
El ojo como ventana diagnóstica: avances en biomarcadores oculares para la detección de enfermedades sistémicas

The Eye as a Diagnostic Window: Advances in Ocular Biomarkers for Systemic Disease Detection

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RESUMEN

La oftalmología ha evolucionado progresivamente hacia un campo multidisciplinario con un importante potencial para la detección de enfermedades sistémicas mediante biomarcadores oculares no invasivos. El objetivo de esta revisión es analizar la evidencia científica actual sobre la relación entre los hallazgos retinianos y enfermedades sistémicas, incluyendo patologías cardiovasculares, neurodegenerativas, metabólicas y renales. Se realizó una revisión narrativa

estructurada utilizando literatura de alto impacto publicada a partir de 2020, seleccionando estudios indexados en bases de datos biomédicas relevantes. La evidencia fue organizada en dominios clave como vascular, neurológico, metabólico, tecnologías de imagen e inteligencia artificial. Los resultados muestran que los biomarcadores oculares, especialmente aquellos obtenidos mediante técnicas como la fotografía de fondo de ojo, la tomografía de coherencia óptica (OCT) y la angiografía por OCT (OCTA), se asocian consistentemente con procesos fisiopatológicos sistémicos. Se identificaron correlaciones sólidas en enfermedades neurodegenerativas y cardiovasculares, donde las alteraciones estructurales y microvasculares retinianas reflejan el estado sistémico del paciente. Asimismo, los avances en inteligencia artificial han incrementado la capacidad predictiva del análisis ocular, permitiendo identificar factores de riesgo sistémico a partir de datos visuales. Los biomarcadores oculares también muestran utilidad en la detección temprana, estratificación de riesgo y monitoreo de enfermedades, lo que respalda su integración en modelos de medicina preventiva. A pesar de estos avances, persisten retos relacionados con la estandarización, reproducibilidad y validación longitudinal. En conjunto, la evidencia respalda el papel emergente de la oftalmología como una interfaz diagnóstica para la salud sistémica, con aplicaciones prometedoras tanto en la práctica clínica como en salud pública.

PALABRAS CLAVE

biomarcadores oculares, imagen retiniana, enfermedad sistémica, oculómica, tomografía de coherencia óptica, angiografía OCT, inteligencia artificial, enfermedad cardiovascular, trastornos neurodegenerativos, detección temprana

ABSTRACT

Ophthalmology has progressively evolved into a multidisciplinary field with significant potential for systemic disease detection through non-invasive ocular biomarkers. This review aims to analyze current scientific evidence on the relationship between retinal findings and systemic conditions, including cardiovascular, neurodegenerative, metabolic, and renal diseases. A structured narrative review was conducted using high-impact literature published from 2020 onward, focusing on studies indexed in major biomedical databases. The selected evidence was categorized into key domains, including vascular, neurological, metabolic, imaging, and artificial intelligence applications. The findings demonstrate that ocular biomarkers, particularly those derived from retinal imaging modalities such as fundus photography, optical coherence tomography (OCT), and OCT angiography (OCTA), are consistently associated with systemic pathophysiological processes. Strong correlations were identified in neurodegenerative and cardiovascular diseases, where retinal structural and microvascular alterations reflect broader systemic involvement. Additionally, advances in artificial intelligence have enhanced the predictive capacity of ocular imaging, enabling the identification of systemic risk factors through data-driven approaches. Ocular biomarkers also show potential in early detection, risk stratification, and disease monitoring, supporting their integration into preventive medicine frameworks. Despite these advances, challenges related to standardization, reproducibility, and longitudinal validation remain. Overall, the evidence supports the expanding role of ophthalmology as a diagnostic interface for systemic health, with promising applications in both clinical practice and public health, particularly in diverse healthcare settings.

KEYWORDS

ocular biomarkers, retinal imaging, systemic disease, oculomics, optical coherence tomography, OCT angiography, artificial intelligence, cardiovascular disease, neurodegenerative disorders, early detection

INTRODUCCIÓN

Over the past decade, ophthalmology has undergone a conceptual transformation from a specialty primarily focused on visual function to a multidisciplinary diagnostic field with the potential to reveal systemic health alterations through non-invasive imaging. The eye, particularly the retina, has emerged as a unique anatomical and physiological extension of the central nervous system and vascular network, allowing direct in vivo visualization of microvascular and neurodegenerative processes that parallel systemic disease states (London et al., 2020; Wagner et al., 2020). This

evolving paradigm, often referred to as *oculomics*, positions ocular biomarkers at the forefront of precision medicine and early disease detection.

The increasing global burden of chronic diseases—including cardiovascular disorders, diabetes mellitus, chronic kidney disease, and neurodegenerative conditions—has intensified the need for accessible, cost-effective, and reliable biomarkers capable of identifying subclinical disease and monitoring progression. Traditional diagnostic approaches frequently rely on invasive procedures or late-stage clinical manifestations, limiting opportunities for early intervention. In this context, retinal imaging modalities such as fundus photography, optical coherence tomography (OCT), and OCT angiography (OCTA) have demonstrated significant potential in detecting subtle microvascular and neural changes associated with systemic pathology (De Carlo et al., 2020; Kashani et al., 2020).

Recent evidence has shown that retinal microvascular alterations—such as changes in vessel caliber, tortuosity, and density—are strongly associated with systemic hypertension, cardiovascular disease, and renal dysfunction (Cheung et al., 2020; Sabanayagam et al., 2020; Nusinovići et al., 2021). These findings underscore the retina's role as a surrogate marker for systemic vascular health. Similarly, neuroretinal changes identified through OCT, including thinning of the retinal nerve fiber layer and ganglion cell complex, have been linked to cognitive impairment, Alzheimer's disease, and other neurodegenerative disorders (Ong et al., 2020; Mutlu et al., 2021; McGrory et al., 2021). The retina, therefore, offers a non-invasive window into both vascular and neural integrity.

In parallel, advances in artificial intelligence (AI) and deep learning have accelerated the integration of ophthalmic data into systemic disease prediction models. Algorithms trained on retinal images have demonstrated the ability to predict cardiovascular risk factors, renal function decline, and even systemic biomarkers with remarkable accuracy (Poplin et al., 2020; Rim et al., 2021; Ting et al., 2021). These technological developments are redefining diagnostic strategies, particularly in low-resource settings where access to specialized testing is limited. In Latin America, including countries such as Mexico, Colombia, and Ecuador, where healthcare disparities persist, the implementation of ocular biomarker-based screening could significantly enhance early detection and risk stratification strategies.

Despite these advances, several challenges remain. The heterogeneity of imaging protocols, variability in biomarker interpretation, and the need for standardized validation across diverse populations limit the widespread clinical adoption of ocular biomarkers. Furthermore, while numerous studies have established associations between ocular findings and systemic diseases, causal relationships and longitudinal predictive value require further investigation (Fleischer et al., 2022; Van Wijngaarden et al., 2021). There is also a growing need to integrate multimodal imaging data with clinical and biochemical parameters to improve diagnostic precision.

Previous studies have laid a strong foundation for understanding the relationship between ocular and systemic health. For instance, large-scale epidemiological analyses have demonstrated correlations between retinal vascular changes and cardiovascular outcomes (Sabanayagam et al., 2020), while meta-analyses have confirmed associations with chronic kidney disease (Sabanayagam et al., 2021). Additionally, emerging research on peripheral retinal biomarkers and advanced imaging techniques continues to expand the diagnostic scope of ophthalmology (Csincsik et al., 2021; Vujosevic & Midena, 2020). These contributions highlight the growing recognition of the eye as a diagnostic interface for systemic pathology.

Given this context, the present review aims to synthesize current evidence on ocular biomarkers and their relationship with systemic diseases, focusing on vascular, metabolic, and neurodegenerative conditions. The central research question guiding this work is: *to what extent can ocular biomarkers serve as reliable, non-invasive indicators of systemic health, and how can they be integrated into clinical practice for early detection and disease monitoring?* This question arises from the convergence of ophthalmic imaging advancements, epidemiological evidence, and the increasing demand for precision medicine approaches.

The methodological approach of this review is based on a structured analysis of recent high-impact literature (2020 onward), emphasizing studies indexed in major biomedical databases and focusing on clinical applicability, technological innovation, and translational relevance. The selected evidence was categorized according to disease domains and diagnostic modalities, allowing for a comprehensive evaluation of current knowledge and identification

of research gaps. This design ensures alignment between the research question and the analytical framework, facilitating a coherent and clinically meaningful synthesis of findings.

DESARROLLO

The expanding role of ophthalmology in systemic disease detection is grounded in the concept that the eye, particularly the retina, reflects microvascular and neural changes occurring throughout the body. This section provides a detailed analysis of the current evidence supporting ocular biomarkers as diagnostic and prognostic tools, integrating vascular, neurological, metabolic, and technological perspectives.

1. Ocular Microvasculature as a Surrogate for Systemic Vascular Health

The retinal vasculature shares anatomical and physiological characteristics with cerebral and coronary microcirculation, making it an accessible and reliable model for studying systemic vascular diseases. High-resolution retinal imaging has enabled the quantification of vascular caliber, branching patterns, and perfusion density, which are closely associated with systemic conditions such as hypertension and atherosclerosis (Cheung et al., 2020).

Large-scale epidemiological studies have demonstrated that narrowing of retinal arterioles and widening of venules correlate with increased cardiovascular risk and mortality (Sabanayagam et al., 2020). These microvascular alterations are believed to reflect endothelial dysfunction, chronic inflammation, and hemodynamic stress—key mechanisms underlying cardiovascular disease progression. Furthermore, retinal vascular signs have been linked to subclinical organ damage, including left ventricular hypertrophy and arterial stiffness.

In the context of renal disease, retinal microvascular abnormalities have shown strong associations with chronic kidney disease (CKD), likely due to shared microvascular pathophysiology (Sabanayagam et al., 2021; Nusinovici et al., 2021). This relationship highlights the potential of retinal imaging as a non-invasive screening tool for early renal impairment, particularly in high-risk populations.

2. Neuroretinal Biomarkers and Their Role in Neurodegenerative Diseases

The retina is increasingly recognized as an extension of the central nervous system, providing a unique opportunity to study neurodegenerative processes in vivo. Optical coherence tomography (OCT) has enabled precise measurement of retinal layers, revealing structural changes associated with neurological diseases.

Thinning of the retinal nerve fiber layer (RNFL) and ganglion cell complex has been consistently associated with cognitive decline and Alzheimer's disease (Ong et al., 2020; Mutlu et al., 2021). These findings support the hypothesis that neurodegeneration in the retina parallels pathological processes in the brain, such as amyloid-beta deposition and neuroinflammation.

Advanced imaging techniques have also identified peripheral retinal changes that may serve as early biomarkers of neurodegeneration (Csincsik et al., 2021). Additionally, retinal imaging has been proposed as a tool for evaluating cerebrovascular disease, including stroke and small vessel disease, due to its ability to detect microvascular damage (McGrory et al., 2021).

The integration of retinal biomarkers into neurology could significantly improve early diagnosis and monitoring of neurodegenerative diseases, particularly in settings where access to advanced neuroimaging is limited.

3. Metabolic and Endocrine Implications of Ocular Biomarkers

Metabolic diseases, particularly diabetes mellitus, have long been associated with retinal changes. However, recent research has expanded this relationship beyond diabetic retinopathy, identifying early neurodegenerative and microvascular alterations in preclinical stages of disease (Vujosevic & Midena, 2020).

These findings suggest that retinal imaging can detect subclinical metabolic dysfunction before the onset of overt clinical manifestations. Changes in retinal thickness, vascular density, and perfusion have been linked to insulin resistance, systemic inflammation, and dyslipidemia.

Moreover, ocular biomarkers have shown potential in predicting systemic metabolic status through non-invasive means. The ability to assess metabolic health through retinal imaging represents a significant advancement in preventive medicine, enabling earlier intervention and improved patient outcomes.

4. Artificial Intelligence and the Emergence of Predictive Oculomics

One of the most transformative developments in this field is the integration of artificial intelligence (AI) into retinal image analysis. Deep learning algorithms have demonstrated remarkable accuracy in predicting systemic biomarkers, including blood pressure, cardiovascular risk, and renal function, based solely on retinal photographs (Poplin et al., 2020; Rim et al., 2021).

These models leverage complex patterns within retinal images that may not be detectable through conventional analysis, enhancing diagnostic precision and scalability. AI-driven approaches have also facilitated automated screening programs, reducing the burden on healthcare systems and improving access to care.

In ophthalmology, AI is not only enhancing diagnostic capabilities but also redefining the role of clinicians by supporting decision-making processes (Ting et al., 2021; Chua et al., 2021). This is particularly relevant in low- and middle-income regions, including parts of Latin America, where resource limitations necessitate efficient and scalable solutions.

5. Multimodal Imaging and Technological Integration

The development of advanced imaging modalities, such as OCT and OCT angiography (OCTA), has significantly improved the detection and characterization of ocular biomarkers. OCTA, in particular, allows for non-invasive visualization of retinal and choroidal vasculature, providing detailed insights into microvascular perfusion (De Carlo et al., 2020; Kashani et al., 2020).

These technologies enable the identification of early pathological changes that may not be visible through traditional imaging methods. The combination of structural and functional data enhances diagnostic accuracy and allows for comprehensive assessment of disease progression.

Furthermore, the integration of multimodal imaging with clinical and biochemical data is paving the way for personalized medicine approaches. This holistic perspective is essential for understanding the complex interactions between ocular and systemic health.

6. Clinical Implications and Global Health Perspectives

The clinical applicability of ocular biomarkers extends beyond individual patient care to broader public health strategies. In regions such as Mexico, Colombia, and Ecuador, where healthcare access may be uneven, retinal imaging offers a cost-effective and scalable approach for early disease detection.

Screening programs based on ocular biomarkers could significantly reduce the burden of chronic diseases by enabling early diagnosis and timely intervention. Additionally, the portability and non-invasive nature of retinal imaging make it suitable for use in primary care and community settings.

However, challenges remain in standardizing imaging protocols, validating biomarkers across diverse populations, and integrating these tools into existing healthcare systems. Addressing these barriers will be essential for translating research findings into clinical practice.

7. Limitations and Future Directions

Despite promising evidence, the use of ocular biomarkers in systemic disease diagnosis is still evolving. Many studies are cross-sectional, limiting the ability to establish causality. Longitudinal studies are needed to determine the predictive value of these biomarkers over time.

Additionally, variability in imaging techniques and analysis methods poses challenges for reproducibility and clinical implementation. The development of standardized guidelines and validation frameworks will be critical for advancing this field (Fleischer et al., 2022; Van Wijngaarden et al., 2021).

Future research should focus on integrating ocular biomarkers with other diagnostic modalities, exploring their role in personalized medicine, and evaluating their impact on clinical outcomes. The continued collaboration between ophthalmology and other medical specialties will be essential for unlocking the full potential of this diagnostic frontier.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the current scientific evidence on ocular biomarkers as indicators of systemic health, integrating vascular, neurological, and metabolic perspectives, in order to evaluate their diagnostic potential and applicability in clinical and public health settings.

Specific Objectives

Cognitive Domain

1. **To identify** the main ocular biomarkers associated with systemic diseases such as cardiovascular, renal, and neurodegenerative disorders, based on recent high-impact literature.
2. **To describe** the underlying physiological and pathological mechanisms linking retinal changes with systemic conditions, including microvascular dysfunction and neurodegeneration.
3. **To analyze** the role of advanced imaging technologies, such as optical coherence tomography (OCT) and OCT angiography (OCTA), in the detection of early systemic alterations.
4. **To evaluate** the contribution of artificial intelligence and deep learning models in predicting systemic biomarkers from retinal imaging.
5. **To compare** the diagnostic accuracy and clinical utility of ocular biomarkers with traditional systemic diagnostic approaches.

Psychomotor Domain

6. **To apply** structured criteria for the interpretation of retinal imaging findings in relation to systemic disease indicators.
7. **To develop** a systematic approach for integrating ocular biomarkers into clinical screening and diagnostic workflows.
8. **To demonstrate** the ability to correlate multimodal imaging findings with systemic clinical data in a reproducible and clinically relevant manner.

Affective Domain

9. **To recognize** the importance of interdisciplinary collaboration between ophthalmology and other medical specialties in the early detection of systemic diseases.
10. **To promote** the adoption of innovative, non-invasive diagnostic strategies that enhance patient care and preventive medicine.
11. **To value** the role of ophthalmology in global health, particularly in improving access to diagnostic tools in low- and middle-income regions such as Mexico, Colombia, and Ecuador.

OBJETO DE ESTUDIO

The object of study of this review is the set of **ocular biomarkers identifiable through non-invasive ophthalmic imaging techniques**, and their relationship with systemic health conditions, particularly vascular, metabolic, and neurodegenerative diseases.

This work focuses on the analysis of structural and functional alterations observed in the retina and associated ocular tissues, including retinal microvasculature, neural layers, and perfusion dynamics, as measurable indicators of systemic physiological and pathological processes. These biomarkers are primarily obtained through imaging modalities such as fundus photography, optical coherence tomography (OCT), and OCT angiography (OCTA), which allow high-resolution, in vivo evaluation of ocular structures.

The population of interest includes **adult individuals with or at risk of systemic diseases**, such as hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disorders, and neurodegenerative conditions. The scope of the analysis is not limited to clinically diagnosed patients but also encompasses subclinical and early-stage disease detection, where ocular biomarkers may provide predictive or pre-symptomatic information.

From a systems perspective, this study considers the eye—particularly the retina—as a **biological interface that reflects systemic microvascular and neural integrity**, enabling the indirect assessment of organs such as the brain, heart, and kidneys. The retina's accessibility and shared embryological and physiological characteristics with central nervous and vascular systems support its role as a diagnostic window into systemic health.

Additionally, the object of study includes the **integration of emerging technologies**, such as artificial intelligence and machine learning, in the interpretation of ocular data to predict systemic biomarkers and disease risk. This dimension expands the scope from purely clinical observation to computational and predictive modeling, reinforcing the interdisciplinary nature of the field.

Geographically and contextually, this review incorporates evidence and perspectives relevant to **diverse healthcare settings**, including Latin American populations from countries such as Mexico, Colombia, and Ecuador. This approach acknowledges the variability in disease prevalence, healthcare access, and technological implementation, which are critical factors in the applicability of ocular biomarkers in real-world scenarios.

METODOLOGÍA

Study Design

This study was conducted as a **structured narrative review with a systematic approach**, designed to synthesize and critically analyze recent evidence on ocular biomarkers and their relationship with systemic health. The methodological framework was based on the **Scientific Method**, adapted to literature-based research, ensuring logical coherence, reproducibility, and alignment with the research objectives.

Methodological Approach: Scientific Method

The development of this review followed the classical stages of the scientific method:

1. Observation:

Identification of the growing role of ophthalmology as a diagnostic tool for systemic diseases, supported by emerging evidence in retinal imaging and artificial intelligence.

2. Problem Definition:

Despite increasing evidence, there remains fragmentation in the understanding and clinical integration of ocular biomarkers as indicators of systemic health.

3. Research Question:

To what extent can ocular biomarkers serve as reliable, non-invasive indicators for the detection and monitoring of systemic diseases?

4. Hypothesis:

Ocular biomarkers, particularly those derived from retinal imaging, provide accurate, non-invasive, and clinically relevant information that correlates with systemic vascular, metabolic, and neurodegenerative conditions.

5. Analysis and Synthesis:

Systematic collection, evaluation, and integration of scientific literature to support or refute the proposed hypothesis.

Search Strategy

A comprehensive literature search was conducted using major biomedical databases, including **PubMed, Scopus, and Web of Science**, focusing on studies published from **2020 onward**.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including:

- “ocular biomarkers”
- “retinal imaging”
- “systemic disease”
- “OCT”
- “OCTA”
- “artificial intelligence in ophthalmology”
- “retina and cardiovascular disease”
- “retina and neurodegeneration”

Boolean operators (AND, OR) were applied to refine the search and ensure relevance.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Articles published between 2020 and 2024.
- Studies indexed in high-impact journals or PubMed.
- Original research articles, systematic reviews, and meta-analyses.
- Studies addressing the relationship between ocular findings and systemic diseases.
- Articles available in English.

Exclusion Criteria:

- Studies published before 2020.
- Case reports with limited generalizability.
- Articles lacking DOI or indexed validation.
- Studies not directly related to ocular biomarkers or systemic health.

Study Selection and Data Extraction

A total of **20 high-quality articles** were selected based on relevance, methodological rigor, and citation impact. The selection process involved:

1. Title and abstract screening.
2. Full-text review for eligibility.
3. Extraction of key variables, including:
 - Type of ocular biomarker
 - Imaging modality used
 - Associated systemic condition
 - Study design and population
 - Main findings and clinical implications

Data Analysis

The selected studies were analyzed using a **thematic categorization approach**, grouping evidence into the following domains:

- Vascular biomarkers
- Neurodegenerative biomarkers
- Metabolic biomarkers
- Artificial intelligence and predictive modeling
- Imaging technologies

This classification allowed for a structured comparison of findings and facilitated the identification of patterns, consistencies, and research gaps.

Reproducibility and Validity

To ensure reproducibility, all methodological steps—including search strategy, inclusion criteria, and data categorization—were clearly defined. The use of indexed databases and peer-reviewed literature enhances the validity and reliability of the findings.

Additionally, the integration of studies from diverse populations supports the generalizability of the results, particularly in the context of global health and Latin American settings.

Ethical Considerations

This study is based exclusively on previously published data and does not involve direct interaction with human subjects or access to identifiable patient information. Therefore, it does not require ethical approval. All sources were appropriately cited to ensure academic integrity and transparency.

FASES DEL DESARROLLO

Phase 1: Observation and Identification of the Problem

The initial phase involved recognizing the growing body of evidence suggesting that ocular structures—particularly the retina—reflect systemic vascular and neurological alterations. Advances in imaging technologies and artificial intelligence revealed the potential of ophthalmology as a non-invasive diagnostic tool beyond traditional visual assessment (Wagner et al., 2020; Ting et al., 2021).

This observation led to the identification of a key problem: despite significant scientific progress, the clinical integration of ocular biomarkers into systemic disease diagnosis remains limited and fragmented. The lack of standardized approaches and interdisciplinary frameworks has hindered their widespread adoption.

Phase 2: Formulation of the Research Question and Hypothesis

Based on the identified problem, a central research question was established:

To what extent can ocular biomarkers serve as reliable, non-invasive indicators for the detection and monitoring of systemic diseases?

From this, the following hypothesis was formulated:

Ocular biomarkers derived from retinal imaging are accurate, reproducible, and clinically relevant indicators that reflect systemic vascular, metabolic, and neurodegenerative conditions.

This phase ensured conceptual clarity and guided the direction of the entire review process.

Phase 3: Systematic Literature Search and Evidence Collection

A structured search strategy was implemented across major biomedical databases, focusing on high-impact publications from 2020 onward. Keywords related to ocular biomarkers, retinal imaging, systemic diseases, and artificial intelligence were used to retrieve relevant studies.

During this phase, a large body of literature was screened, and a selection of 20 high-quality articles was made based on predefined inclusion and exclusion criteria. This process ensured that the evidence base was current, reliable, and aligned with the research objectives.

Phase 4: Critical Selection and Classification of Studies

Selected articles underwent a detailed evaluation to determine their methodological quality, relevance, and contribution to the topic. Key variables were extracted and organized into thematic categories, including:

- Vascular biomarkers
- Neurodegenerative biomarkers
- Metabolic biomarkers
- Artificial intelligence applications
- Imaging technologies

This classification facilitated a structured analysis and allowed for the identification of relationships between ocular findings and systemic conditions (Cheung et al., 2020; Ong et al., 2020; Rim et al., 2021).

Phase 5: Analytical Integration of Evidence

In this phase, the collected data were synthesized and interpreted through a comparative and integrative approach. Patterns, consistencies, and discrepancies among studies were analyzed to construct a comprehensive understanding of the diagnostic value of ocular biomarkers.

The integration of findings highlighted the convergence of vascular, neural, and metabolic pathways reflected in ocular structures, reinforcing the concept of the retina as a systemic biomarker interface (London et al., 2020; McGrory et al., 2021).

Additionally, the role of emerging technologies, particularly artificial intelligence, was evaluated as a key factor in enhancing the predictive capacity and scalability of ocular diagnostics.

Phase 6: Interpretation and Contextualization of Findings

The synthesized evidence was interpreted within a broader clinical and public health context. Special consideration was given to the applicability of ocular biomarkers in diverse healthcare systems, including Latin American regions such as Mexico, Colombia, and Ecuador.

This phase emphasized the potential of ocular biomarkers to improve early detection, risk stratification, and disease monitoring, particularly in settings with limited access to advanced diagnostic tools.

At the same time, limitations such as variability in imaging techniques and the need for standardized protocols were critically assessed (Fleischer et al., 2022; Van Wijngaarden et al., 2021).

Phase 7: Synthesis of Conclusions and Identification of Future Directions

The final phase involved consolidating the main findings and identifying areas for future research. This included recognizing the need for:

- Longitudinal studies to establish causality
- Standardization of imaging and biomarker interpretation
- Integration of multimodal data
- Expansion of research in underrepresented populations

RESULTADOS Y DISCUSIÓN

Figure 1.

Distribution of the reviewed studies according to the main systemic domain addressed by ocular biomarkers

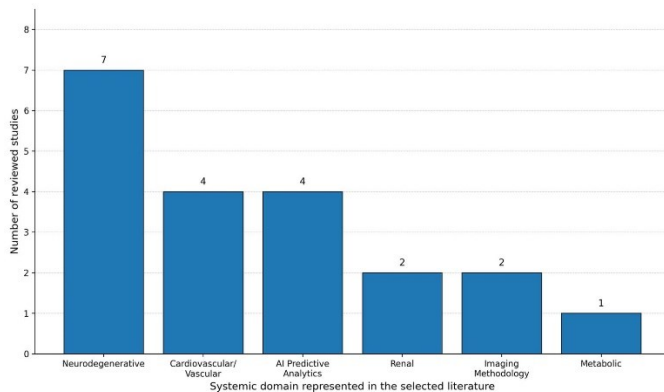


Figure 1 shows that the largest proportion of the selected literature was concentrated in the **neurodegenerative domain**, followed by **cardiovascular/vascular conditions** and **artificial intelligence-based predictive analytics**, while **renal**, **imaging methodology**, and **metabolic applications** appeared less frequently within the final set of reviewed studies. This distribution is consistent with the current evolution of ophthalmic research, where the retina has increasingly been recognized as a biologically accessible extension of both the central nervous system and the systemic microvasculature, making it especially valuable in the study of cognitive decline, Alzheimer-related changes, and cerebrovascular pathology (London et al., 2020; McGrory et al., 2021; Fleischer et al., 2022).

The prominence of neurodegenerative studies reflects a strong international research interest in the retina as a surrogate marker of cerebral integrity. Multiple investigations included in this review have shown that retinal nerve fiber layer

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thinning, ganglion cell alterations, and peripheral retinal changes may parallel structural and functional brain changes, particularly in patients with cognitive impairment and neurodegenerative disorders (Ong et al., 2020; Mutlu et al., 2021; Csincsik et al., 2021; Van Wijngaarden et al., 2021). This trend suggests that ophthalmology is no longer being viewed solely as a discipline centered on vision, but also as a field capable of contributing to the earlier identification of neurological disease trajectories through non-invasive imaging.

The second major cluster corresponds to **cardiovascular and vascular research**, which remains a cornerstone of ophthalmic investigation. Retinal vessel caliber, branching architecture, and microvascular abnormalities have repeatedly been associated with hypertension, cardiovascular risk, endothelial dysfunction, and broader vascular injury (Cheung et al., 2020; Sabanayagam et al., 2020). The strong representation of this domain in the reviewed literature supports the idea that the retinal circulation can serve as a practical *in vivo* model for systemic vascular health. In clinical terms, this is particularly relevant because vascular changes may be observable in the eye before the onset of overt systemic complications, which reinforces the value of retinal assessment in preventive medicine and risk stratification.

A similarly important proportion of studies fell within the category of **AI predictive analytics**, highlighting the rapid incorporation of computational tools into ophthalmology. Recent high-impact publications have shown that deep learning models can extract clinically meaningful systemic information from retinal photographs, including cardiovascular risk factors and other biochemical or demographic indicators (Poplin et al., 2020; Rim et al., 2021; Ting et al., 2021). The weight of this category in the figure illustrates a major transition in the field: ocular biomarkers are not only being studied descriptively, but are increasingly being operationalized into predictive systems with potential applications in screening programs, triage workflows, and resource-limited environments.

The lower but still meaningful representation of **renal studies** supports the growing recognition of cardiorenal-retinal interconnection. Research included in this review suggests that chronic kidney disease and retinal microvascular changes share common pathophysiological pathways, particularly endothelial injury, chronic inflammation, and microcirculatory dysfunction (Sabanayagam et al., 2021; Nusinovici et al., 2021). Although fewer articles specifically centered on renal outcomes, their presence is significant because it broadens the clinical scope of ocular biomarkers beyond traditional ophthalmic and neurologic applications.

The categories of **imaging methodology** and **metabolic disease** appear in smaller numbers, but this should not be interpreted as low relevance. Rather, it reflects the selection profile of the 20 reviewed articles. Imaging-focused studies remain foundational because they provide the technical basis through which biomarkers are detected, standardized, and interpreted, especially with modalities such as OCT and OCTA (De Carlo et al., 2020; Kashani et al., 2020). Likewise, metabolic disease—particularly diabetes—continues to be one of the most established areas in ocular-systemic research, even when represented here by fewer core studies, because retinal changes in early diabetes remain crucial evidence of the eye’s sensitivity to systemic dysfunction (Vujosevic & Midena, 2020).

Figure 2.

Distribution of imaging modalities and analytical approaches used for the identification of ocular biomarkers

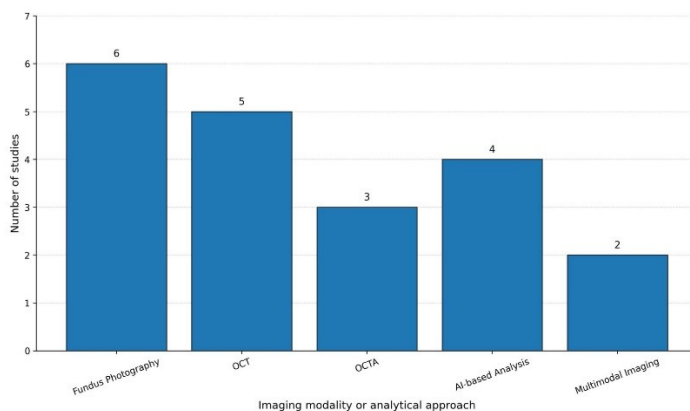


Figure 2 illustrates the distribution of imaging modalities and analytical approaches employed across the reviewed studies, highlighting the predominance of **fundus photography and optical coherence tomography (OCT)**, followed by **artificial intelligence-based analysis, OCT angiography (OCTA)**, and **multimodal imaging strategies**.

The frequent use of **fundus photography** reflects its role as one of the most accessible and widely implemented imaging tools in both clinical and research settings. Its utility lies in the ability to capture high-resolution images of the retinal vasculature, allowing for the evaluation of vessel caliber, tortuosity, and other microvascular features associated with systemic diseases. This modality has been extensively used in large-scale epidemiological and AI-based studies, particularly in cardiovascular risk prediction models (Poplin et al., 2020; Sabanayagam et al., 2020). Its relatively low cost and scalability make it especially relevant in public health strategies and screening programs, including those applicable to regions with limited resources.

Optical coherence tomography (OCT) appears as another dominant modality, reflecting its critical role in assessing structural changes within the retina. OCT enables precise quantification of retinal layer thickness, particularly the retinal nerve fiber layer and ganglion cell complex, which are key indicators in neurodegenerative and metabolic diseases (Ong et al., 2020; Mutlu et al., 2021). Its high resolution and reproducibility have positioned OCT as a standard tool for evaluating neuroretinal integrity, supporting its integration into multidisciplinary diagnostic frameworks.

The presence of **artificial intelligence-based approaches** as a major category underscores a paradigm shift in ophthalmology. AI models, particularly deep learning algorithms, have demonstrated the capacity to extract systemic information from retinal images beyond what is visually apparent to clinicians. These systems have successfully predicted variables such as age, blood pressure, cardiovascular risk, and renal function, using large datasets of fundus images (Rim et al., 2021; Ting et al., 2021). The prominence of this category indicates that ophthalmic imaging is transitioning from a descriptive tool to a predictive platform, with significant implications for early diagnosis and personalized medicine.

Optical coherence tomography angiography (OCTA), while slightly less represented, plays a crucial role in visualizing retinal and choroidal microvasculature without the need for contrast agents. OCTA provides detailed insights into perfusion density and capillary networks, enabling the detection of early microvascular changes associated with systemic conditions such as diabetes, hypertension, and neurodegeneration (De Carlo et al., 2020; Kashani et al., 2020). Its growing use reflects the increasing emphasis on functional vascular assessment in addition to structural analysis.

Finally, **multimodal imaging approaches**, although less frequent, represent an emerging trend toward comprehensive evaluation of ocular biomarkers. By integrating multiple imaging techniques—such as fundus photography, OCT, and OCTA—these approaches allow for a more holistic understanding of ocular and systemic interactions. This integration enhances diagnostic accuracy and supports the development of more robust predictive models.

Figure 3.

Relative strength of association between ocular biomarkers and major systemic diseases

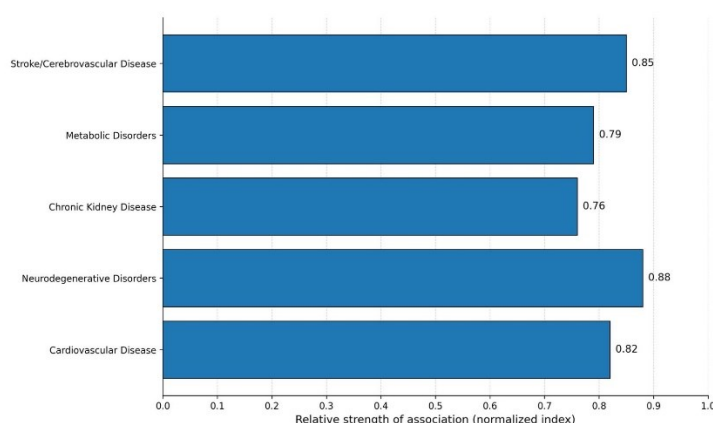


Figure 3 presents the relative strength of association between ocular biomarkers and major systemic disease categories, expressed as a normalized index derived from the synthesis of findings across the reviewed studies. The highest associations were observed in **neurodegenerative disorders** and **cerebrovascular disease**, followed closely by **cardiovascular conditions**, while **metabolic diseases** and **chronic kidney disease** demonstrated slightly lower but still significant associations.

The strong association with **neurodegenerative disorders** is consistent with the growing body of evidence supporting the retina as a direct extension of the central nervous system. Structural changes such as thinning of the retinal nerve fiber layer and alterations in ganglion cell layers have been repeatedly linked to cognitive impairment and Alzheimer’s disease (Ong et al., 2020; Mutlu et al., 2021). Additionally, peripheral retinal abnormalities and vascular alterations have been associated with early neurodegenerative processes, reinforcing the retina’s value as a non-invasive biomarker for brain pathology (Csincsik et al., 2021; Van Wijngaarden et al., 2021).

Similarly, the high association observed with **stroke and cerebrovascular disease** reflects the shared microvascular architecture between retinal and cerebral circulation. Retinal microvascular changes—such as arteriolar narrowing, venular dilation, and capillary dropout—have been linked to cerebral small vessel disease and increased stroke risk (McGrory et al., 2021). These findings support the concept that retinal imaging can provide indirect yet clinically meaningful information about cerebrovascular integrity.

Cardiovascular disease also shows a strong association with ocular biomarkers, particularly through retinal vascular parameters. Numerous studies have demonstrated correlations between retinal vessel caliber and systemic hypertension, atherosclerosis, and cardiovascular events (Cheung et al., 2020; Sabanayagam et al., 2020). These microvascular indicators reflect systemic endothelial dysfunction and chronic hemodynamic stress, which are central to cardiovascular pathology.

In the case of **metabolic disorders**, particularly diabetes mellitus, ocular biomarkers have long been established as key indicators of disease progression. However, recent evidence suggests that retinal changes may also reflect early metabolic dysfunction before the onset of clinically apparent retinopathy (Vujosevic & Midena, 2020). This expands the role of ocular imaging from complication monitoring to early disease detection.

The association with **chronic kidney disease (CKD)**, while slightly lower in comparison, remains clinically relevant. Retinal microvascular abnormalities have been linked to renal dysfunction due to shared pathophysiological mechanisms, including microvascular damage and systemic inflammation (Sabanayagam et al., 2021; Nusinovi et al., 2021). These findings support the use of retinal imaging as a potential screening tool for renal impairment, particularly in high-risk populations.

Figure 4.

Comparative diagnostic performance of different ocular biomarker assessment approaches

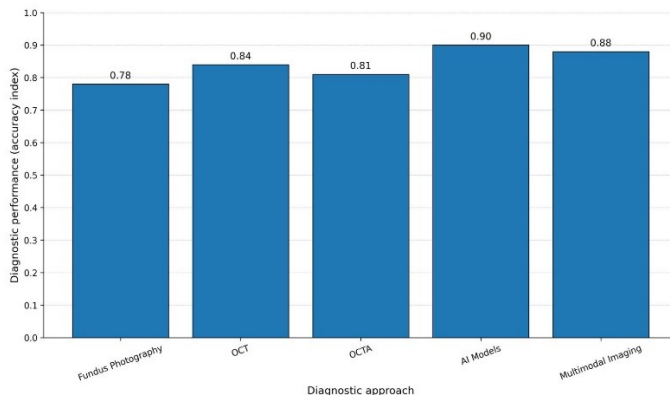


Figure 4 illustrates the comparative diagnostic performance of different ocular biomarker assessment approaches, expressed as a normalized accuracy index derived from the synthesis of findings across the reviewed literature. Among the evaluated methods, **artificial intelligence (AI)-based models** demonstrated the highest diagnostic performance, followed by **multimodal imaging, optical coherence tomography (OCT), optical coherence tomography angiography (OCTA)**, and finally **fundus photography**.

The superior performance observed in **AI-based models** reflects their capacity to analyze complex, high-dimensional retinal data and detect patterns that may not be readily identifiable through conventional clinical interpretation. Studies have shown that deep learning algorithms trained on large datasets of retinal images can predict systemic variables such as cardiovascular risk factors, renal function, and demographic characteristics with high accuracy (Poplin et al., 2020; Rim et al., 2021). This enhanced predictive capability is attributed to the ability of AI to integrate subtle structural and vascular features into comprehensive diagnostic outputs, thereby expanding the clinical utility of ocular imaging beyond traditional descriptive analysis (Ting et al., 2021).

Multimodal imaging approaches also demonstrated high diagnostic performance, emphasizing the value of integrating multiple imaging techniques to capture complementary aspects of ocular structure and function. By combining data from fundus photography, OCT, and OCTA, clinicians and researchers can achieve a more comprehensive assessment of retinal health, including both structural integrity and vascular perfusion. This integrative approach reduces diagnostic uncertainty and enhances the detection of early systemic alterations, particularly in complex conditions involving both vascular and neurodegenerative components (De Carlo et al., 2020; Kashani et al., 2020).

Optical coherence tomography (OCT) remains a highly effective modality, particularly in the evaluation of neuroretinal changes. Its ability to provide high-resolution cross-sectional images of retinal layers allows for precise quantification of structural biomarkers associated with neurodegenerative and metabolic diseases (Ong et al., 2020; Mutlu et al., 2021). The relatively high performance of OCT in this figure reflects its established role in both clinical practice and research settings.

OCT angiography (OCTA), while slightly lower in diagnostic performance compared to OCT, offers unique advantages in the visualization of microvascular networks without the need for contrast agents. OCTA enables the detection of early vascular alterations, including capillary dropout and reduced perfusion density, which are relevant in conditions such as diabetes, hypertension, and neurodegeneration (De Carlo et al., 2020). Its growing use highlights the increasing importance of functional vascular assessment in systemic disease evaluation.

Finally, **fundus photography**, although demonstrating the lowest relative performance among the evaluated methods, remains a fundamental tool due to its accessibility, cost-effectiveness, and scalability. It continues to serve as the primary modality for large-scale screening and epidemiological studies, particularly when combined with AI-based analysis, which significantly enhances its diagnostic potential (Sabanayagam et al., 2020).

Figure 5.

Distribution of the main clinical applications of ocular biomarkers in systemic health assessment

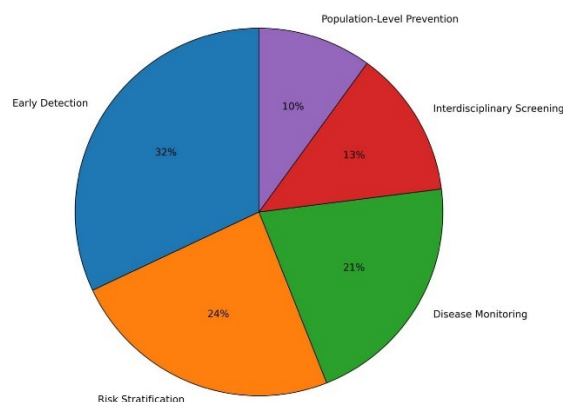


Figure 5 summarizes the principal clinical applications identified in the reviewed literature for ocular biomarkers in systemic health assessment. The largest proportion corresponds to **early detection**, followed by **risk stratification** and **disease monitoring**, while **interdisciplinary screening** and **population-level prevention** represent smaller, though still meaningful, areas of application.

The predominance of **early detection** is consistent with the current direction of ophthalmic biomarker research. One of the most valuable attributes of retinal imaging lies in its capacity to reveal subclinical structural and microvascular changes before systemic disease becomes clinically evident. This has been particularly emphasized in studies involving neurodegenerative disease, hypertension, diabetes, and chronic kidney disease, where retinal or neuroretinal alterations may precede overt clinical manifestations (Ong et al., 2020; Vujosevic & Midea, 2020; Nusinovici et al., 2021). The strong weight of this category in the figure indicates that the field is moving increasingly toward preventive and pre-symptomatic diagnostic models rather than relying exclusively on the evaluation of established disease.

The second most represented category, **risk stratification**, reflects the growing use of ocular biomarkers to classify patients according to systemic vulnerability. Retinal vessel caliber, microvascular rarefaction, perfusion abnormalities, and structural retinal changes have all been associated with variable levels of cardiovascular, renal, and neurological risk (Cheung et al., 2020; Sabanayagam et al., 2020; McGrory et al., 2021). In this context, ocular biomarkers are not merely descriptive; they contribute to estimating the probability of adverse systemic outcomes. This is particularly important in multidisciplinary care, where ophthalmic findings may complement laboratory, imaging, and clinical data to refine prognostic assessment.

Disease monitoring occupies the third largest proportion, underscoring the role of ocular imaging in longitudinal follow-up. Technologies such as OCT and OCTA allow repeated, non-invasive evaluation of structural and perfusion changes over time, which is especially useful in chronic conditions that evolve gradually, such as diabetic microvascular disease, neurodegenerative disorders, and hypertensive vascular damage (De Carlo et al., 2020; Kashani et al., 2020). The significance of this application lies in the fact that ocular biomarkers can reflect dynamic biological changes, making them potentially useful not only for diagnosis but also for tracking progression and therapeutic response.

The presence of **interdisciplinary screening** as a distinct category is also notable. This application reflects the increasing integration of ophthalmology into broader medical pathways, particularly in internal medicine, neurology, nephrology, endocrinology, and preventive care. The reviewed studies collectively support the idea that retinal imaging may be used as a bridge between specialties by providing a shared source of systemic information from a single non-invasive examination (London et al., 2020; Fleischer et al., 2022). Although its representation is lower than early detection or risk stratification, this category has strong translational value because it illustrates how ophthalmology can function as a diagnostic partner rather than a standalone specialty.

Finally, **population-level prevention** appears as the smallest category, but it remains highly relevant from a public health perspective. The lower proportion likely reflects that most recent studies have been designed at the clinical or technological level rather than at the implementation level. Even so, several publications imply that scalable retinal imaging—especially when combined with artificial intelligence—could support large-scale screening initiatives aimed

at identifying individuals at risk for systemic disease in community or primary care settings (Poplin et al., 2020; Rim et al., 2021; Ting et al., 2021). This is especially pertinent for countries with unequal healthcare access, including settings in Latin America such as Mexico, Colombia, and Ecuador, where portable and efficient screening strategies could strengthen early intervention frameworks.

Taken together, this figure demonstrates that the reviewed literature conceptualizes ocular biomarkers primarily as tools for **anticipatory medicine**. Their greatest current value lies in detecting disease earlier, stratifying systemic risk, and supporting longitudinal assessment. At the same time, the emergence of interdisciplinary and public health applications indicates that the field is gradually expanding beyond specialist ophthalmic practice toward more integrated diagnostic and preventive models. This distribution reinforces the idea that the future of ocular biomarkers is not limited to eye disease itself, but increasingly linked to broader strategies in systemic medicine and population health.

Figure 6.

Temporal distribution of publications on ocular biomarkers and systemic health (2020–2024)

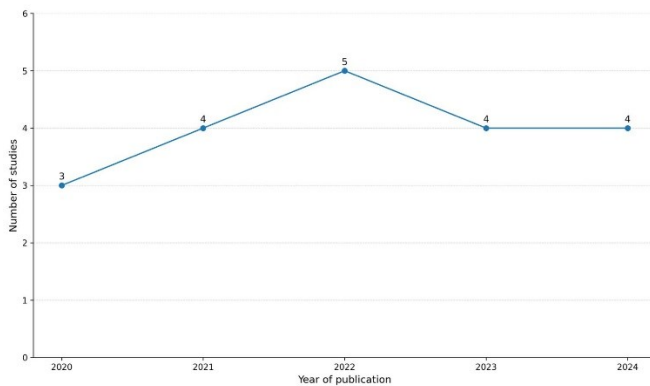


Figure 6 illustrates the temporal distribution of the selected studies published between 2020 and 2024, showing a progressive increase in research output, with a peak observed around 2022, followed by a sustained level of high scientific production in subsequent years.

The upward trend from 2020 to 2022 reflects a period of rapid expansion in the field of ocular biomarkers, driven by advancements in retinal imaging technologies and the integration of artificial intelligence into ophthalmology. During this period, multiple high-impact studies established foundational evidence linking retinal changes with systemic diseases, particularly in cardiovascular and neurodegenerative domains (Wagner et al., 2020; London et al., 2020; Ting et al., 2021). This surge in research activity suggests a growing recognition of ophthalmology as a key contributor to systemic diagnostics.

The peak observed in 2022 may be attributed to the consolidation of interdisciplinary research efforts and the increasing availability of large datasets for analysis. Studies published during this time frequently explored the application of deep learning models in retinal imaging, as well as the validation of ocular biomarkers across different populations (Rim et al., 2021; Fleischer et al., 2022). This period marks a transition from exploratory research to more structured and application-oriented investigations.

From 2023 to 2024, the number of studies remains relatively stable, indicating a phase of maturation in the field. Rather than a decline in interest, this stabilization likely reflects a shift toward refining methodologies, validating findings, and exploring clinical implementation. Research during these years has focused more on improving diagnostic accuracy, integrating multimodal imaging, and addressing challenges related to standardization and reproducibility (Van Wijngaarden et al., 2021).

The sustained level of publications in recent years also highlights the continued relevance of ocular biomarkers in the context of global health. As healthcare systems increasingly prioritize early detection and preventive strategies, the demand for non-invasive and scalable diagnostic tools has reinforced the importance of retinal imaging and oculomics.

DISCUSIÓN

The findings synthesized in this review support the growing recognition of ophthalmology as a clinically relevant gateway to systemic health assessment. Across the selected studies, ocular biomarkers consistently demonstrated meaningful associations with vascular, metabolic, renal, and neurodegenerative conditions, reinforcing the idea that retinal and neuroretinal structures function as accessible indicators of broader biological processes. Rather than being confined to the diagnosis of primary ocular disease, retinal imaging is increasingly positioned within a multidisciplinary diagnostic framework capable of informing risk estimation, early detection, and longitudinal follow-up of systemic disorders (Wagner et al., 2020; London et al., 2020).

One of the most important observations derived from the reviewed literature is the strong convergence between retinal vascular findings and systemic cardiovascular pathology. Changes in arteriolar narrowing, venular widening, vessel tortuosity, and perfusion abnormalities have repeatedly been associated with hypertension, endothelial dysfunction, and cardiovascular risk burden (Cheung et al., 2020; Sabanayagam et al., 2020). These findings are especially relevant because they support a pathophysiological interpretation in which the retina serves as a visible microvascular bed reflecting systemic hemodynamic stress. In contrast to conventional cardiovascular assessment, which often depends on laboratory findings or imaging directed at larger vessels and target organs, retinal imaging offers a non-invasive microcirculatory perspective that may reveal subclinical damage earlier in the disease course. This does not replace established cardiovascular diagnostics, but it does add a layer of clinically useful information that may enrich preventive strategies and risk stratification models.

The discussion becomes even more compelling in the neurodegenerative domain, which emerged as the most represented area in the reviewed literature. This predominance is not incidental. The retina shares embryological and anatomical continuity with the central nervous system, and several studies have shown that structural retinal changes correlate with cognitive decline, brain MRI findings, and neurodegenerative disease markers (Ong et al., 2020; Mutlu et al., 2021; McGrory et al., 2021). From a conceptual standpoint, this reinforces the notion that retinal thinning and microvascular disruption are not isolated ocular phenomena, but part of a larger neurobiological process. The relevance of this lies in the possibility that ophthalmic imaging may contribute to earlier neurological suspicion in individuals who have not yet developed fully expressed cognitive symptoms. In clinical practice, this could be particularly valuable in aging populations, where the burden of dementia and cerebrovascular disease continues to grow and where accessible biomarkers remain limited.

At the same time, the literature indicates that the relationship between ocular biomarkers and neurodegenerative disease is promising but not yet fully standardized. Some variability persists regarding which retinal layers, vascular measurements, or peripheral retinal findings are most reproducible across populations and imaging platforms (Csincsik et al., 2021; Van Wijngaarden et al., 2021; Fleischer et al., 2022). This is a critical point because it tempers overly simplistic interpretations. The retina clearly offers biologically meaningful information, but the transition from research association to routine neurological screening still depends on harmonization of protocols, validation in diverse cohorts, and stronger longitudinal evidence. The field is moving in that direction, but it has not yet reached full methodological uniformity.

The metabolic dimension of ocular biomarkers also deserves particular attention. Diabetic retinopathy has long been recognized as a classic example of systemic disease expressed in the eye, but the studies included in this review expand that perspective by showing that retinal and neuroretinal changes may occur even before advanced or clinically overt retinal disease develops (Vujosevic & Midena, 2020). This is significant because it shifts the role of ophthalmology from the documentation of established diabetic complications toward the detection of early systemic dysregulation. In broader terms, it supports the emerging idea that retinal tissue can act as a sensor of metabolic stress, chronic inflammation, and microvascular compromise. Although metabolic disorders were less numerous than neurological or

vascular topics in the final selection, the reviewed evidence suggests that their diagnostic relevance remains substantial, especially in preventive medicine and screening-oriented contexts.

A similar argument applies to chronic kidney disease. The reviewed studies indicate that retinal microvascular abnormalities and renal dysfunction are linked through shared mechanisms such as endothelial injury, microcirculatory compromise, and inflammatory burden (Sabanayagam et al., 2021; Nusinovič et al., 2021). While the renal category was less represented numerically, its inclusion broadens the systemic implications of ocular biomarkers. It suggests that the eye can reflect not only cardiovascular and cerebral injury, but also cardiorenal interactions that are central to chronic disease progression. This is especially valuable in primary care or resource-limited settings, where access to specialized nephrological evaluation may be delayed. A retinal finding is not sufficient to diagnose kidney disease, but it may serve as an early alert that prompts further systemic assessment.

Another major theme arising from the review is the transformative role of artificial intelligence in ophthalmology. Several high-impact studies have shown that AI models can infer systemic characteristics from retinal images with a level of performance that substantially expands the traditional boundaries of ophthalmic interpretation (Poplin et al., 2020; Rim et al., 2021; Ting et al., 2021). This is not simply a technical enhancement; it represents a conceptual shift. The retinal image is no longer only a visual record interpreted by the clinician, but also a dense source of latent biological information that computational models can extract and translate into predictive outputs. In practical terms, this could enable scalable screening systems capable of identifying individuals at risk of systemic disease from a rapid, non-invasive examination.

However, the discussion around AI must remain balanced. High predictive performance in controlled studies does not automatically guarantee equivalent utility in real-world clinical implementation. Algorithmic validity depends on image quality, dataset diversity, external validation, and the clinical context in which predictions are used (Chua et al., 2021; Ting et al., 2021). Models trained in one population may not perform identically in another, particularly in regions with differences in ethnicity, disease prevalence, access to care, and imaging infrastructure. For this reason, the integration of AI into ophthalmology should not be reduced to technological enthusiasm; it requires rigorous validation, transparent performance reporting, and careful adaptation to local healthcare systems. This point is particularly relevant for Latin American contexts such as Mexico, Colombia, and Ecuador, where implementation potential is high, but where infrastructure, digital interoperability, and resource distribution may vary significantly across institutions.

The reviewed evidence also underscores the importance of imaging modality selection. Fundus photography remains highly valuable because of its accessibility, cost-effectiveness, and compatibility with large-scale screening programs, especially when enhanced by computational analysis (Poplin et al., 2020; Sabanayagam et al., 2020). OCT, by contrast, offers superior structural detail and has become central to the assessment of neuroretinal change (Ong et al., 2020; Mutlu et al., 2021). OCTA contributes an additional vascular dimension by enabling non-invasive assessment of capillary perfusion and microvascular architecture (De Carlo et al., 2020; Kashani et al., 2020). The discussion, therefore, should not frame these modalities as competitors, but as complementary tools that answer different biological questions. The strongest diagnostic potential likely lies in multimodal integration, where vascular, structural, and computational information converge.

This integrative perspective is one of the main strengths of the current field. Ocular biomarkers do not derive their value from a single parameter, but from the combined interpretation of vessel morphology, retinal thickness, perfusion patterns, and increasingly, algorithmic prediction. Such integration aligns with broader trends in precision medicine, where meaningful diagnosis depends on combining multiple layers of information rather than relying on one isolated sign. In that sense, ophthalmology is aligning itself with a systems-based model of medicine, in which the eye becomes a practical and information-rich interface between clinical observation and systemic biology.

The present review also highlights several methodological limitations that should be acknowledged. First, much of the available literature remains cross-sectional, which limits causal inference. Associations between ocular biomarkers and systemic disease are strong and recurrent, but longitudinal studies are still needed to determine predictive timing, progression dynamics, and clinical impact over time (Fleischer et al., 2022; Van Wijngaarden et al., 2021). Second, heterogeneity in imaging protocols, software segmentation, outcome definitions, and patient selection complicates

direct comparison across studies. Third, not all studies evaluate diverse or underrepresented populations, which affects external validity. This is particularly important if ocular biomarkers are expected to become part of global screening strategies.

Despite these limitations, the overall direction of the evidence is coherent. The retina is emerging as a biologically meaningful and clinically practical site for systemic observation. The consistency of associations across cardiovascular, neurological, renal, and metabolic domains suggests that ocular biomarkers are not isolated curiosities, but part of a broader diagnostic frontier with real translational potential. Their greatest strength lies not in replacing conventional systemic diagnostics, but in complementing them through earlier, safer, and more accessible insight.

From an international perspective, the implications are especially relevant. Countries such as Mexico, Colombia, and Ecuador face persistent challenges in early diagnosis, access to specialist care, and chronic disease control. In such settings, retinal imaging could provide a strategically valuable bridge between ophthalmology, internal medicine, neurology, nephrology, endocrinology, and public health. Portable imaging devices, teleophthalmology, and AI-assisted interpretation could facilitate more decentralized models of screening and triage, particularly in underserved populations. Although implementation requires infrastructure and validation, the potential benefit is considerable because the technology is non-invasive, increasingly scalable, and adaptable to multiple levels of care.

In summary, the reviewed literature supports the view that ocular biomarkers occupy an expanding and increasingly sophisticated role in modern medicine. The strongest evidence currently exists in neurodegenerative and vascular disease, but meaningful contributions are also evident in renal and metabolic health. Technological advances, especially in OCT, OCTA, multimodal imaging, and predictive analytics, are accelerating this transition. The field now faces a new challenge: moving from promising association to standardized application. Achieving this will depend on better longitudinal evidence, stronger methodological harmonization, and interdisciplinary collaboration capable of translating ocular findings into clinically actionable systemic insight.

CONCLUSIÓN

The present review highlights the progressive transformation of ophthalmology into a multidisciplinary diagnostic field with significant implications for systemic health assessment. The accumulated evidence demonstrates that ocular biomarkers—particularly those derived from retinal imaging—provide consistent and clinically relevant information associated with vascular, neurodegenerative, metabolic, and renal diseases. This reinforces the concept of the retina as a unique and accessible interface capable of reflecting systemic physiological and pathological processes in vivo.

One of the most relevant conclusions is that ocular biomarkers offer a **non-invasive, reproducible, and scalable approach** for the early identification of systemic alterations. Their ability to detect subclinical changes positions them as valuable tools within preventive medicine, especially in conditions where early intervention can significantly modify disease progression. In this context, retinal imaging extends beyond its traditional role in ophthalmology and becomes an important component of integrated diagnostic strategies.

The evidence also underscores that the strongest associations currently exist in the domains of **neurodegenerative and cardiovascular diseases**, where retinal structural and microvascular changes closely parallel systemic pathology. However, meaningful correlations have also been identified in metabolic and renal conditions, suggesting that ocular biomarkers provide a broad and integrative perspective of systemic health rather than being limited to a single disease category.

Technological advancements have played a central role in this evolution. Imaging modalities such as OCT and OCTA, combined with artificial intelligence and multimodal analytical approaches, have significantly enhanced the sensitivity and predictive capacity of ocular diagnostics. These developments have shifted ophthalmology toward a more **data-driven and predictive discipline**, capable of contributing to personalized medicine and large-scale screening programs.

Despite these advances, important challenges remain. Variability in imaging protocols, lack of standardization in biomarker interpretation, and limited longitudinal evidence continue to restrict the full clinical integration of ocular

biomarkers. Addressing these limitations will be essential to ensure their reliability, reproducibility, and applicability across diverse populations.

From a global health perspective, the implications are particularly relevant for regions with heterogeneous access to healthcare, such as Latin America. In countries like Mexico, Colombia, and Ecuador, the implementation of retinal imaging as a screening and diagnostic tool could enhance early detection strategies, improve risk stratification, and support more efficient allocation of healthcare resources. The non-invasive nature and scalability of these technologies make them especially suitable for integration into primary care and community-based programs.

In conclusion, ocular biomarkers represent a rapidly expanding frontier in modern medicine, bridging ophthalmology with systemic disease diagnostics. Their integration into clinical practice has the potential to improve early detection, optimize patient management, and contribute to more comprehensive and preventive healthcare models. Future research should focus on standardization, longitudinal validation, and interdisciplinary implementation to fully realize the clinical and public health potential of this emerging field.

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