune-complex vasculitis and ischemic occlusion. Ocular ischemic syndrome mirrors advanced carotid atherosclerosis and carries high cerebrovascular risk. Novel imaging tools—especially OCT-angiography, adaptive optics, and AI-based retinal analytics—allow quantification of subclinical microvascular changes and prediction of systemic outcomes. **Conclusion:** The ocular circulation functions as a dynamic biomarker of systemic vascular health. By uniting clinical observation, advanced imaging, and computational analysis, modern ophthalmology provides unprecedented insight into systemic microvascular pathology. Integrating ocular biomarkers into cardiovascular and metabolic risk assessment may transform early diagnosis and personalized prevention strategies across medicine.

Keywords: Ophthalmic manifestations; systemic vascular disease; retinal microangiopathy; optical coherence tomography angiography; oculomics.

Introduction

The eye is often described as a window to systemic circulation, offering a unique, noninvasive view of the human microvasculature. Through retinal examination, ophthalmologists can observe in vivo the effects of systemic vascular pathology on small arteries, veins, and capillaries—an opportunity that no other organ offers. These ocular findings not only mirror systemic vascular conditions but may also precede their clinical manifestations, positioning the retina as both a diagnostic and prognostic biomarker of cardiovascular and metabolic disease.

Systemic vascular diseases comprise a broad range of disorders that alter the integrity and function of blood vessels, including hypertension, diabetes mellitus, atherosclerosis, and autoimmune vasculitides. Each of these entities can profoundly affect ocular circulation, resulting in structural and functional changes involving the retina, choroid, and optic nerve. Given its high metabolic demand and delicate autoregulatory mechanisms, the retina is particularly susceptible to ischemic and inflammatory injury. Subtle changes such as arteriolar narrowing, microaneurysms, cotton wool spots, or venous beading often serve as early indicators of systemic disease activity and progression.

Among systemic disorders, hypertension and diabetes remain the most widely studied, due to both their global prevalence and their well-established microvascular sequelae. Hypertensive retinopathy reflects chronic vascular stress and endothelial dysfunction, with retinal arteriolar changes correlating strongly with cardiovascular morbidity. Diabetic retinopathy, in turn, stands as the prototype of systemic microangiopathy, illustrating the mechanisms of capillary leakage, ischemia, and neovascular proliferation. Beyond these, autoimmune diseases such as Behçet's disease, systemic lupus erythematosus, and polyarteritis nodosa can trigger sight-threatening occlusive vasculitis, emphasizing the eye's sensitivity to systemic immune-mediated vascular injury.

In recent years, advances in ocular imaging—particularly optical coherence tomography angiography (OCT-A) and fundus autofluorescence—have revolutionized the understanding of how systemic vascular diseases manifest in the eye. These technologies allow precise quantification of retinal and choroidal microcirculation, while the integration of artificial intelligence enables automated analysis of vascular parameters such as caliber, tortuosity, and perfusion density. Collectively, these tools have given rise to the field of oculomics, which explores ocular biomarkers as predictors of systemic disease burden and risk.

Despite an abundance of disease-specific studies, there remains a lack of integrative literature that unites these findings under a common vascular framework. Most publications examine single entities in isolation, without fully articulating how ocular and systemic vascular processes reflect one another. Recognizing these shared mechanisms is crucial, not only for early detection of systemic illness but also for guiding management strategies aimed at preserving both visual and systemic health.

This narrative review therefore seeks to synthesize the current evidence regarding the ophthalmic manifestations of systemic vascular diseases, highlighting their pathophysiologic foundations, clinical patterns, and diagnostic implications. By bridging the perspectives of ophthalmology, cardiology, endocrinology, and rheumatology, it aims to establish a cohesive understanding of how vascular health—and its disruption—is mirrored within the eye.

Objectives

The primary objective of this narrative review is to synthesize and critically examine the available evidence regarding the ophthalmic manifestations of systemic vascular diseases. By integrating data across multiple specialties, it aims to clarify how systemic vascular pathology—whether metabolic, hypertensive, inflammatory, or autoimmune—translates into detectable changes within the ocular microcirculation.

Specifically, the review seeks to outline the clinical spectrum of ocular findings associated with major systemic vascular disorders, describe the underlying pathophysiologic mechanisms that link systemic and retinal circulation, and discuss how advances in imaging and diagnostics have enhanced early detection and disease monitoring. In addition, it intends to explore how ophthalmic signs can serve as prognostic indicators of systemic disease burden, thereby reinforcing the role of ophthalmologists in multidisciplinary vascular care.

Beyond description, this review aspires to promote a more integrated understanding of systemic vascular disease as reflected in the eye—emphasizing that ophthalmic examination is not merely a tool for detecting local pathology, but a dynamic biomarker of systemic health. Ultimately, the objective is to establish a conceptual framework through which ocular vascular findings can contribute to earlier diagnosis, personalized treatment, and improved outcomes for patients with systemic vascular disorders.

Methods

This study was designed as a narrative literature review aimed at summarizing the ophthalmic manifestations of systemic vascular diseases and exploring their pathophysiologic and clinical relationships. The review followed a descriptive and integrative approach rather than a systematic or meta-analytical framework, allowing for the inclusion of a broader range of clinically relevant evidence.

A comprehensive search of the PubMed, Scopus, and Embase databases was conducted for studies published up to May 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms such as *"systemic vascular disease," "ocular manifestations," "hypertensive retinopathy," "diabetic retinopathy," "vasculitis," "Behçet's disease," "ocular ischemia," "choroidal circulation,"* and *"retinal biomarkers."* No language restrictions were applied to maximize inclusion of relevant literature.

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Studies were included if they met the following criteria: (1) clinical or observational research addressing ocular manifestations of systemic vascular disorders; (2) case series or cohort studies reporting vascular findings through ophthalmoscopy, fluorescein angiography, optical coherence tomography (OCT), or OCT angiography (OCT-A); and (3) review articles or meta-analyses providing syntheses of these topics. Experimental or molecular studies were included only when they offered direct clinical insight into vascular pathophysiology. Publications exclusively focused on isolated ocular diseases without systemic correlation were excluded.

Titles and abstracts were screened to assess relevance, followed by full-text evaluation of eligible papers. Additional studies were identified by cross-referencing bibliographies of key publications. Extracted information included disease category, ocular findings, imaging characteristics, systemic correlations, and clinical implications.

Given the heterogeneity of study designs, populations, and outcome measures, no quantitative meta-analysis was performed. Instead, data were synthesized narratively and grouped into major thematic categories: (1) pathophysiologic link between systemic and ocular vasculature, (2) hypertensive and atherosclerotic retinopathy, (3) diabetic microangiopathy, (4) vasculitic and autoimmune vascular disorders, and (5) emerging vascular biomarkers in ophthalmology. The interpretative synthesis prioritized clinical relevance, mechanistic understanding, and multidisciplinary context, consistent with the objectives of a narrative review.

Review

Pathophysiologic Link Between Systemic and Ocular Vasculature

The intimate connection between systemic and ocular vasculature lies at the core of understanding how systemic vascular diseases manifest in the eye. The retina and choroid are among the most metabolically active tissues in the human body, relying on an intricate microvascular network regulated by autonomic control, endothelial signaling, and autoregulatory feedback loops[1,2]. Because retinal vessels lack autonomic innervation and depend primarily on local metabolic and myogenic control, even subtle systemic alterations in perfusion, oxygenation, or endothelial function can produce measurable ocular changes[3].

Endothelial dysfunction represents a unifying pathophysiologic mechanism across virtually all systemic vascular diseases. It leads to impaired nitric oxide synthesis, increased vascular permeability, and chronic low-grade inflammation[4,5]. In the retina, these processes translate into breakdown of the blood-retinal barrier, capillary dropout, and microaneurysm formation, findings common to both hypertensive and diabetic retinopathy[4,6]. The choroidal circulation, although less directly observable, exhibits parallel changes, including vascular rarefaction and impaired autoregulation that may contribute to choroidopathy and optic nerve ischemia[7,8].

The blood-retinal barrier (BRB) functions analogously to the blood–brain barrier, and its disruption is a central feature in ocular manifestations of systemic vascular injury. Tight junctions between retinal endothelial cells maintain homeostasis by reg-

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ulating molecular exchange and protecting against serum leakage. In hypertension and diabetes, chronic shear stress and hyperglycemia weaken this barrier, promoting leakage of plasma proteins and lipids into the retinal parenchyma[9,10]. Over time, this culminates in hard exudates, macular edema, and neuronal damage.

Inflammation further amplifies vascular dysfunction. Systemic inflammatory mediators—such as tumor necrosis factor-alpha, interleukin-6, and vascular endothelial growth factor (VEGF)—alter endothelial permeability and recruit leukocytes that obstruct capillary flow[11]. This "leukostasis" mechanism, well characterized in diabetic microangiopathy, leads to focal ischemia and reactive neovascularization[5,6]. In autoimmune diseases such as systemic lupus erythematosus or Behçet's disease, immune complex deposition and complement activation within retinal vessels cause vasculitis, occlusion, and ischemic infarction, linking systemic immune dysregulation to sight-threatening ocular inflammation[11–13].

The ocular ischemic syndrome (OIS) provides a paradigmatic example of how systemic atherosclerosis manifests in the eye. Severe carotid artery stenosis reduces ocular perfusion, producing delayed choroidal filling, mid-peripheral hemorrhages, and neovascular glaucoma[7,8]. This condition mirrors systemic large-vessel pathology and often signals advanced atherosclerotic burden. Similarly, microvascular changes observed in retinal imaging—such as arteriolar narrowing and venular dilation—correlate strongly with systemic hypertension and cardiovascular mortality[15,16]. These vascular signatures reflect generalized endothelial stress and provide a measurable "window" into systemic hemodynamic health.

Modern imaging technologies have deepened this pathophysiologic understanding. Optical coherence tomography angiography (OCT-A) has revealed microvascular alterations even in early, subclinical stages of systemic disease. Reduced vessel density, enlargement of the foveal avascular zone, and decreased choriocapillaris flow have been reported in hypertensive, diabetic, and autoimmune patients, preceding overt fundoscopic changes[9,10,15]. Such findings suggest that retinal vascular imaging may serve as a sensitive biomarker for systemic endothelial function and microvascular health.

Collectively, these mechanisms emphasize that the eye is not merely affected by systemic vascular disease—it is a mirror of it. The retinal and choroidal circulation function as microcosms of systemic vascular physiology, allowing direct visualization of processes that remain hidden elsewhere in the body. The structural and functional parallels between ocular and systemic vasculature make ophthalmic evaluation an invaluable component of vascular medicine, capable of transforming the retina into a real-time monitor of systemic health.

Hypertensive and Atherosclerotic Retinopathy

Hypertensive and atherosclerotic retinopathy remain among the most well-characterized ocular manifestations of systemic vascular disease. They provide a visible record of the effects of chronic vascular stress, endothelial dysfunction, and arterial remodeling on microcirculatory integrity[1,2]. Because the retinal vasculature mirrors the state of systemic arterioles, changes observed in the fundus often parallel those in the brain, kidneys, and heart[3]. Thus, retinal examination offers a direct, noninvasive method for assessing systemic vascular burden and predicting future cardiovascular events[4,5].

In hypertension, sustained elevation of blood pressure leads to progressive vascular remodeling. The earliest changes—known as vasoconstrictive or functional retinopathy—involve generalized arteriolar narrowing and increased vascular tone, resulting from autoregulatory spasm of smooth muscle[6]. Chronic exposure induces sclerotic changes, characterized by thickening of the arteriolar wall, intimal hyperplasia, and hyaline deposition[7]. These alterations produce the classic "copper" and "silver wiring" appearance, as well as arteriovenous nicking, where thickened arterioles compress crossing venules[8]. At more advanced stages, vascular leakage causes flame-shaped hemorrhages, cotton wool spots, and hard exudates, collectively reflecting retinal ischemia and breakdown of the blood-retinal barrier[9].

The Keith–Wagener–Barker classification, although developed nearly a century ago, continues to provide a clinical framework for staging hypertensive retinopathy—from mild arteriolar narrowing to malignant forms with papilledema[10]. However, modern imaging modalities such as optical coherence tomography (OCT) and OCT angiography (OCT-A) have expanded the diagnostic landscape. These tools allow quantification of retinal and choroidal perfusion, revealing microvascular dropout and reduced vessel density even in asymptomatic patients[11,12]. Tan et al. demonstrated through meta-analysis that OCT-A metrics correlate significantly with systemic blood pressure and duration of hypertension[12], providing a new avenue for early, noninvasive vascular risk assessment.

Atherosclerotic changes compound the microvascular injury of hypertension by inducing endothelial dysfunction and luminal narrowing in larger arterioles. Retinal signs of atherosclerosis—such as focal arteriolar wall opacification or the "silver-wire" appearance—often indicate widespread systemic involvement[13]. These structural alterations are driven by oxidative stress, lipid deposition, and inflammatory activation within the vascular wall[14]. The resulting ischemia extends beyond the retina, predisposing to ocular ischemic syndrome (OIS), which arises from severe carotid artery stenosis or occlusion[7,15]. Patients with OIS typically present with midperipheral retinal hemorrhages, delayed choroidal filling, and neovascular glaucoma—findings that reflect advanced atheromatous disease[7].

Beyond local findings, the prognostic value of hypertensive and atherosclerotic retinopathy is now well established. Epidemiologic studies have demonstrated strong correlations between retinal arteriolar narrowing, venular dilation, and systemic cardiovascular outcomes, including stroke and coronary heart disease[16]. The Atherosclerosis Risk in Communities (ARIC) study, for instance, showed that individuals with moderate-to-severe hypertensive retinopathy faced a two- to threefold increased risk of stroke and cardiac mortality independent of blood pressure levels[16]. These data underscore the concept of the retina as a barometer of systemic vascular health—a living tissue where microvascular injury can be visualized and quantified in real time.

Emerging research also highlights the contribution of renal and cerebrovascular interactions to retinal vascular pathology. In patients with renal hypertension, OCT-A has demonstrated reductions in superficial and deep capillary plexus densities, suggesting systemic microvascular compromise beyond the kidney itself[15]. Such cross-organ correlations reinforce the systemic nature of hypertensive microangiopathy, in which the eye, kidney, and brain share homologous vascular vulnerabilities.

Ultimately, hypertensive and atherosclerotic retinopathy exemplify how ocular findings serve as a surrogate marker for systemic disease progression. The integration of multimodal imaging, artificial intelligence, and large-scale population data is transforming these observations from descriptive phenomena into quantitative biomarkers. As technology advances, the retinal vasculature may become an integral part of cardiovascular risk stratification—bridging ophthalmology and systemic medicine more closely than ever before.

Diabetic Microangiopathy and Retinal Vascular Disease

Diabetic retinopathy (DR) is one of the most thoroughly studied examples of systemic microangiopathy manifesting in the eye. It epitomizes the chronic interplay between metabolic dysregulation, vascular injury, and neuroinflammation that underlies systemic diabetic complications[1,2]. Persistent hyperglycemia induces a cascade of structural and biochemical changes in the retinal microvasculature, including pericyte loss, basement membrane thickening, endothelial dysfunction, and capillary occlusion[3,4]. These processes lead to ischemia, neovascularization, and, ultimately, vision-threatening complications such as proliferative diabetic retinopathy and diabetic macular edema[5].

The pathophysiologic foundation of diabetic retinal disease begins with hyperglycemia-driven oxidative stress and the accumulation of advanced glycation end products (AGEs). These compounds crosslink with vascular basement membranes, increasing stiffness and permeability while activating inflammatory pathways[6]. Concurrently, protein kinase C (PKC) activation and sorbitol accumulation within retinal cells exacerbate endothelial injury and impair autoregulation[7]. The resultant imbalance between proangiogenic and antiangiogenic factors—most notably elevated vascular endothelial growth factor (VEGF) and decreased pigment epithelium-derived factor (PEDF)—triggers neovascularization and vascular leakage[8,9].

Histopathologic hallmarks of diabetic microangiopathy include microaneurysm formation, capillary dropout, and intraretinal microvascular abnormalities (IRMA), reflecting focal ischemia and compensatory vessel proliferation[3]. As perfusion declines, hypoxic retinal tissue upregulates VEGF, leading to fragile neovascular membranes prone to hemorrhage and tractional retinal detachment[9,10]. These features mirror the systemic vascular remodeling seen in diabetic nephropathy and neuropathy, emphasizing the shared microvascular substrate of diabetic complications[6].

Recent advances in multimodal imaging—including optical coherence tomography angiography (OCT-A), fluorescein angiography, and adaptive optics—have revolutionized early detection. OCT-A studies demonstrate that vessel density reduction and foveal avascular zone (FAZ) enlargement can be detected even before clinical retinopathy is visible[11,12]. Machine learning algorithms are now capable of identifying such subclinical patterns, enabling automated risk stratification and population-based screening[13]. These innovations represent a paradigm shift from reactive to predictive ophthalmic care, bridging imaging data with systemic metabolic control.

Inflammation and neurodegeneration are increasingly recognized as critical contributors to diabetic retinal disease. Elevated intraocular cytokines—including interleukin-6, monocyte chemoattractant protein-1, and tumor necrosis factor-alpha—sustain a chronic inflammatory milieu that exacerbates endothelial dysfunction and accelerates neuronal apoptosis[14]. Functional alterations in Müller cells and microglia disrupt the neurovascular unit, further compromising retinal perfusion[15]. This interplay underscores that diabetic retinopathy is not merely a vascular disorder but a neurovascular disease that reflects systemic metabolic stress.

Therapeutically, the advent of anti-VEGF agents has transformed the management of proliferative and edematous stages. However, these treatments address the downstream effects rather than the upstream metabolic and inflammatory drivers[9],[16]. Novel approaches—such as intravitreal corticosteroids, PKC inhibitors, and gene therapies targeting VEGF signaling—are under investigation to achieve more durable control of disease progression[17]. Furthermore, systemic optimization of glycemic, lipid, and blood pressure parameters remains the cornerstone of prevention, emphasizing the interdependence between systemic metabolic homeostasis and retinal vascular integrity[5].

In essence, diabetic microangiopathy of the retina exemplifies the concept that the eye is both a target and a barometer of systemic disease. Its vascular changes reflect the cumulative burden of metabolic dysregulation across the body, while its accessibility allows for direct, real-time monitoring of microvascular health. As emerging technologies integrate ophthalmic imaging with systemic data analytics, diabetic retinopathy may evolve from a complication of diabetes to a sentinel biomarker guiding whole-body vascular management.

Autoimmune Vasculopathies and Retinal Involvement

Autoimmune vasculopathies constitute a broad group of disorders characterized by immune-mediated vascular inflammation, endothelial injury, and subsequent ischemic or hemorrhagic events that may involve the ocular circulation[1],[2]. Because the retina and choroid are highly vascularized and immunologically active, they are particularly susceptible to these systemic processes[3]. Ocular findings not only reflect local tissue damage but also serve as early indicators of systemic disease activity, making ophthalmic examination an essential component of multidisciplinary management.

Among autoimmune conditions, systemic lupus erythematosus (SLE) exhibits one of the most diverse spectrums of ocular involvement. Immune complex deposition within retinal arterioles triggers complement activation, leukocyte adhesion, and microvascular occlusion[4]. The classic "lupus retinopathy" presents with cotton-wool spots, retinal hemorrhages, and vascular sheathing, mirroring the microangiopathic injury seen in the kidney and brain[5]. In severe cases, vaso-occlusive retinopathy can progress to extensive ischemia, neovascularization, or optic neuropathy[6]. Recent stud-

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ies highlight the strong correlation between active lupus retinopathy and systemic disease flares, underscoring the prognostic value of fundoscopic monitoring[7].

Behçet's disease (BD) represents another paradigmatic autoimmune vasculitis affecting the ocular circulation. It is characterized by relapsing, necrotizing inflammation that can involve both arteries and veins, distinguishing it from most vasculitides that target a single vascular compartment[8]. Ocular manifestations typically include retinal vasculitis, occlusive phlebitis, and recurrent uveitis, which may lead to irreversible vision loss if inadequately controlled[9]. The pathophysiology involves T-cell dysregulation, endothelial activation, and elevated cytokines such as TNF-α and IL-6, which perpetuate vascular injury[10]. Recent imaging studies using fluorescein angiography and OCT-A demonstrate persistent microvascular alterations even during clinical remission, suggesting subclinical inflammation and cumulative vascular damage[11].

In systemic sclerosis (SSc) and polyarteritis nodosa (PAN), ocular involvement is less frequent but clinically significant. SSc leads to obliterative microangiopathy due to fibroblast activation and excessive collagen deposition, which can manifest as conjunctival telangiectasia, retinal arterial narrowing, or ischemic optic neuropathy[12]. PAN, a necrotizing vasculitis of medium-sized arteries, may produce retinal arteritis and choroidal infarction, often in association with systemic hypertension or renal disease[13]. In both disorders, ocular ischemia signals extensive systemic vascular compromise and demands urgent immunosuppressive therapy.

Autoimmune vasculitis may also coexist with systemic hypercoagulability, compounding vascular occlusion and ischemia. Antiphospholipid antibody syndrome (APS), either primary or secondary to lupus, predisposes to retinal artery and vein occlusions, mimicking thromboembolic disease but arising from immune-mediated endothelial injury[14]. The overlap between inflammation and thrombosis—termed "immunothrombosis"—highlights how immune dysregulation can propagate vascular pathology through both inflammatory and coagulative pathways[15].

From a diagnostic standpoint, advances in multimodal imaging have refined the evaluation of autoimmune vasculopathies. OCT-A and indocyanine green angiography (ICGA) allow noninvasive visualization of retinal capillary dropout, choriocapillaris hypoperfusion, and perivascular leakage, correlating with disease activity across multiple autoimmune syndromes[11,16]. Furthermore, serum biomarkers such as anti-endothelial cell antibodies (AECAs) and circulating cytokine profiles may assist in differentiating active inflammation from chronic fibrotic changes[16,17].

Therapeutically, management focuses on aggressive control of systemic inflammation to preserve ocular perfusion and prevent irreversible damage. Corticosteroids remain first-line therapy for acute flares, often combined with immunosuppressive agents such as azathioprine, mycophenolate mofetil, or cyclophosphamide[9,17]. In refractory cases, biologic therapies targeting TNF-α or interleukin pathways—particularly infliximab, adalimumab, and tocilizumab—have demonstrated substantial efficacy in reducing recurrence and improving visual outcomes[10].

Overall, autoimmune vasculopathies exemplify how the eye functions as a micro-

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cosm of systemic immune injury. The retinal vasculature provides a unique, accessible window to observe immune-mediated endothelial dysfunction in vivo, bridging the gap between systemic rheumatology and ophthalmology. Recognizing these patterns is not only crucial for preserving vision but also for preventing life-threatening systemic complications.

Ocular Ischemic Syndrome and Carotid Artery Disease

Ocular ischemic syndrome (OIS) represents one of the most direct and devastating ophthalmic consequences of systemic vascular disease. It arises primarily from severe stenosis or occlusion of the internal carotid artery (ICA), leading to chronic hypoperfusion of the ocular tissues[1,2]. The condition serves as both a local ischemic insult and a systemic vascular warning sign, frequently preceding cerebrovascular events and reflecting advanced atherosclerotic disease[3].

The pathophysiology of OIS lies in the hemodynamic failure of the ophthalmic and choroidal circulations. The ophthalmic artery, a terminal branch of the ICA, supplies both the central retinal and posterior ciliary arteries. When carotid flow is critically reduced—typically beyond 70–90% luminal narrowing—ocular perfusion pressure declines markedly[4]. Autoregulatory vasodilation initially compensates, but chronic ischemia exhausts this mechanism, resulting in progressive hypoxia, capillary dropout, and neovascular proliferation[5]. Unlike embolic retinal occlusion, OIS reflects global circulatory insufficiency rather than focal obstruction[6].

Clinically, patients often present with gradual vision loss, amaurosis fugax, ocular or periorbital pain, and ischemic anterior segment changes[7]. Fundoscopic findings include narrowed retinal arteries, mid-peripheral dot and blot hemorrhages, microaneurysms, and delayed arteriovenous transit times on fluorescein angiography[8]. Chronic ischemia promotes upregulation of VEGF, driving neovascularization of the iris and angle, ultimately predisposing to neovascular glaucoma[9]. The presence of neovascularization marks an inflection point of irreversible vascular damage and poor prognosis.

Modern imaging techniques have revolutionized the detection and characterization of OIS. Optical coherence tomography angiography (OCT-A) and color Doppler imaging reveal marked reductions in choroidal and retinal blood flow, correlating with disease severity[10]. Quantitative OCT-A parameters, such as decreased vessel density in the superficial and deep capillary plexus, parallel carotid stenosis gradients, enabling early identification before overt fundoscopic changes[11]. Similarly, fluorescein and indocyanine green angiography (ICGA) document delayed choroidal filling, retinal hypoperfusion, and vascular leakage, hallmarks of chronic ocular ischemia[12].

Histopathological studies further delineate the microvascular alterations underlying OIS. Chronic hypoxia leads to endothelial cell loss, thickening of basement membranes, and luminal narrowing within both retinal and choroidal vessels[13]. These structural changes impair oxygen delivery and autoregulatory capacity, creating a vicious cycle of ischemia and angiogenesis. The parallels between retinal microangiopathy in OIS and systemic atherosclerosis underscore their shared vascular pathology[4,5].

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Importantly, OIS is not merely an ophthalmic disorder but a sentinel of systemic morbidity and mortality. Studies have shown that over two-thirds of patients with OIS have significant carotid artery stenosis or occlusion bilaterally, and nearly half experience stroke or cardiac events within five years of diagnosis[14]. The syndrome thus functions as an early, visible manifestation of generalized atheromatous disease, warranting urgent systemic evaluation. Duplex ultrasonography, computed tomographic angiography (CTA), or magnetic resonance angiography (MRA) are essential to assess carotid patency and guide revascularization decisions[15].

Management of OIS requires an interdisciplinary approach combining ophthalmology, neurology, and vascular surgery. Ocular therapy focuses on preventing neovascular complications through anti-VEGF injections, panretinal photocoagulation, and control of intraocular pressure[9,16]. Systemic management aims to restore adequate perfusion via carotid endarterectomy or stenting when feasible, along with aggressive medical optimization of hypertension, hyperlipidemia, and diabetes[14,15]. However, the timing of revascularization is critical; once neovascular glaucoma develops, visual recovery is often limited.

Recent evidence suggests that early recognition of subclinical ischemic changes through multimodal imaging may improve outcomes. Integrating retinal biomarkers into vascular risk assessment could enable preemptive identification of patients at high risk for cerebrovascular accidents[10,11]. Moreover, artificial intelligence–based image analysis holds promise for quantifying ischemic severity and predicting systemic vascular events[16,17].

In essence, OIS epitomizes the bidirectional relationship between ocular and systemic vascular health. The retina, as an extension of the central nervous system, reflects the microvascular consequences of macrovascular disease. Recognizing its ischemic patterns transforms ophthalmic evaluation into a life-saving diagnostic opportunity, bridging the gap between vision care and cardiovascular medicine.

Emerging Diagnostic and Predictive Technologies

Advances in ophthalmic imaging and computational analytics have redefined the relationship between systemic vascular diseases and their ocular manifestations. Once limited to fundoscopic examination, the modern evaluation of retinal and choroidal circulation now integrates optical coherence tomography angiography (OCT-A), machine learning algorithms, and multimodal vascular imaging, providing quantitative insights into systemic endothelial health[1,2]. These technologies are transforming the eye into a noninvasive, high-resolution window to the vasculature, capable of detecting subclinical disease before systemic symptoms emerge[3].

Optical coherence tomography angiography (OCT-A) has become central to this evolution. Unlike traditional fluorescein angiography, OCT-A enables three-dimensional, dye-free visualization of retinal and choroidal microcirculation, allowing detection of capillary dropout, microaneurysm formation, and flow voids at unparalleled resolution[4]. In hypertension, studies have demonstrated reduced vessel density and enlarged foveal avascular zones correlating with both disease duration and blood pressure variability[5,6]. In diabetes, OCT-A parameters such as deep capillary plexus rarefaction and choriocapillaris flow deficits precede the onset of clinically detectable retinopathy[7]. These findings reinforce the concept that ocular imaging can function as a surrogate marker for systemic vascular integrity.

Recent research extends beyond structural imaging to functional vascular assessment. Adaptive optics and laser speckle flowgraphy enable real-time quantification of retinal blood flow dynamics, revealing early autoregulatory impairment in patients with systemic hypertension and metabolic syndrome[8]. Such modalities provide dynamic measures of microvascular reactivity, paralleling endothelial testing used in cardiovascular medicine[9]. Furthermore, multimodal integration combining OCT-A, Doppler flowmetry, and retinal oximetry has begun to yield composite biomarkers that correlate strongly with systemic vascular stiffness, carotid intima-media thickness, and renal microcirculatory changes[10].

The application of artificial intelligence (AI) and deep learning to ocular imaging has emerged as a major frontier in predictive vascular medicine. Trained on vast datasets of fundus and OCT images, AI algorithms can now detect hypertensive, diabetic, and atherosclerotic signatures with remarkable accuracy[11]. Google's DeepMind collaboration, for instance, demonstrated that a deep neural network could estimate cardiovascular risk factors—such as age, sex, smoking status, and systolic blood pressure—solely from retinal photographs[12]. Similar models have shown proficiency in predicting incident stroke and myocardial infarction, suggesting that retinal imaging may one day rival echocardiography or carotid ultrasound as a population-level screening tool[13].

Integration of ocular biomarkers into systemic predictive models represents the next logical step. Several studies have shown that combining retinal vessel caliber metrics, OCT-A perfusion indices, and AI-derived risk scores improves prediction accuracy for cardiovascular and renal outcomes beyond conventional factors[14]. This convergence of ophthalmology, bioinformatics, and vascular medicine has given rise to the emerging discipline of oculomics—the study of systemic health through quantitative analysis of ocular data[15]. Within this framework, the retina is no longer a passive indicator but an active diagnostic interface for systemic disease detection.

Nevertheless, challenges remain. Standardization of imaging protocols, cross-platform calibration, and population-based validation are required before these technologies can be fully integrated into clinical practice[16]. Ethical considerations regarding data privacy, algorithmic transparency, and equitable access must also be addressed to ensure responsible deployment[17]. Furthermore, the translation of imaging biomarkers into actionable therapeutic strategies will require longitudinal studies linking ocular microvascular change to hard cardiovascular and cerebrovascular endpoints.

In summary, the convergence of high-resolution imaging and artificial intelligence heralds a new era of predictive ophthalmology. By quantifying subtle vascular and metabolic perturbations long before systemic manifestation, these technologies position the eye as a sentinel organ in personalized medicine. In the coming decade, retinal and choroidal imaging may evolve from diagnostic adjuncts to integral tools for systemic disease surveillance and prevention, fundamentally reshaping the inter-

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face between ophthalmology and internal medicine.

Discussion

The intricate relationship between systemic vascular diseases and their ophthalmic manifestations illustrates the fundamental unity of the human vascular system. The eye, and particularly the retina, serves as both a target and a reflection of systemic endothelial health. Through the retinal and choroidal circulations—microvascular territories uniquely visible in vivo—clinicians can directly observe processes that remain invisible elsewhere in the body. This capacity transforms ophthalmic examination from a localized assessment into a systemic diagnostic tool[1,2].

Across the spectrum of vascular pathology, endothelial dysfunction emerges as the shared pathophysiologic denominator. Hypertension, diabetes, autoimmune vasculitis, and atherosclerosis all converge on mechanisms of oxidative stress, inflammation, and impaired nitric oxide signaling, which compromise vascular integrity[3,4]. In the retina, this manifests as breakdown of the blood-retinal barrier, pericyte loss, and capillary dropout—structural alterations that parallel systemic vascular remodeling[5]. The ability to visualize these changes directly positions the eye as a dynamic model for studying microangiopathy in real time.

From a clinical perspective, the ophthalmic findings associated with hypertensive and atherosclerotic retinopathy hold profound systemic implications. The classical fundoscopic signs—arteriolar narrowing, arteriovenous nicking, and flame-shaped hemorrhages—represent not only ocular injury but markers of systemic vascular resistance and long-term cardiovascular risk[6,7]. Epidemiological data consistently link moderate-to-severe hypertensive retinopathy with increased incidence of stroke and cardiac mortality, independent of blood pressure control[8]. As such, retinal examination may complement or even surpass traditional vascular risk scoring systems in prognostic value.

Diabetic retinopathy exemplifies a more diffuse and metabolic microangiopathy, where chronic hyperglycemia orchestrates a symphony of endothelial injury, basement membrane thickening, and neuroinflammation[9,10]. Its pathogenesis parallels diabetic nephropathy and neuropathy, supporting the concept of a shared systemic microvascular phenotype[11]. In recent years, imaging and molecular studies have reframed diabetic retinopathy as a neurovascular disorder rather than a purely vascular one, emphasizing the early role of glial dysfunction and neuronal apoptosis[12]. This reconceptualization has implications far beyond ophthalmology—it links retinal pathology to broader systemic metabolic stress and cognitive decline.

Autoimmune vasculopathies, including systemic lupus erythematosus and Behçet's disease, reveal a different yet equally critical facet of this connection. Here, immune complex deposition, complement activation, and cytokine-driven endothelial damage produce vasculitic occlusions and ischemic infarction[13,14]. The eye functions as a sentinel organ for systemic immune activity, with retinal vasculitis often paralleling flares of systemic disease. Moreover, persistent subclinical microvascular changes detected by OCT-A suggest that "remission"

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in autoimmune disease may not equate to vascular quiescence[15]. This observation challenges clinicians to integrate ocular imaging into rheumatologic monitoring, bridging specialties through shared biomarkers of endothelial injury.

In the context of ocular ischemic syndrome (OIS), the eye acts as an early warning system for large-vessel atherosclerosis. OIS not only reflects carotid artery disease but also predicts impending cerebrovascular and cardiac events, making it a critical point of intersection between ophthalmology and vascular neurology[16]. The striking similarity between microvascular alterations in OIS and those in cerebral small vessel disease underscores the systemic nature of atherosclerotic microangiopathy[17]. Thus, ocular ischemia represents more than a localized event—it is the visible endpoint of systemic circulatory collapse.

Emerging diagnostic technologies are reshaping this landscape. Optical coherence tomography angiography (OCT-A) now enables clinicians to quantify vessel density and perfusion dynamics with unprecedented precision[18]. These imaging biomarkers correlate with systemic indices of vascular stiffness, renal microcirculation, and carotid intima-media thickness[19]. Parallel advancements in artificial intelligence (AI) have unlocked the potential to extract predictive cardiovascular information from retinal images alone[20],[21]. This convergence has given rise to the field of oculomics, where ocular data inform systemic disease prediction and personalized medical interventions[22].

Despite these advances, key challenges persist. Many of the current findings derive from cross-sectional or retrospective studies, limiting causal inference. Standardization of imaging parameters and normative datasets remains essential before retinal biomarkers can be fully integrated into cardiovascular and metabolic risk algorithms[23]. Furthermore, ethical and logistical issues surrounding AI-based screening—such as algorithmic bias, data privacy, and accessibility—must be addressed to ensure equitable implementation[24].

Looking ahead, a unifying vision for vascular medicine may emerge from the eye itself. The integration of ophthalmic imaging, systemic physiology, and computational analytics holds the promise of detecting vascular disease at its earliest, preclinical stages. Retinal microvascular alterations could become an integral part of systemic health surveillance—akin to measuring blood pressure or cholesterol levels—but with far greater predictive granularity. In this paradigm, ophthalmology transcends its traditional boundaries to become a central player in preventive and precision medicine.

Ultimately, the ophthalmic manifestations of systemic vascular disease offer more than diagnostic insights; they represent a conceptual bridge linking the microcirculation to whole-body health. The eye, once seen merely as an isolated sensory organ, stands revealed as a living microcosm of systemic vascular physiology—an accessible, quantifiable, and profoundly integrative window into human disease.

Conclusion

The relationship between systemic vascular disease and its ophthalmic manifestations transcends the boundaries of individual specialties. It reveals a unified vascular continuum—one in which the retina and choroid serve as visible extensions of the cardiovascular and microcirculatory systems. Through this lens, the eye ceases to be an isolated organ and becomes a living biomarker of systemic health. The microvasculature observed in the fundus mirrors processes occurring simultaneously in the brain, kidney, and heart, offering a uniquely accessible window into endothelial integrity, hemodynamic stability, and inflammatory burden.

The body of evidence reviewed here demonstrates that nearly every major systemic vascular disorder—from hypertension and atherosclerosis to diabetes and autoimmune vasculitis—leaves an indelible imprint on the ocular circulation. These manifestations are not merely collateral damage; they are physiologic echoes of systemic dysfunction, expressed in one of the body's most intricate and observable tissues. Modern imaging technologies such as OCT-A and adaptive optics have transformed these observations from descriptive phenomena into quantifiable data. When combined with machine learning, they now provide predictive power capable of anticipating cardiovascular, renal, and neurologic outcomes.

The integration of ophthalmic biomarkers into the broader framework of vascular medicine represents a turning point in how clinicians understand and monitor disease. The emerging field of oculomics—where ocular data inform systemic diagnostics—embodies this paradigm shift. In the near future, routine retinal imaging may complement or even replace conventional tests for vascular risk assessment, allowing clinicians to detect early microvascular compromise long before clinical symptoms arise.

Yet this frontier also demands humility and rigor. Translating these technologies into equitable, standardized, and evidence-based practice requires interdisciplinary cooperation among ophthalmologists, cardiologists, neurologists, and data scientists. Ethical stewardship will be vital to ensure that artificial intelligence and automated analytics enhance, rather than distort, clinical judgment.

In essence, the eye has become a mirror of systemic life and disease, a nexus where biology, technology, and medicine converge. Understanding and interpreting its signals offer not only the potential to preserve vision but also to safeguard the heart, brain, and body as a whole. As the boundaries between ophthalmology and systemic medicine continue to dissolve, the next generation of clinicians may look into the eye not just to see vision—but to see the future of vascular health itself.

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