Ocular surface pathology and the liver-eye axis; ophthalmological manifestations as early potential clinical indicators of chronic liver disease: A scoping review

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Abstract. Dry eye disease (DED) has traditionally been considered a local disorder of the ocular surface. However, accumulated evidence indicates that DED often reflects systemic metabolic, immune and neurosensory disorders. In recent years, interest has grown in interorgan interactions, particularly the 'liver-ocular surface' axis, given the central role of the liver in regulating lipid metabolism, vitamin metabolism, systemic inflammation and immune tolerance. The aim of the present scoping review was to summarize and structure published data on ocular manifestations of various forms of chronic liver disease, analyze key pathogenetic mechanisms of the 'liver-ocular surface' axis, identify gaps in the evidence base, and evaluate the clinically oriented 'ophthalmology-first' concept, wherein atypical or refractory DED may precede the diagnosis of liver pathology. The present scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews recommendations. Only peer-reviewed publications from ophthalmology, hepatology and interdisciplinary journals addressing the epidemiology, pathogenesis and clinical phenotypes of DED in liver diseases were included. A meta-analysis was not planned due to significant heterogeneity in study designs, populations and ophthalmological outcomes. It was established that chronic liver diseases can affect the ocular surface through several interconnected pathogenetic mechanisms, including impaired vitamin A metabolism, systemic inflammation and immune dysregulation, dyslipidemia with meibomian gland dysfunction, and neurosensory disorders. These mechanisms are closely associated with specific clinical phenotypes of DED, often characterized by atypical or refractory course, the disproportionate severity of objective changes and reduced corneal sensitivity. DED should be viewed not only as a local ophthalmological pathology, but also as a potential indicator of systemic disorders, including subclinical liver dysfunction. The 'ophthalmology-first' concept emphasizes the diagnostic role of the ophthalmologist in the early detection of chronic liver diseases and justifies the need for an interdisciplinary approach in managing patients with severe and atypical forms of DED.

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Abbreviations: DED, dry eye disease; IL, interleukin; MASLD, metabolic dysfunction-associated steatotic liver disease; MeSH, medical subject headings; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; TNF-α, tumor necrosis factor-α

Key words: dry eye disease, ocular surface, liver diseases, MASLD, vitamin A, systemic inflammation, ophthalmology-first, liver-eye axis

Introduction

Dry eye disease (DED) is currently defined as a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis, accompanied by inflammation, hyperosmolarity and neurosensory abnormalities (1). According to the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) consensus, the key pathophysiological event in DED is the disruption of tear film stability, followed by a cascade of epithelial damage and sensitization of corneal afferent nerve pathways (1,2). Epidemiological studies have demonstrated that the prevalence of DED varies from 5 to 50%, depending on the diagnostic criteria used, as well as the geographic and demographic characteristics of the population (3,4). The pathogenesis of DED involves a sophisticated network of interconnected etiological factors. Central to this condition is the disruption of ocular homeostasis, primarily driven by tear film instability and hyperosmolarity. These elements function as catalysts for the induction and chronic propagation of inflammatory responses within the ocular surface tissues. Consequently, this inflammatory milieu may contribute to the development of neurosensory abnormalities and subsequent disruption of visual function (5).

Increasing data indicate an association between DED and systemic diseases, namely metabolic, autoimmune, endocrine and chronic inflammatory conditions, that goes beyond viewing DED as solely a local ophthalmological pathology (3,4). These observations have contributed to the formation of the concept of DED as a 'systemic phenotype', reflecting the overall metabolic and immune state of the organism (3,4). Traditionally viewed as an age-related ophthalmological inconvenience or one linked to contact lens use, DED warrants a paradigm shift based on the findings of the Lifelines study (6). Some researchers have identified DED associations with comorbidities across nearly all bodily systems, including musculoskeletal, psychiatric, and notably gastrointestinal and hepatic systems (6,7). In recent years, specific attention has been given to interorgan interactions, particularly the formation of the 'liver-eye axis'. The liver serves as the central organ for lipid, vitamin, bile acid and hormone metabolism, as well as a key immunological filter regulating the systemic inflammatory response (7,8). Liver dysfunction is accompanied by the development of chronic systemic inflammation, oxidative stress and an altered neuroendocrine regulation, which can potentially exert direct and indirect effects on tear film homeostasis and the ocular surface condition (7,9).

Despite the existence of individual clinical and review publications dedicated to the ophthalmic manifestations of chronic liver diseases, the majority of these consider ocular surface pathology primarily as a secondary complication of already diagnosed liver dysfunction (7,8). The present scoping review proposes an alternative, clinically oriented perspective, in which ophthalmic symptoms particularly atypical or refractory DED are viewed as a potential entry point for detecting subclinical liver pathology. Unlike previously published works, the present scoping review systematizes the pathophysiological mechanisms of the 'liver-ocular surface' axis from the standpoint of DED phenotyping, with an emphasis on the ophthalmologist's diagnostic vigilance, thereby expanding the clinical interpretation of ocular surface homeostasis disruptions and justifying an interdisciplinary approach to early detection of chronic liver diseases.

Data and methods

Literature search methods. The present scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. As detailed in the PRISMA 2020 flow diagram (Fig. 1), a total of 76 records were initially identified from databases and registers. Prior to screening, 11 duplicate records were removed. Of the remaining 65 records that were screened for relevance, 16 were excluded. Subsequently, all 49 reports sought for retrieval were successfully retrieved. These 49 reports were then assessed for eligibility, which resulted in the exclusion of six reports: One for ineligible study design, four for ineligible outcomes, and one due to reporting outcomes with odds ratios (OR) only. Consequently, a total of 42 studies were included in the present systematic review, encompassing a range of designs, including clinical and prospective studies (n=12), specialized reviews (n=9), case reports (n=6), and large cohort/epidemiological studies (n=4). This methodological approach was selected to systematically map and synthesize heterogeneous data regarding the association between chronic liver diseases and ocular surface pathology. Furthermore, it facilitates a conceptual analysis of clinically-oriented models, including the 'ophthalmology-first' scenario, where ophthalmic manifestations may precede the diagnosis of underlying hepatic pathology.

Literature search strategy. A comprehensive literature search was conducted across the PubMed/MEDLINE, Scopus and Web of Science international databases (Table I). The present scoping review included articles published between 2000 and 2025, a period reflecting the contemporary evolution of the concept of DED as a systemic phenotype and the emerging understanding of the 'liver-ocular surface' axis. The search strategy employed combinations of keywords and Medical Subject Headings (MeSH) terms, including: 'dry eye disease', 'ocular surface', 'cornea', 'liver disease', 'chronic liver disease', 'non-alcoholic fatty liver disease (NAFLD)', 'metabolic dysfunction-associated steatotic liver disease (MASLD)', 'cholestasis', 'cirrhosis', 'vitamin A deficiency', 'meibomian gland dysfunction' and 'systemic inflammation'. In addition, the reference lists of key reviews and original studies were manually screened to identify relevant publications that may have been missed during the primary database search.

Inclusion and exclusion criteria. The present scoping review included peer-reviewed publications that met the following eligibility criteria: The inclusion criteria were the following: i) Original clinical studies, systematic and narrative reviews and scoping reviews; ii) studies focused on the epidemiology, pathogenesis, or clinical manifestations of DED and/or ocular surface pathology in patients with chronic liver diseases; iii) publications in ophthalmology, hepatology and multidisciplinary scientific journals; iv) articles published in the English language. The following exclusion criteria were used: i) Isolated case reports without an analytical component; ii) experimental studies lacking clinical interpretation; iii) non-peer-reviewed sources (textbooks, clinical websites, expert blogs), unless used exclusively to illustrate well-established clinical context.

Data selection and analysis process. The selection of publications was conducted in stages, beginning with the screening of titles and abstracts, followed by a full-text analysis of articles meeting the inclusion criteria. Data extracted from the selected publications included the type of liver disease, ophthalmic manifestations, proposed pathogenetic mechanisms and clinical phenotypes of DED. Given the significant heterogeneity in study designs, patient populations, types of chronic liver diseases and reported ophthalmic outcomes, a formal systematic review with a meta-analysis was not planned. The primary objective of the analysis was the qualitative integration of data and the development of a conceptual model reflecting the pathophysiological and clinical interconnections of the 'liver-ocular surface' axis.

Results

Data synthesis approach. Data synthesis in the present scoping review was performed narratively, with a focus on

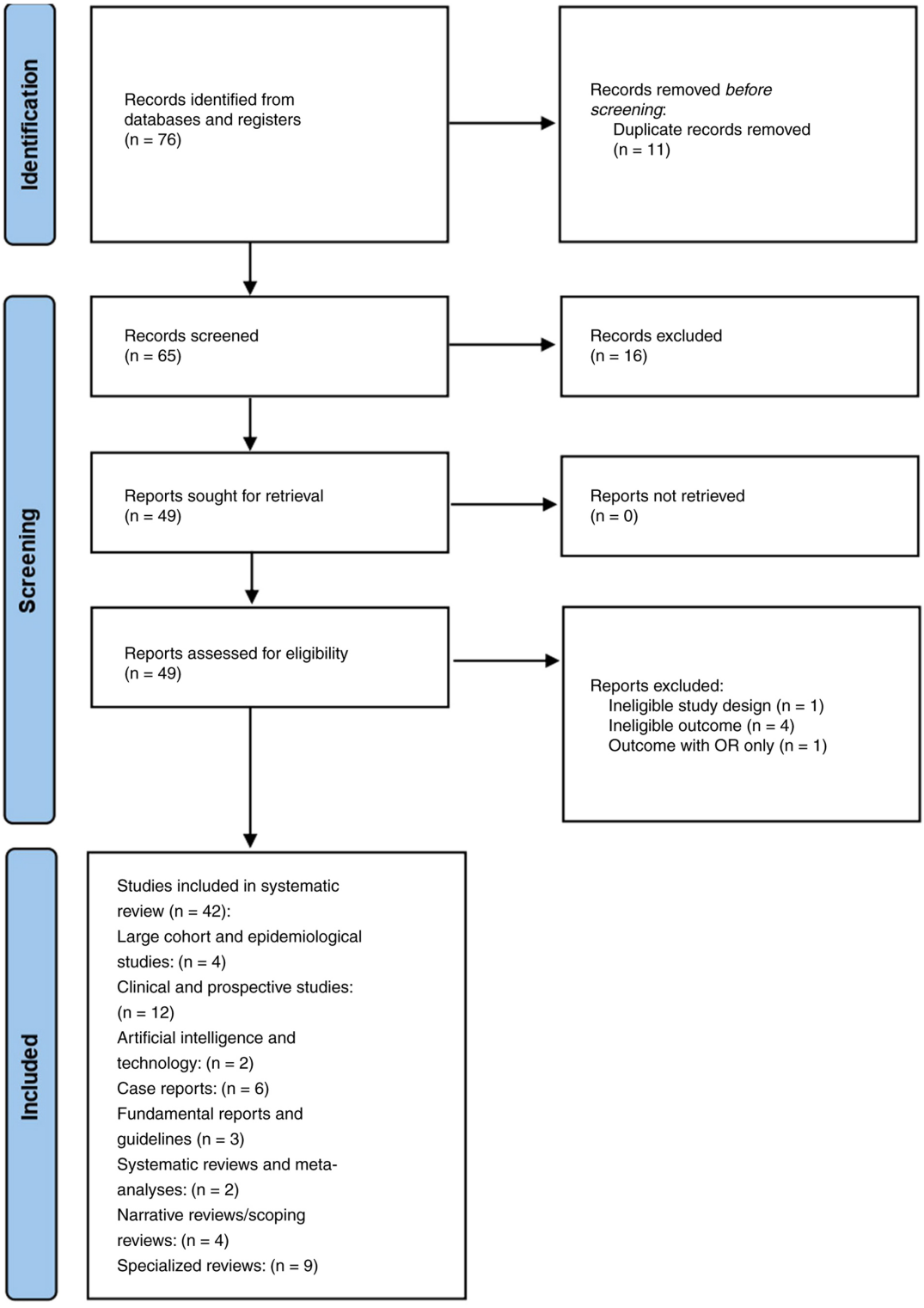

Figure 1. PRISMA 2020 flow diagram of the study selection process and evaluation outcomes.

integrating pathophysiological and clinical evidence derived from heterogeneous sources. The analysis aimed to identify and systematize the key mechanisms through which chronic liver diseases impact the ocular surface, including impaired vitamin A metabolism, persistent systemic inflammation, immune dysregulation, alterations in lipid metabolism may contribute to meibomian gland dysfunction and neurosensory disorders (Table II).

Particular attention was given to characterizing the typical clinical phenotypes of dry eye disease associated with various types of chronic liver disease, emphasizing their pathogenetic features, clinical course, and potential resistance to standard ophthalmic therapies. This phenotypic analysis facilitated the correlation of ocular manifestations with specific systemic mechanisms and stages of hepatic dysfunction. Furthermore, the clinical significance of the identified ophthalmic findings

Table I. Detailed literature search strategy.

Database	Search query (search strings)	Filters/limits
PubMed/MEDLINE	('Dry Eye Syndromes'[Mesh] OR 'Keratoconjunctivitis Sicca' OR 'Meibomian Gland Dysfunction' OR 'Ocular Surface') AND ('Liver Diseases'[Mesh] OR 'Chronic Liver Disease' OR 'NAFLD' OR 'MASLD' OR 'Liver Cirrhosis' OR 'Cholestasis')	Years: 2000-2025; Language: English; Species: Humans.
Scopus	TITLE-ABS-KEY [('dry eye' OR 'ocular surface' OR 'meibomian gland') AND ('liver disease' OR 'cirrhosis' OR 'hepatitis' OR 'steatotic liver')]	Document type: Article, Review; Language: English.
Web of Science	TS=(('dry eye' OR 'keratoconjunctivitis sicca' OR 'ocular surface') AND ('chronic liver disease' OR 'NAFLD' OR 'MASLD' OR 'cirrhosis'))	Timespan: 2000-2025; Language: English.

Table II. Summary of the included studies on the liver-ocular surface axis.

Category/pathogenetic axis	Study types	Primary findings and ocular manifestations	(Refs.)
General overview and epidemiology	Population-based cohorts, scoping reviews	Prevalence of DED in liver disease; identification of risk factors and systemic comorbidities.	(6-8,33,37)
Vitamin A and metabolic axis	Case reports, clinical reviews	Link between hepatic Vitamin A storage (Ito cells) and xerophthalmia, keratomalacia, and goblet cell loss.	(10-13,27)
Immune-mediated/viral hepatitis	Prospective studies, Multicenter trials	Association of HCV with Sjögren's-like syndrome and immune-complex-mediated inflammation.	(18,19,21,22,24-26)
Autoimmune liver diseases (PBC, AIH)	Case-control studies, clinical reviews	Overlap between primary biliary cholangitis (PBC) and severe aqueous-deficient DED; uveitis in AIH.	(27-29,31,32)
Dyslipidemia and meibomian gland dysfunction	Meta-analyses, cross-sectional studies	Correlation between serum lipid profiles (cholesterol, triglycerides) and MGD severity/tear film instability.	(34-36,38-41)
Advanced cirrhosis and neurosensory changes	Prospective pilot studies, clinical trials	Changes in corneal endothelial density, microcirculation, and evoked potentials in decompensated cirrhosis.	(9,14-16)

was analyzed in the context of early detection of subclinical hepatic pathology. Within this framework, clinical scenarios were evaluated where atypical or severe DED could serve as a primary indicator of systemic imbalance, justifying a broader multidisciplinary evaluation of the patient. To enhance clarity and clinical utility, the results were structured using tables and conceptual models that summarize the interconnections between the type of hepatic pathology, pathophysiological mechanisms, and ophthalmic phenotypes. This approach was selected to facilitate the translation of the findings of the review into practical ophthalmic and multidisciplinary clinical settings.

Discussion

Mechanistic insights into the 'liver-ocular surface' axis: Disruption of Vitamin A Metabolism. The liver serves as the primary reservoir for Vitamin A, sequestering 70-80% of total body stores within hepatic stellate cells (Ito cells) as retinal esters. Systemic retinoid availability is subsequently regulated through the hepatic synthesis of retinol-binding protein 4 (RBP4) (7,8). In the retina, vitamin A plays a pivotal role in phototransduction, the conversion of light into electrical signals. When hepatic functions are impaired, the storage and transport mechanisms of vitamin A are compromised, which may contribute to localized deficiency of retinoid within the eye (10).

In chronic liver diseases, particularly cholestatic and cirrhotic forms, both the storage and mobilization mechanisms of vitamin A are compromised (Fig. 2). This results in a functional retinoid deficiency that persists, regardless of adequate dietary intake. This also results in the development of a functional retinoid deficiency, which persists even in the presence of adequate dietary intake (8,9).

The pathogenesis of vitamin A deficiency in liver disease is multifactorial: i) Loss of storage capacity: The progression of fibrosis activates hepatic stellate cells, leading to a diminished capacity for retinoid storage (7). ii) Impaired absorption: Cholestasis reduces the intestinal absorption of fat-soluble

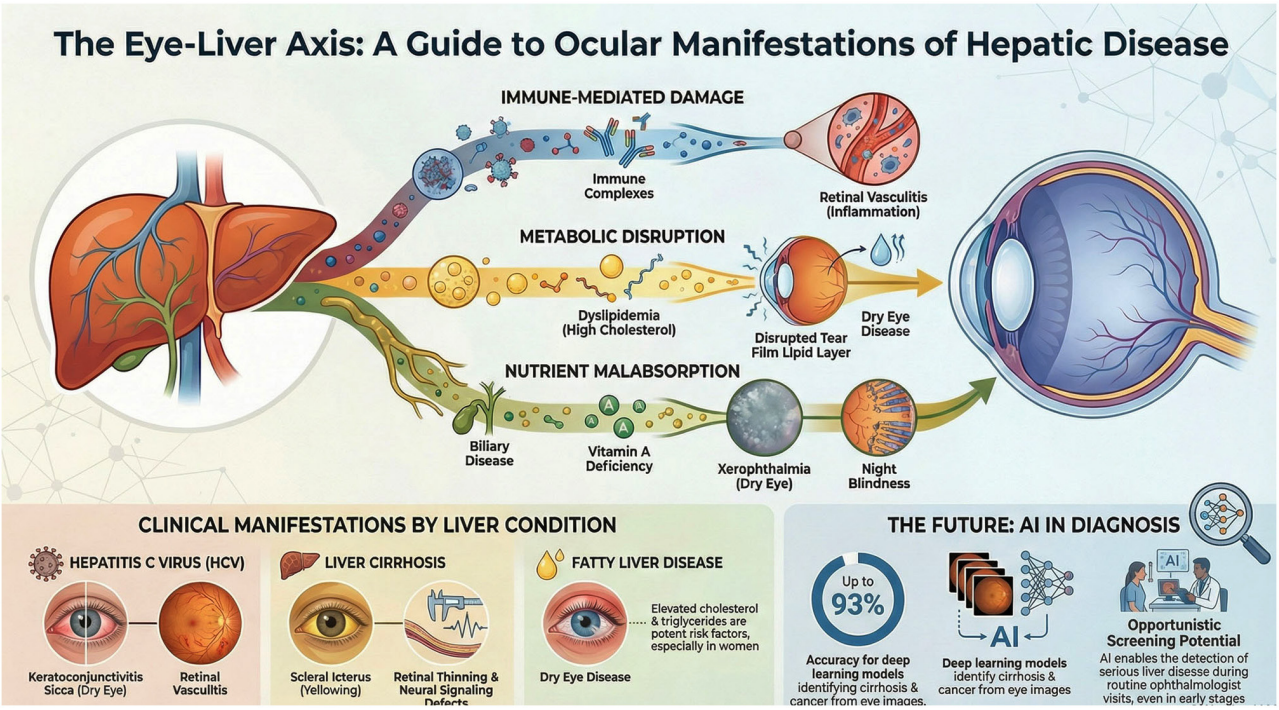

Figure 2. Illustration depicting the association between the eye-liver axis and hepatic disease.

vitamins due to bile acid deficiency (8). iii) Transport failure: In decompensated cirrhosis, reduced synthesis of transport proteins (RBP4 and transthyretin) impairs retinoid delivery to peripheral tissues, including the ocular surface (9).

At the cellular level, itamin A deficiency disrupts the differentiation of corneal and conjunctival epithelial cells, resulting in decreased goblet cell density and reduced mucin expression (1,3,8). This mucin-deficient state compromises tear film stability, rendering the corneal epithelium vulnerable to osmotic and mechanical stress, which may contribute to the initiation of the inflammatory cascade characteristic of DED (11). Clinically, these changes manifest as severe epitheliopathy, filamentary keratitis, and recurrent corneal erosions (8,9). Prolonged and severe deficiency may progress to xerophthalmia, featuring squamous metaplasia and colliquative stromal necrosis. These manifestations are most pronounced in patients with primary biliary cholangitis and decompensated cirrhosis, where cholestasis and systemic nutritional deficits create an unfavorable environment for ocular surface homeostasis (8,9).

Systemic inflammation and immune dysregulation. Chronic liver diseases are accompanied by the persistent activation of innate immunity, characterized by elevated systemic levels of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β, as well as the disruption of immune tolerance mechanisms (7,9). These mediators originate from activated Kupffer cells, monocytes, and other innate immunity effector cells, sustaining a state of chronic low-grade inflammation typical of cirrhosis, MASLD and cholestatic liver diseases (7).

Pro-inflammatory cytokines exert both direct and indirect effects on ocular surface structures. At the level of lacrimal glands, they promote acinar cell apoptosis, reduce secretion of the aqueous component of the tear film, and alter its protein composition (1,9). Systemic inflammation disrupts the differentiation and the lipid metabolism of meibocytes in the meibomian glands, which may contribute to altered meibum quality and the formation of an unstable lipid layer in the tear film (1,2). The cytokine-mediated activation of corneal and conjunctival epithelial cells simultaneously enhances the expression of adhesion molecules and pro-inflammatory mediators, forming a self-sustaining inflammatory cascade characteristic of DED (1,3).

An additional pathogenetic link involves the dysregulation of the adaptive immune response. In chronic liver diseases, an imbalance occurs between regulatory T-cells and effector Th1/Th17 populations, promoting autoimmune activation and the loss of peripheral tolerance (7,8). These mechanisms hold particular clinical significance when liver pathology combines with autoimmune diseases, particularly secondary Sjögren's syndrome. In secondary Sjögren's syndrome associated with autoimmune and cholestasis liver diseases (including primary biliary cholangitis), the lymphocytic infiltration of the lacrimal glands develops, which may contribute to the progressive destruction of their secretory apparatus (8,9). Evidence suggests that these mechanisms may be associated with the development of an aqueous-deficient DED phenotype. This manifestation, marked by reduced tear production and inflammation, appears to be more resistant to standard ophthalmic interventions, although further prospective studies are required to confirm this therapeutic resistance (1,9). In clinical practice, such patients often exhibit refractory DED, necessitating immunomodulatory and interdisciplinary treatment approaches. Thus, systemic inflammation and immune dysregulation in chronic liver diseases form the pathogenetic basis of the inflammatory DED phenotype, exacerbated by autoimmune comorbidities, underscoring the need to assess

systemic status in patients with severe or atypical ocular surface disease courses.

Dyslipidemia and meibomian gland dysfunction. The liver plays a key role in regulating lipid metabolism, ensuring the synthesis, modification, and clearance of lipoproteins, fatty acids and cholesterol, while also controlling systemic lipid homeostasis (7). In MASLD and other metabolic hepatopathies, a characteristic dyslipidemia profile develops, including elevated triglyceride levels, altered low-density to high-density lipoprotein ratios, and the accumulation of atherogenic and pro-inflammatory lipid fractions (7,9). These systemic changes affect not only the vascular bed, but also the lipid composition of secretions from exocrine glands, including the meibomian glands of the eyelids.

Meibomian glands are specialized sebaceous glands that secrete a complex mixture of non-polar and polar lipids (meibum), forming the outer lipid layer of the tear film. Alterations in systemic lipid metabolism in MASLD may contribute to disrupted meibocyte differentiation, changes in meibum qualitative composition, and an increased proportion of saturated and pro-inflammatory lipids (1,2). These changes impair the fluidity and spreading of the lipid layer, reducing its ability to prevent evaporation of the tear film's aqueous component (1).

An additional pathogenetic factor is the systemic chronic inflammation characteristic of MASLD, in which pro-inflammatory cytokines and lipotoxic metabolites exacerbate meibomian gland dysfunction, contributing to obstruction of the excretory ducts and formation of subclinical meibomian gland dysfunction (7). As a result, tear film instability develops with accelerated evaporation, increased osmolarity, and secondary activation of the inflammatory cascade on the ocular surface (1,3).

Thus, in metabolic liver pathology, DED often manifests as an evaporative phenotype associated with meibomian gland dysfunction, even in the absence of pronounced local risk factors such as ophthalmic surgery, contact lens correction, or adverse environmental conditions (2,7). This DED phenotype may remain underrecognized in clinical practice, as classical signs of ocular surface inflammation often combine with moderate subjective symptoms, underscoring the importance of considering the patient's systemic metabolic status when evaluating is associated with of tear film instability.

Neurosensory impairments. According to the neurosensory concept of dry eye syndrome, chronic inflammation and tear film hyperosmolarity may contribute to structural and functional damage of corneal afferent nerve endings, the disruption of their excitability, and altered central processing of sensory signals (1,2). These processes are accompanied by a reduction in the density of the subbasal nerve plexus, altered expression of neurotrophic factors, and the dysregulation of the 'cornea-lacrimal gland' reflex arc, which exacerbates tear film instability and perpetuates the vicious cycle of DED (1). In chronic liver diseases, neurosensory impairments may be exacerbated by systemic neurometabolic mechanisms. Liver dysfunction is accompanied by the accumulation of neurotoxic metabolites (including ammonia and aromatic amino acids), the disruption of trace element metabolism, and altered neurotransmitter balance, which underlie hepatic encephalopathy, including its subclinical forms (7,9). Even in the absence of overt neurological symptoms, these changes can reduce the sensitivity of peripheral nerve endings, including corneal afferents, and disrupt sensory integration (7).

An additional factor is systemic inflammation characteristic of chronic liver diseases, in which pro-inflammatory cytokines (TNF-α and IL-6) exert neurotoxic effects, contributing to dysfunction of peripheral and central sensory pathways (7). Collectively, these mechanisms may contribute to reduced corneal sensitivity and altered perception of painful and discomforting stimuli from the ocular surface (1,9).

Clinically, these pathogenetic processes manifest as DED phenotypes where pronounced corneal epithelial changes and severe tear film instability combine with minimal or atypical subjective symptoms (1,2). Such a dissonance between objective findings and patient complaints represents an important diagnostic 'red flag' for the ophthalmologist and may indicate the presence of systemic neurometabolic disorders, including previously undiagnosed liver dysfunction (7). Recognizing this phenotype holds particular significance within the 'ophthalmology-first' concept, as it enables viewing reduced corneal sensitivity and neurosensory dysfunction as potential indicators of subclinical liver damage.

Clinical phenotypes of ocular manifestations in liver diseases. Ocular manifestations frequently accompany various metabolic disorders. Despite comprehensive biochemical, molecular and metabolic insights into many inherited metabolic disorders, their pathogenesis (particularly the link between systemic metabolic dysfunction and ocular pathology) remains poorly understood. Eye abnormalities may arise from direct toxicity of aberrant metabolites, accumulation due to synthetic pathway defects, or impaired energy metabolism (12). Chronic ocular surface desiccation may contribute to a spectrum of debilitating symptoms, ranging from foreign body sensation and blurred vision to sight-threatening complications such as epithelial erosions, corneal ulceration, and secondary infections (Table III). Consequently, the presence of keratoconjunctivitis sicca necessitates a comprehensive systemic evaluation to rule out Sjögren's syndrome and chronic liver disease (Fig. 3). While conservative management with lubricants may provide symptomatic relief, persistent or severe cases require urgent referral to an ophthalmologist for specialized intervention (13).

Liver cirrhosis and ocular manifestations. Due to the observed correlations between ocular morphometry and liver function, chorioretinal parameters can be utilized as non-invasive indicators of hepatic microvascular health. Specifically, significant declines in macular volume and retinal thickness have been associated with advancing cirrhosis across diverse etiologies (14). In patients with cirrhosis, regardless of the underlying etiology, whether viral, alcoholic, or related to non-alcoholic steatohepatitis, the clinical appearance of scleral icterus serves as a critical indicator of advanced hepatic dysfunction or an acute-on-chronic failure (15). Detecting minimal hepatic encephalopathy in patients with compensated cirrhosis is vital for preventing further neurological deterioration. Research indicates that visual electrophysiology

Table III. Association between hepatic pathology, ocular manifestations and pathophysiological mechanisms.

Hepatic pathology	Ocular manifestations	Pathophysiological mechanisms	(Refs.)
Hepatitis C virus	Keratoconjunctivitis sicca (Dry Eye syndrome), retinal vasculitis, ischemic retinopathy, 'cotton-wool' spots.	Deposition of circulating immune complexes, systemic immune activation, and cryoglobulinemia.	(19,21,22,24,26)
Autoimmune hepatitis	Uveitis, episcleritis, decreased basal tear secretion (Sjögren's-like syndrome).	Loss of systemic self-tolerance; autoantibody-mediated attack on exocrine glands and the uveal tract.	(18,29,31,32)
Liver cirrhosis	Eyelid xanthelasmas, conjunctival icterus, fundus vascular remodeling, delayed visual evoked potentials.	Dyslipidemia, portal hypertension, and accumulation of systemic neurotoxins (e.g., ammonia).	(9,14-16)
Liver cancer	Iris morphological shifts, retinal microvascular alterations (detected via AI-driven models).	Neoplastic toxemia, systemic metabolic shifts, and altered paraneoplastic angiogenesis.	(7,17)
Minimal hepatic encephalopathy	Impaired contrast sensitivity, subclinical neurophysiological deficits (mfVEP latency).	Astrocyte swelling due to hyperammonemia; disruption of neurotransmission in the visual cortex.	(16)
Non-alcoholic fatty liver disease/metabolic dysfunction-associated steatotic liver disease	Early-stage iris pigmentation changes, subtle retinal microvascular anomalies.	Chronic low-grade systemic inflammation and increased oxidative stress.	(7,34,35,38)
Cholestatic disorders (e.g., primary biliary cholangitis)	Xerophthalmia, nyctalopia (night blindness), Bitot's spots.	Malabsorption of bile-dependent fat-soluble vitamins (specifically vitamin A deficiency).	(8,11,27,28)

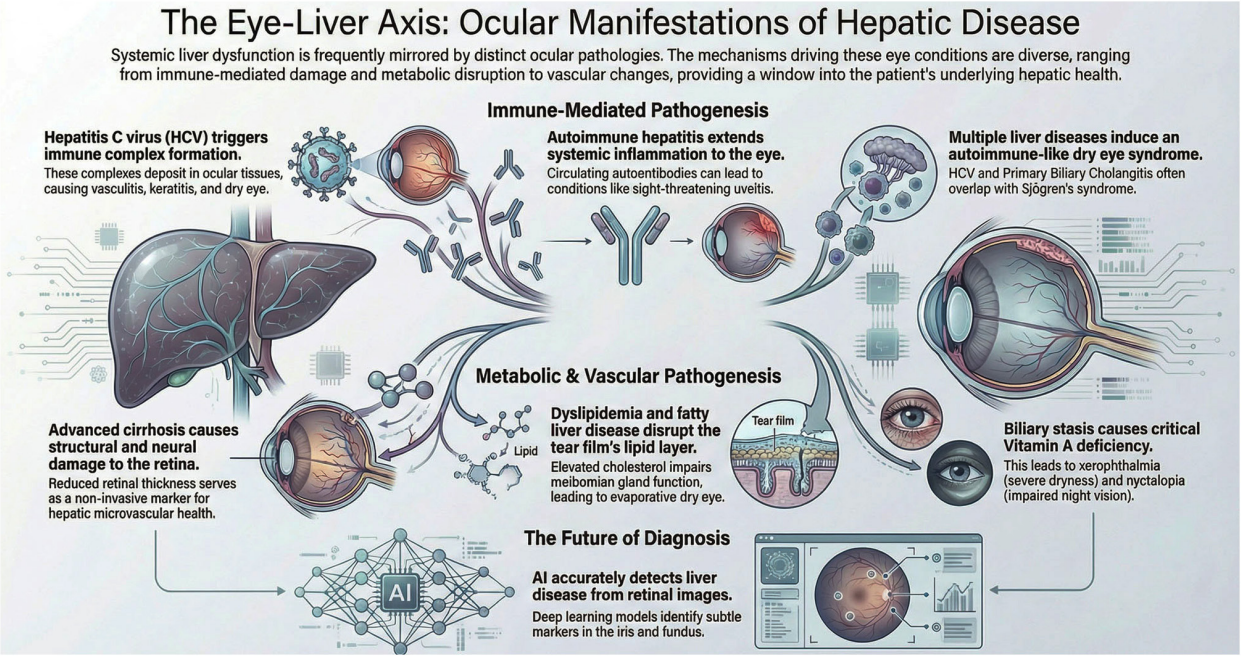

Figure 3. Illustration depicting the ocular manifestations of hepatic disease.

can reveal subtle abnormalities in neural signaling before they manifest as global cognitive impairment. These findings suggest that patients with cirrhosis, even those without overt encephalopathy, may harbor underlying visual-cortical dysfunction. Using the visual system as a diagnostic proxy allows for a more objective and early identification of patients

at risk, significantly outperforming traditional associative learning or visual retention tests (16).

Viral hepatitis and ocular manifestations. While chronic viral and autoimmune hepatitis are associated with various ocular findings, these manifestations are typically non-specific or relatively rare (17). By contrast, hepatitis B virus lacks distinctive ophthalmic features, with ocular involvement generally limited to complications arising from secondary cirrhosis (18). Hepatitis C virus (HCV) has been specifically linked to dry eye syndrome (19), particularly in patients with concurrent autoimmune disorders. Furthermore, during the era of interferon-based therapies, a transient form of retinopathy characterized by the presence of cotton wool spots were frequently observed as a treatment-related side-effect (20).

The ophthalmic spectrum of HCV infection is diverse, encompassing conditions, such as retinal vasculitis, keratoconjunctivitis sicca, DED, keratitis, scleritis and various retinopathies. The pathogenesis of these manifestations is primarily attributed to a heightened immune response against HCV antigens, may contribute to the formation and systemic deposition of circulating immune complexes. Furthermore, the persistent presence of HCV can act as a warrant consideration for broader autoimmune dysregulation, precipitating secondary ocular pathologies that mirror other systemic autoimmune syndromes (21). Current evidence points toward a possible relationship between ocular surface pathology and systemic factors such as immune complex deposition or HCV-related autoimmunity. However, given the cross-sectional nature of available data, these processes should be viewed as contributing factors rather than confirmed direct association. Clinical observations support this, demonstrating retinal changes such as soft exudates and peripheral white dots. Moreover, specular microscopy reveals that advanced cirrhosis negatively impacts the ocular surface, specifically resulting in a diminished corneal epithelial cell count (21).

In patients with HCV infection, microvascular alterations within the lacrimal gland are linked to glandular dysfunction. This condition is characterized by increased tear film osmolarity and a notable reduction in corneal sensitivity. Clinically, patients with HCV frequently report subjective symptoms, such as itching and burning sensations. Comparative analyses have demonstrated that tear break-up time values are significantly lower in HCV-positive individuals than in healthy controls, reflecting the higher prevalence and severity of dry eye symptoms in this population (22).

While pathognomonic ocular indicators of HCV infection remain unidentified, various syndromes have been documented in the literature. The most frequent clinical presentations include ischemic retinopathy, primarily driven by HCV-induced vasculitis and keratoconjunctivitis sicca. Furthermore, although the ocular region (specifically the conjunctiva, lacrimal gland and orbital soft tissues) is a prevalent site for extra-nodal lymphomas, the overall incidence of HCV-associated ocular adnexal lymphoma remains low, with only limited studies investigating this association (23). In a large-scale prospective study, Cacoub *et al* (24) evaluated 321 patients with chronic HCV infection and found that extrahepatic manifestations were present in 38% of the cohort. Notably, 10% of these patients presented with xerophthalmia (dry eye) and 12% with xerostomia (dry mouth), underscoring the significant prevalence of sicca syndrome in this population (24). HCV infection frequently overlaps with the clinical presentation of Sjögren's syndrome, a chronic autoimmune condition primarily affecting the salivary and lacrimal glands. The resulting dryness of the oral and ocular mucosae in patients with HCV underscores the role of the virus in driving systemic autoimmunity, necessitating a careful differential diagnosis between idiopathic Sjögren's and HCV-induced sicca syndrome (25). Consequently, as HCV infection advances, routine screening for ocular abnormalities becomes imperative. Manifestations, such as ocular surface damage and DED demonstrate a positive association with the progression of hepatic fibrosis, suggesting that the severity of liver scarring may serve as a clinical predictor for the worsening of sicca symptoms (26).

Primary biliary cholangitis and ocular manifestations. Chronic biliary stasis in primary biliary cholangitis frequently results in the malabsorption of lipophilic nutrients. The subsequent deficiency in vitamin A is a critical factor in the development of xerophthalmia and impaired dark adaptation (nyctalopia). When combined with the progression to cirrhosis and portal hypertension, these metabolic disturbances exacerbate the damage to the ocular surface and visual function (27). In the context of primary biliary cholangitis (PBC), chronic cholestasis-induced hyperlipidemia often manifests dermatologically as eyelid xanthelasmas. Although benign, these lesions are strong clinical indicators of biliary pathology when observed alongside systemic symptoms like pruritus. Additionally, the high prevalence of dry eye symptoms (sicca syndrome) in patients with PBC highlights a frequent autoimmune overlap with Sjögren's syndrome, necessitating a multidisciplinary diagnostic approach (28).

Autoimmune hepatitis and ocular manifestations. Characterized by high titers of circulating autoantibodies, autoimmune hepatitis is associated with significant extrahepatic involvement, including various ophthalmic conditions. This association necessitates regular ophthalmological surveillance for patients diagnosed with autoimmune hepatitis to ensure the early detection of immune-mediated ocular surface and intraocular diseases (29,30). The clinical data provided by Citirik *et al* (31) highlight that patients with autoimmune liver disease frequently exhibit impaired basal tear production and diminished tear film break-up time. These objective indicators of ocular surface instability, coupled with reported dry eye symptoms, underscore the necessity for systematic ophthalmic assessment in the management of autoimmune hepatitis (31). While comprehensive literature regarding the ophthalmic manifestations of autoimmune hepatitis remains limited, a growing body of evidence from clinical case reports suggests a significant association between the two (31,32). These preliminary findings indicate that autoimmune hepatitis may present with a broader spectrum of ocular involvement than previously recognized, necessitating further prospective studies to establish definitive prevalence and pathophysiology. Furthermore, Romanelli *et al* (32) documented a significant clinical association between autoimmune hepatitis and uveitis. This suggests that the systemic inflammatory process

characteristic of autoimmune hepatitis can extend to the uveal tract, potentially resulting in sight-threatening intraocular inflammation that requires coordinated immunosuppressive management (32).

Fatty liver disease and ocular manifestations. In a large-scale nationwide survey involving 17,364 Korean adults, researchers identified a significant association between DED and systemic metabolic health (33). That study revealed that patients with DED exhibited markedly higher rates of systemic comorbidities; specifically, dyslipidemia was established as a potent risk factor, with an adjusted odds ratio of 1.63. These findings suggest that ocular surface stability is closely intertwined with lipid metabolism and systemic inflammatory status (33). The association between dyslipidemia and DED is robustly supported by large-scale epidemiological data. In addition to nationwide surveys, specific studies involving 5,627 Korean women (34) and 15,294 Korean adults (35) have consistently demonstrated that elevated serum cholesterol and triglyceride levels are associated with an increased prevalence of DED. This suggests that lipid imbalances may compromise the meibomian gland secretions, may contribute to evaporative tear film instability.

Research involving adults aged 25-70 years has identified the female sex as a significant risk factor for DED (36). The increased prevalence in this group underscores the necessity for sex-stratified screening, particularly when assessing extrahepatic manifestations in women with chronic liver disease or metabolic syndrome (36). A previous retrospective analysis of 306 patients (ages 18-87 years) further corroborated these findings, demonstrating a significantly elevated incidence of DED among women >40 years of age and individuals with concurrent dyslipidemia. These data suggest a critical intersection between age-related hormonal shifts and lipid metabolic dysfunction, both of which appear to act as compounding risk factors for ocular surface deterioration (37).

Another critical limitation concerns the geographic and ethnic concentration of the current evidence base. A significant portion of the large-scale epidemiological data linking dyslipidemia to DED is derived from East Asian populations (33-35) (e.g., the Korean National Health and Nutrition Examination Survey) and specific European cohorts (37) (e.g., the Dutch Lifelines study). Geographic variations in climate, air quality and dietary habits, alongside ethnic differences in the genetic susceptibility to metabolic syndrome and MASLD, may influence the strength of the liver-ocular surface association. Consequently, the findings presented herein should be interpreted with caution when applied to other populations, such as African or Hispanic cohorts, where longitudinal data on this specific axis remain limited.

Evidence from systematic reviews and meta-analyses has consolidated the link between dyslipidemia and ocular health, establishing that elevated levels of total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol are associated with an increased risk of DED (38). This association is particularly pronounced in female populations (39). Furthermore, cross-sectional data suggest that abnormal total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, and triglyceride profiles contribute to the progression of DED. The underlying pathophysiology likely involves impaired tear film stability and meibomian gland dysfunction, where systemic lipid imbalances disrupt the lipid layer of the tear film (40). Evidence suggests that lipoprotein-mediated pathways link systemic lipid dysregulation to DED. While early ophthalmic screening for patients with dyslipidemia offers a pathway to mitigate ocular morbidity, further research is required to map the exact mechanistic intersections between these conditions (41). Furthermore, the role of lipid-lowering therapies, such as statins, as a treatment modality for DED remains largely unexplored. Future clinical investigations are warranted to determine if modulating systemic lipids can serve as a primary or adjunctive therapy for alleviating DED.

The 'ophthalmology-first' concept. The majority of published studies focus on analyzing ophthalmic manifestations in patients with an already established diagnosis of chronic liver disease, where ocular symptoms are considered one of the systemic complications of the primary process (7-9). In such studies, DED, corneal epitheliopathies, and tear film instability are typically interpreted as consequences of pronounced metabolic, inflammatory, or autoimmune liver dysfunction. However, accumulated clinical observations and epidemiological data indicate that in some patients, atypical or refractory DED course may precede the detection of liver pathology and serve as the first clinical manifestation of subclinical liver dysfunction (6,7).

In particular, DED phenotypes have been described that are characterized by disproportionately severe epithelial changes despite minimal local risk factors, reduced corneal sensitivity, and weak or paradoxical subjective symptoms, which do not fit into classical models of ocular surface disease (1,2). Such clinical scenarios may reflect systemic pathogenetic processes; disruptions in vitamin A metabolism, dyslipidemia, chronic systemic inflammation and neurosensory dysfunction-associated with the early stages of MASLD, cholestasis diseases, or other forms of chronic liver disease (7,9).

Evidence suggests that refractory DED and reduced corneal sensitivity may be associated with extrahepatic manifestations. Therefore, in cases where local associations are insufficient to explain the clinical picture, clinicians may consider a systemic evaluation as part of a comprehensive diagnostic approach, acknowledging the associative nature of the current evidence (1,7). Such an approach includes minimal screening of liver function through assessment of biochemical markers, metabolic profile and risk factors for chronic hepatopathies, which is particularly relevant in preoperative ophthalmologic practice and in managing patients with atypical DED forms.

The physiological and pathological links between the liver and eye are profound, with various ocular manifestations often serving as the first clinical indicators of underlying hepatic dysfunction. These ophthalmic signs, spanning viral, congenital and autoimmune etiologies, are instrumental in the early detection of liver disease. Facilitating such timely diagnosis is paramount, as it enables the implementation of early intervention and targeted management strategies, ultimately optimizing patient prognosis and long-term clinical outcomes (42). The 'ophthalmology-first' approach emphasizes the associative link between the ocular surface and systemic health. Rather

Table IV. Clinical phenotypes and suggested multidisciplinary diagnostic pathways.

Ocular clinical presentation	Suspected systemic/hepatic association	Recommended initial diagnostic action	(Refs.)
Severe aqueous-deficient DED (disproportionate to local risk factors, e.g., age, screen time)	Autoimmune liver diseases (e.g., primary biliary cholangitis, autoimmune hepatitis)	Referral for autoimmune markers (ANA, AMA, ASMA) and liver transaminases (ALT/AST).	(18,27,28,31,32)
Refractory MGD and tear film instability (resistant to standard eyelid hygiene and lubricants)	Metabolic dysfunction-associated steatotic liver disease (MASLD/NAFLD)	Comprehensive serum lipid profile (TC, LDL-C, TG) and hepatic ultrasound/ FibroScan.	(34,38-41)
Diminished corneal sensitivity (in the absence of contact lens wear or ocular surgery)	Chronic cholestasis or severe cirrhosis (leading to secondary vitamin A deficiency)	Serum retinol (vitamin A) levels and assessment of biliary markers (GGT, alkaline phosphatase).	(8,10,11,13,27)
Persistent corneal epitheliopathy (slow healing without local neurotrophic triggers)	Advanced hepatic fibrosis/ systemic metabolic dysregulation	Evaluation of albumin levels and systemic inflammatory markers (CRP) to assess liver synthetic function.	(7,9,14,15)

DED, dry eye disease; ANA, antinuclear antibody; AMA, antimitochondrial antibody; ASMA, anti-smooth muscle antibody; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; MGD, meibomian gland dysfunction; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; CRP, C-reactive protein.

than acting as a definitive diagnostic tool, atypical ophthalmic manifestations may represent subclinical signals that warrant consideration for a multidisciplinary workup, particularly when conventional dry eye therapies yield suboptimal results (7,8).

Implementation and clinical contextualization. To operationalize the 'ophthalmology-first' concept, specific clinical scenarios were identified where DED manifestations may justify further systemic investigation (Table IV). These include the following: i) Phenotypic discordance: Severe aqueous-deficient DED disproportionate to the age of a patient, medication profile, or environmental risk factors; ii) refractory course: DED that remains non-responsive to optimized Tier 1 and Tier 2 therapies for a period of 3-6 months in the absence of Sjögren's syndrome; iii) concurrent neurotrophic signs: Reduced corneal sensitivity or persistent epithelial defects without traditional local neurotrophic triggers.

It should be noted that this screening approach is recommendation-based and context-dependent. Its implementation should be tailored to local clinical practice settings, specialist availability, and patient risk profiles. In appropriate settings, an ophthalmologist may consider initiating a 'liver-surface axis' evaluation by requesting a baseline metabolic and hepatic profile, focusing on serum cholesterol, triglycerides, and liver transaminases, particularly in patients >40 years of age with concurrent dyslipidemia. This proactive approach aims to facilitate early interdisciplinary dialogue rather than replacing formal hepatological diagnostic protocols.

Operationalizing the 'ophthalmology-first' hypothesis. Given the current evidence, it is suggested that certain DED phenotypes serve as clinical cues for systemic investigation. This approach is intended as a hypothesis-generating framework rather than a formal clinical guideline.

High-suspicion phenotypes. i) The 'metabolic' phenotype: Severe meibomian gland dysfunction and tear film instability in patients with existing dyslipidemia, potentially signaling MASLD; ii) the 'autoimmune' phenotype: Profound aqueous deficiency (Schirmer <5 mm) in middle-aged women, suggesting a link to PBC or autoimmune hepatitis; iii) the 'neuro-nutritional' phenotype: Reduced corneal sensitivity and persistent epithelial defects, which may be associated with vitamin A malabsorption in chronic cholestasis.

Minimalist screening panel. When these phenotypes are encountered without obvious ocular causes, a baseline systemic evaluation is justified: i) Liver function tests: Alanine transaminase, aspartate aminotransferase, gamma-glutamyl transferase and alkaline phosphatase to assess hepatocyte integrity and cholestasis; ii) lipid profile: Total cholesterol, low-density lipoprotein and triglycerides; iii) optional: Serum retinol levels in the event that nutritional deficiency is suspected.

Priority populations. Screening should be prioritized in: i) Patients with refractory DED (unresponsive to standard therapy for >6 months); ii) patients with concurrent metabolic syndrome (obesity and/or hypertension); iii) female patients aged 40-70 years presenting with new-onset severe sicca symptoms.

Current evidence gaps and research perspectives. The current evidence base is characterized by a predominance of associative and predominantly cross-sectional studies (2,3,38), along with significant heterogeneity in the ophthalmological

protocols and diagnostic criteria for dry eye syndrome used. The absence of standardized approaches to ocular surface assessment and the limited number of prospective studies complicate establishing causal associations between chronic liver diseases and the development of DED ophthalmic phenotypes. In this regard, promising directions for future research include prospective cohort projects with an ophthalmological entry point, as well as the development and validation of objective bioindicators, including the use of artificial intelligence technologies for analyzing images of the ocular surface and anterior eye segment as potential indicators of systemic pathology.

Methodology note. Only peer-reviewed scientific publications from ophthalmological, hepatological, and interdisciplinary journals were included in the evidence section of the present scoping review, used to form conclusions on the epidemiology, pathogenesis, and clinical phenotypes of dry eye syndrome in liver diseases. This approach was selected to ensure methodological rigor and reproducibility of the findings.

Resource classification. Individual clinical-information and educational resources (including MSD Manual, NHS, Mayo Clinic, Ophthalmology Advisor and similar sources) were placed in a non-numbered 'Additional Clinical-Information Resources' section and used solely for illustrating clinical context and describing well-known clinical syndromes. In accordance with the International Committee of Medical Journal Editors (ICMJE) recommendations and EQUATOR Network standards, these resources were not considered sources of scientific evidence and were not used in forming the key analytical conclusions of the review.

Limitations. Despite the significant correlations identified in this review, several limitations should be acknowledged. First, the majority of the included clinical evidence is derived from cross-sectional or retrospective studies. While these data establish a robust association between chronic liver diseases and ocular surface pathology, their inherent design limits the ability to confirm a definitive causal relationship or to establish a precise temporal sequence of events. For instance, although a strong correlation exists between systemic dyslipidemia and meibomian gland dysfunction, it remains unclear whether lipid imbalances serve as the primary driver of ocular surface deterioration or represent a concurrent manifestation of a broader metabolic syndrome.

Furthermore, there is a notable lack of large-scale, prospective longitudinal studies that track the progression of DED in parallel with the stages of hepatic dysfunction. The heterogeneity in study populations, diagnostic criteria for DED, and the varying etiologies of liver disease (viral vs. metabolic vs. autoimmune) further complicate the generalization of these findings. Finally, while emerging AI-based models show promise in identifying hepatobiliary pathologies through ocular bioindicators, these tools require rigorous external validation in diverse clinical settings before they can be integrated into standard diagnostic protocols. Future research should prioritize longitudinal cohorts to transition from identifying associations to validating the 'ophthalmology-first' concept as a reliable clinical pathway.

Conclusion. Current Evidence and Mechanistic Insights into Systemic Associations data suggest that dry eye syndrome and corneal epithelial diseases may be more than localized ophthalmological conditions. Disruptions in ocular surface homeostasis often correlate with systemic metabolic, immune, and neurosensory processes, within which the liver is hypothesized to play a significant regulatory role. The 'liver-ocular surface' axis concept serves as a conceptual model to integrate disparate clinical observations into a framework that may explain various DED phenotypes observed in patients with chronic liver diseases.

Key pathogenetic mechanisms. The present scoping review identifies several pathways through which liver dysfunction is associated with ocular surface changes, including disruptions in vitamin A metabolism, systemic inflammation, immune dysregulation, and dyslipidemia-related meibomian gland dysfunction. These pathways are closely linked to DED clinical phenotypes that frequently present with atypical or refractory courses, potentially diverging from traditional localized disease models.

Clinical implications and the 'ophthalmology-first' concept. The 'ophthalmology-first' concept proposes that severe or atypical dry eye syndrome, persistent corneal epitheliopathies, and reduced corneal sensitivity may serve as potential clinical indicators of undiagnosed hepatic dysfunction. Rather than acting as definitive diagnostic markers, these findings suggest the utility of an expanded diagnostic mindset and emphasize the importance of interdisciplinary collaboration, particularly when managing patients with DED that is disproportionate to local risk factors.

Practical significance. Recognizing the associative nature of DED and chronic liver disease provides a basis for improved risk stratification and personalized management. Incorporating a systemic (including hepatic) assessment into examination algorithms for patients with severe or atypical DED might facilitate the earlier detection of occult somatic pathology, although these integrated diagnostic pathways require further clinical validation.

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Authors' contributions

AK, AS and DK were involved in the writing, reviewing and editing of the manuscript, as well as in the writing and preparation of the original draft of the manuscript, and the

conceptualization of the study. AB, NK and AA supervised the study, and were also involved in project administration, in the literature search and in the conceptualization of the study. All authors have read and approved the final manuscript. AK and AS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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