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REVIEW ARTICLE

Metabolomics of ocular immune diseases

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Abstract

Background Ocular Immune Diseases (OID) are a heterogeneous group of disorders characterized by immune-mediated inflammatory responses affecting various parts of the eye. OID encompass infectious forms caused by pathogens and non-infectious forms driven by immune dysregulation, which may occur as isolated ocular conditions or as part of systemic diseases. Nonspecific early symptoms often lead to misdiagnosis and significant risks of visual impairment. The unclear etiology and pathogenesis of OID present challenges in achieving effective treatments. Metabolomics, a cutting-edge omics tool, provides critical insights into disease-relevant phenotypes and advancing the understanding of OID.

Aim of review This review synthesizes recent advancements in metabolomics, focusing on methodologies and sample sources for comprehensive profiling. It provides a holistic overview of metabolomics applications in OID, including keratitis, conjunctivitis, dry eye disease, scleritis, uveitis, and thyroid eye disease. Additionally, it discusses current limitations and outlines future directions for improving precision diagnostic and therapeutic strategies.

Key scientific concepts of review Metabolomic studies have identified distinct metabolic signatures in biofluids and tissues, bridging localized ocular inflammation with systemic immune dysregulation in OID. Perturbations in energy, lipid, and amino acid metabolism, oxidative stress regulation, and gut-derived metabolites highlight the metabolic reprogramming in OID. These findings enable the discovery of novel biomarkers, deeper insights into disease mechanisms, and the development of targeted therapies. As metabolomics evolves, it holds substantial promise for advancing precision medicine and optimizing outcomes in OID.

Keywords Ocular immune diseases · Metabolomics · Biomarkers · Metabolic pathways · Precision medicine

1 Introduction

Ocular Immune Diseases (OID) encompass a diverse spectrum of disorders caused by aberrant immune-mediated inflammatory responses affecting the ocular surface, intraocular structures, and the orbit. These diseases arise from complex interactions between localized inflammation and systemic immune dysregulation. Despite clinical advancements, their pathogenesis remains elusive, leading to delayed diagnoses and non-specific therapies. Emerging evidence implicates the pivotal role of metabolic changes in OID pathogenesis. Metabolomics, with its capacity to identify disease-specific metabolic signatures, offers transformative potential for uncovering OID mechanisms and guiding precision medicine. This review synthesizes current metabolomics applications in OID research, highlighting its role in biomarker discovery, pathogenesis exploration, and therapeutic innovation to improve disease outcome.

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2 Overview of OID

Ocular immune diseases are broadly classified into infectious and non-infectious categories. Infectious OID may originate from direct pathogen invasion or hematogenous dissemination of systemic infections (Al Akrash et al., 2021; Azari & Barney, 2013). Non-infectious OID are primarily immune-mediated and include both ocular specific conditions (Foeldvari et al., 2023; Sainz de la Maza et al., 2012) and ocular manifestations of systemic diseases (Bjordal et al., 2020; Joye & Suhler, 2021; Karadag & Bolek, 2020). Thus, evaluating ocular pathology within the context of systemic immunity is essential for accurate diagnosis and proper treatment for OID.

Globally, OID exhibit wide variability in prevalence, influenced by disease entities, geographic regions, and demographic factors (Tsirouki et al., 2018). Infectious OID are disproportionately prevalent in developing regions due to healthcare disparities, profoundly impacting vision health (Betzler et al., 2021; Won et al., 2008). Non-infectious OID show even greater epidemiological diversity, with Dry Eye Disease affecting 5–50% of the population (Song et al., 2018; Stapleton et al., 2017) and uveitis accounting for 9-15% of blindness (Ghadiri et al., 2023).

OID pathogenesis varies by type. Infectious OID present acutely due to pathogen invasion, while non-infectious OID follow a chronic, relapsing course driven by immune dysregulation (Bonacini et al., 2020; Solomon et al., 2022; Zhang et al., 2024a, b). Overlapping early symptoms, such as eye pain, redness, photophobia, and blurred vision, complicate diagnosis (Morales-Mancillas et al., 2024; Rietveld et al., 2003; Wu et al., 2023). Current treatments include pathogen-specific therapies combined with corticosteroids for infectious OID (Lee et al., 2017), while non-infectious OID require immunosuppressants and biologics (Rosenbaum et al., 2019). However, the lack of targeted therapies and limited understanding of OID pathogenesis underscore the need for further research on precise diagnostics and treatments (Egwuagu et al., 2021; Maleki et al., 2022; Zhong et al., 2023) (Fig. 1).

3 Overview of metabolomics

Metabolomics is the comprehensive study of small-molecule metabolites, which are end products or intermediates of metabolic pathways. It provides crucial insights into biochemical processes under various physiological and pathological conditions (Johnson et al., 2016; Qiu et al., 2023; Wishart, 2019). Primary metabolites, such as lipids, amino acids, nucleic acids, and sugars, are conserved across species, while exogenous metabolites vary with external factors like diet and environment (Jin et al., 2019; Peregrín-Alvarez et al., 2009; Wei et al., 2022). Metabolomics captures a dynamic snapshot of an organism's metabolic state, links genetic variations to phenotypic traits, and provides critical insights into health states, disease mechanisms, and precision medicine (Tan et al., 2024; Xiao et al., 2022).

3.1 Workflow and analytical approaches

Metabolomics involves sample collection, metabolite extraction, separation, analysis, and quantification (Marques & Justino, 2023). Metabolomics employs two complementary approaches (Wei et al., 2021). Untargeted metabolomics provides a broad view of the metabolome by profiling both known and unknown metabolites (Chen et al., 2021). It can uncover novel biomarkers without prior assumptions but is limited to relative quantification (Kontou et al., 2023; Schrimpe-Rutledge et al., 2016). In contrast, targeted metabolomics quantifies predefined metabolites with high sensitivity, making it ideal for validating specific metabolic pathways or conditions (Sarmad et al., 2023; Urbanski et al., 2021).

The two cornerstone analytical platforms in metabolomics are nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) (Borges et al., 2021; Dunn et al., 2011b; Zampieri et al., 2017). NMR is renowned for its quantitative accuracy, broad detection capabilities (e.g., ^{1}H, ^{13}C, ^{31}P), and the non-destructive nature, but its relatively low sensitivity demands higher metabolite concentrations (Dunn et al., 2011). MS offers superior sensitivity and specificity for small-volume samples, but faces challenges in complex sample preparation, data interpretation difficulties, limited reproducibility, and reliance on robust databases (Macedo et al., 2021; Strathmann et al., 2020). Gas chromatography-MS (GC-MS) excels in volatile compound analysis (e.g., short-chain fatty acids) but requires derivatization for non-volatiles, limiting its role in lipidomics (Einoch Amor et al., 2023). Liquid chromatography-MS (LC-MS) offers broader applicability for polar and non-polar metabolites (e.g., amino acids, lipids) with high sensitivity and minimal sample preparation but relies on extensive databases (Cui et al., 2018). In OID research, LC-MS is preferred for low-abundant metabolite detection in tears and aqueous humor and is widely used in lipidomics, while GC-MS aids in targeted analysis of volatile compound. Refined methodologies, such as matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) for spatial imaging (Planque et al., 2023), and high-resolution mass spectrometry (HRMS) for precise mass measurements (e.g. TOF-MS and Orbitrap) (Guan et al., 2022; Misra, 2021), further expand MS applications.

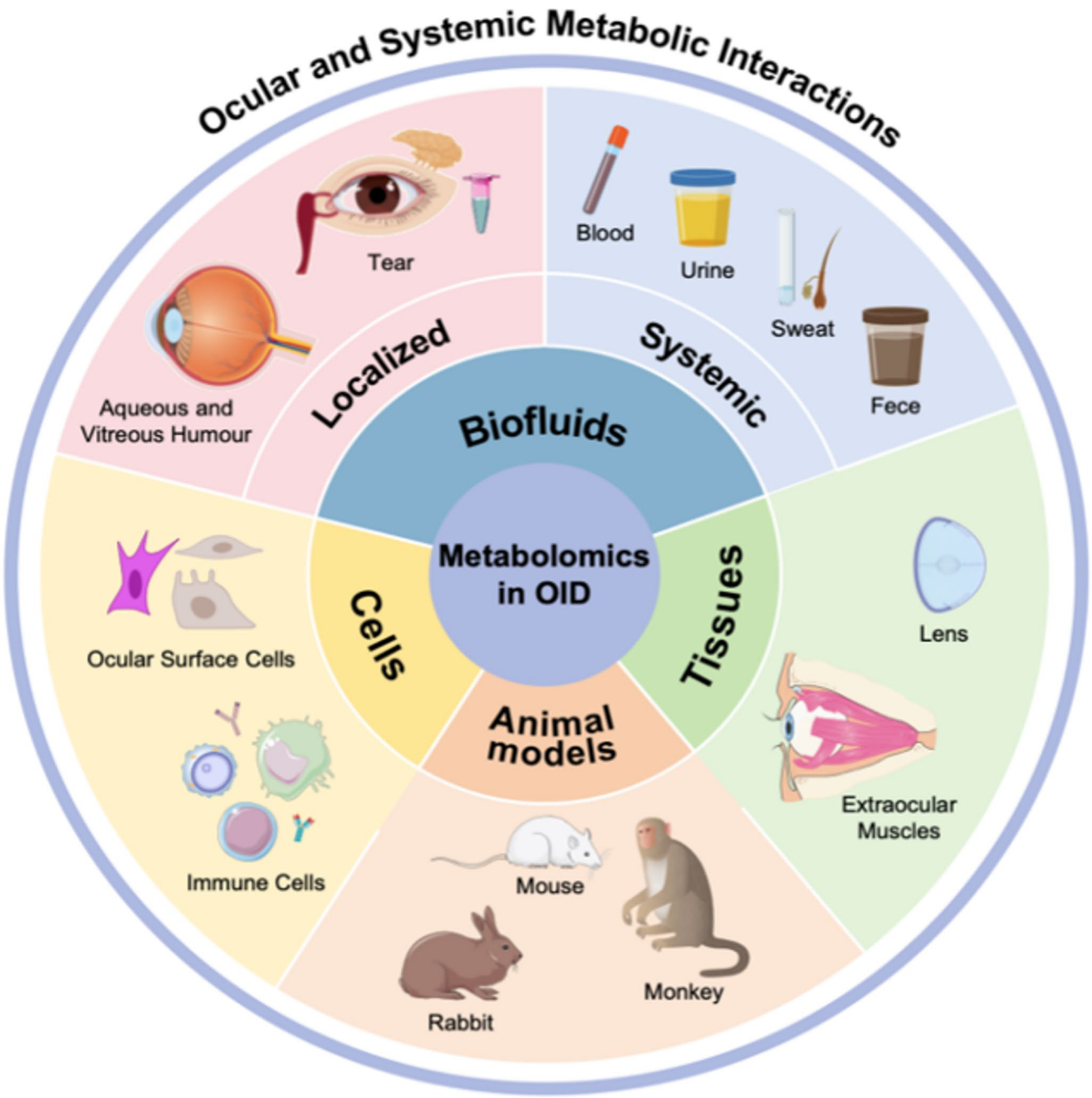

Fig. 1 Various sample types used in metabolomics studies of ocular immune diseases

3.2 Sample sources

Accurate metabolomic analysis depends on appropriate sample selection, with biofluids, tissues, cells, and animal models offering unique advantages and limitations (Du et al., 2022b).

Local biofluids provide direct insights into the ocular microenvironment. Tears, collected non-invasively using microcapillary tubes or Schirmer strips (Nättinen et al., 2020), are highly indicative of both ocular surface diseases and systemic conditions (Khanna et al., 2022; Yazdani et al., 2019; Zhan et al., 2021). However, their small volume and variability pose challenges. Aqueous humor and vitreous humor provide a direct window into intraocular conditions (Barbosa Breda et al., 2020; Tomita et al., 2021), with AH reflecting systemic influences *via* microfluidic exchange with cerebrospinal fluid (Serrano-Marín et al., 2023). However, both require invasive collection during surgeries, limiting accessibility (Fang et al., 2023). Systemic biofluids, including blood, urine, sweat, and feces, capture a broader

metabolic profile. Blood, despite its accessibility, may not fully reflect intraocular states due to blood-ocular barriers (Chen et al., 2020; Teabagy et al., 2023). Urine and sweat are non-invasive options but less relevant to ocular processes (Ahn et al., 2017; Cui et al., 2021). Fecal samples provide valuable insights into gut microbiota (GM), which influences immune regulation and is linked to OID pathogenesis though the gut-eye axis (Campagnoli et al., 2023). Challenges include individual variability and complex composition (Nam et al., 2022).

Tissue samples, like cornea, sclera, and lens, reveal localized metabolic changes at the structural level but require invasive collection (Tamara et al., 2016). Cell samples offer a controlled environment for reproducible studies but may not fully replicate in vivo complexity (Su et al., 2015; Ziemanski et al., 2021). Animal models capture systemic interactions within living organisms and facilitate dynamic analyses of disease progression (Parker et al., 2022). However, interspecies differences and ethical concerns limit their translational applicability.

A comprehensive understanding of OID requires integrated analyses that encompass local and systemic levels, as well as human and animal investigations. Moreover, ensuring consistency and comparability of samples is also critical for obtaining reliable and reproducible metabolomic results (Dunn et al., 2011). Standardized protocols, including rigorous selection criteria, collection methods, appropriate sample volumes, controlled timing, proper storage, and effective quality control, can minimize variability and enhance the robustness of metabolomic data (Yazdani et al., 2019).

3.3 Clinical applications

Metabolomics offers versatile applications in disease understanding by identifying disease-specific metabolic signatures (Daphne Teh et al., 2021). It facilitates early diagnosis by detecting metabolic changes preceding clinical symptoms, supports disease monitoring by longitudinal profiling, and predicts therapeutic efficacy (Chng et al., 2018). Beyond biomarker discovery, metabolomics aids in therapeutic development by uncovering disrupted pathways and novel targets, advancing precision medicine through tailored therapies based on individual metabolic profiles. Together, these applications underscore the potential of metabolomics to revolutionize clinical practice of OID by advancing diagnostic precision, disease monitoring, therapeutic development, and precision medicine.

4 Disease-specific metabolic findings in OID

Ocular immune diseases (OID), such as keratitis, conjunctivitis, dry eye disease, scleritis, uveitis, and thyroid eye disease involve complex metabolic alterations that disrupt ocular homeostasis. Metabolomics has provided key insights into these diseases by identifying metabolic biomarkers and enriched pathways that contribute to disease pathophysiology and progression.

4.1 Ocular surface: cornea and conjunctiva

The ocular surface, mainly comprising the cornea and conjunctiva, maintains homeostasis through dynamic metabolic adaptations (Knop & Knop, 2007). The cornea primarily relies on glucose metabolism, transitioning from aerobic to anaerobic glycolysis under hypoxic conditions (Leung et al., 2011; Pinsky, 2014). The conjunctiva adapts to hyperosmotic stress by upregulating osmoprotectants and activating pathways such as prostaglandin synthesis (Chen et al., 2015). These adaptations are essential for maintaining ocular surface integrity and immune defense (Walker et al., 2020).

4.1.1 Infectious keratitis and conjunctivitis

Infectious keratitis and conjunctivitis, caused by bacterial (Astley et al., 2019; Betzler et al., 2021), viral (Terada et al., 2021), fungal (Thomas & Kaliamurthy, 2013), or parasitic (Hauber et al., 2011) pathogens, induce profound metabolic disturbances. Metabolomics has revealed disrupted energy metabolism as a shared feature across diverse pathogens, resulting from the exploitation of host resources and metabolic reprogramming to support survival and virulence. Immune response pathways, including oxidative stress and inflammation, are also affected, reflecting the host's defense mechanisms (Ma et al., 2024; Shrestha et al., 2023).

Key metabolic alterations include dysregulation in purine metabolism, such as adenine and adenosine depletion alongside xanthine accumulation in bacterial keratitis, highlighting disruptions in nucleotide signaling and energy imbalance (Shrestha et al., 2023). Similarly, tear metabolomics in Herpes simplex keratitis (HSK) demonstrates changes in energy and amino acid metabolism, with tear-derived extracellular vesicles-based metabolic signatures achieving high diagnostic accuracy (77% in the internal testing set and 83% in the validation set) (Ma et al., 2024).

4.1.2 Non-infectious keratitis and conjunctivitis

Non-infectious keratitis and conjunctivitis, triggered by immune-mediated inflammation, allergens, irritants, or systemic diseases, exhibit distinct metabolic profiles.

Allergic conjunctivitis (AC) is characterized by T helper type 2 (Th2) cell activation and IgE-mediated mast cell activation (Tariq, 2024). Metabolomic and lipidomic analyses in AC mouse models highlight significant increases in pro-inflammatory mediators like prostaglandins and leukotrienes derived from arachidonic acid, supporting the therapeutic potential of dietary omega-3 fatty acids in modulating inflammation (Hirakata et al., 2019a, 2019b). Blood metabolite profiling identified 8 key biomarkers, such as palmitate, 3-methoxytyrosine, and carnitine, associated with AC heritability and susceptibility (Zou et al., 2024).

Superior Limbic Keratoconjunctivitis (SLK) is a chronic inflammation disorder caused by mechanical injury, tear film instability, or autoimmune factors (Lahoti et al., 2022). It is driven by an imbalance of polyunsaturated fatty acids (PUFAs), particularly altered ω-3/ω-6 ratios, emphasizing lipid metabolism as a potential avenue for biomarker discovery and therapeutic intervention (Zong et al., 2024).

Ocular mucous membrane pemphigoid (MMP) is a rare autoimmune disease affecting the conjunctiva and other mucous membranes, mainly characterized by lipid signaling alterations, with 9(S)-HOTrE and (±)5-HEPE identified as potential diagnostic biomarkers (Di Zazzo et al., 2020; Du et al., 2022a).

4.1.3 Dry eye disease

Dry eye disease (DED) is a multifactorial condition affecting the ocular surface, often associated with systemic conditions like primary Sjögren's syndrome (pSS) (Bjordal et al., 2020). Metabolomic studies have identified significant local and systemic metabolic disruptions in DED.

Tears, being a direct reflection of ocular surface health, have been extensively analyzed in DED (Yazdani et al., 2019). Energy metabolism emerges as a central factor in DED pathogenesis. Reduced levels of L-carnitine impair fatty acid oxidation and ATP production, leading to mitochondrial dysfunction and oxidative damage (Pescosolido et al., 2009). Disruptions in purine metabolism, highlighted by elevated levels of Ap4A and Ap5A, contribute to energy imbalance and chronic inflammation (Carracedo et al., 2016; Peral et al., 2006). Further downstream, amino acid metabolism compensates by supporting protein synthesis to mitigate oxidative stress. This metabolic adaptation enables the ocular surface to cope with chronic inflammation (Chen et al., 2019).

Lipid metabolism is also significantly disrupted in DED, with altered tear film lipid composition and reduced lipid diversity destabilizing the lipid layer structure (Khanna et al., 2022). Pro-inflammatory lipid mediators, such as prostaglandins and leukotrienes, exacerbate chronic inflammation (Shim et al., 2012), while lipid dysregulation in meibum further contributes to tear film instability, aggravating DED symptoms (Garcia-Queiruga et al., 2024).

Beyond the ocular surface, systemic metabolic disruptions also play a role in DED. In saliva, reduced levels of hypotaurine, a key metabolite in osmoprotection, contributes to impaired antioxidative defense mechanisms (Fineide et al., 2023). In serum, disruptions in androgen metabolism correlate with DED severity, suggesting the broader systemic hormonal imbalances impacting DED (Vehof et al., 2017). Altered phosphatidylcholine (PC) and lysophosphatidylcholine (LysoPC) levels in plasma also reflect systemic immune dysregulation in DED (Li et al., 2023). Furthermore, fecal metabolomics uncovers disrupted amino acid and lipid metabolism linked to gut dysbiosis and proinflammatory pathways, emphasizing the gut-eye axis in DED (Yang et al., 2022).

Besides, metabolomic analyses indicate that DED subtypes can be differentiated by severity and etiology based on their metabolic profiles (Galbis-Estrada et al., 2014). For example, a nine-metabolite signature enables discrimination between pSS and non-pSS-related DED with an ROC-AUC of 0.83 (Urbanski et al., 2021).

By combining insights from localized tear film alterations and systemic contributions, metabolomics provides a comprehensive framework for understanding the multifactorial nature of DED and supports the development of tailored therapeutic approaches (Table 1).

4.2 Sclera and scleritis

The sclera, a dense connective tissue, provides mechanical protection to the retina and optic nerve, maintains ocular shape, and blocks off-axis light to ensure visual clarity (Kano, 2023). While metabolically quiescent, the sclera exhibits active extracellular matrix (ECM) remodeling under mechanical stress *via* oxidative phosphorylation and the pentose phosphate pathway (Jiang et al., 2014).

Scleritis is a severe inflammatory condition, often associated with systemic autoimmune diseases like rheumatoid arthritis and IgG4-related diseases (Nevares et al., 2020). Immune-mediated mechanisms, such as T and B cell activation, cytokines release, and antibody-mediated mechanisms, are commonly implicated (Wakefield et al., 2013).

Although direct metabolomics studies on scleritis remain scarce, related research underscores the role of lipid mediators in inflammatory ocular conditions (Das, 2020; Shim et

Table 1 Detailed information of metabolomics studies on dry eye disease (DED)

Author, Year	Sample types	Number of Cases	Methodology (Identified Metabolites)	Key Pathways and Major Differential Metabolites
(Pescoso-lido et al., 2009)	Tear	Total: 20 10 DED and 10 HCs	HPLC	Lipid and energy metabolism. DED vs. HC ↓: Carnitine and its derivatives
(Peral et al., 2006)	Tear	Total: 97 46 symptomatic cases and 51 nonsymptomatic controls	Targeted HPLC-MS	Nucleotide metabolism. Symptomatic cases vs. controls ↑: Ap4A and Ap5A
(Chen et al., 2019)	Tear	Total: 37 18 DED and 19 HCs	Untargeted UPLC/Q-TOF-MS/MS (156)	Complement and coagulation cascades, glycolysis / gluconeogenesis, amino acid metabolism, and glutathione metabolism. DED vs. HC ↑: 33 metabolites, 3-hydroxyanthranilic acid, urocanic acid, uridine, carnitine, tyrosine, glutamic acid, proline, lysine, arginine, LysoPC 22:6, LysoPE 22:6, xanthine, inosine, nicotinamide ↓: 1,2-dimethyl-4-(6-methyl-4-heptenyl)-1,3-cyclohexadiene
(Shim et al., 2012)	Tear	Total: 40 23 DED and 17 HCs	Targeted nano-LC-MS/MS (Prostaglandins)	Arachidonic acid metabolism. DED vs. HC ↑: PGE2 ↓: PGD2
(Garcia-Queiruga et al., 2024)	Meibum	Total: 44 11 DED and 11 HCs	Untargeted Elute UHPLC system coupled with timsTOF Pro MS/MS (131)	Lipid metabolism. DED vs. HC ↑: polar lipids, ceramides, lysophosphatidylcholines ↓: non-polar lipids, cholesterol esters, triacylglycerols, diacylglycerols
(Galbis-Estrada et al., 2014)	Tear	Total: 90 55 DED (22 mild-to-moderate and 33 moderate) and 35 HCs	NMR	Energy metabolism, lipid metabolism, amino acid metabolism, and neurotransmitter metabolism. DED vs. HC ↑: Glucose, phenylalanine, arginine and phosphoethanolamine ↓: Cholesterol, N-acetylglucosamine
(Urbanski et al., 2021)	Tear	Total: 80 40 pSS DED and 40 non-pSS DED	Targeted LC-MS (104)	Lipid metabolism, amino acid and biogenic amine metabolism. pSS DED vs. non-pSS DED ↑: LysoPCs (C16:1, C18:1, C18:2), SM (C16:0, C22:3), PCaa (C42:4) ↓: serine, aspartate, dopamine
(Fineide et al., 2023)	Tear Saliva	Total: 31 19 DED and 12 HCs	Untargeted LC-HRMS (174)	Lipid metabolism, polyamine metabolism, and oxidative stress. DED vs. HC ↑: Cartine, spermine, spermidine, arachidonic, DHA ↓: Oleamide, panthenol, resorcinol
(Vehof et al., 2017)	Serum	Total: 2819 436 DED and 2383 HCs	Untargeted GC-MS and LC-MS (341)	Lipid metabolism. DED vs. HC ↓: Androsterone sulfate, epiandrosterone sulfate, 4-Androsten-3β,17β-diol disulfate 1,4-Androsten-3β,17β-diol disulfate 2, DHEA-S, glycerophosphocholines
(Yang et al., 2022)	Fecal microbiota	Total: 50 30 pSS and 20 HCs	Untargeted UPLC-MS (2051 in ESI+mode and 923 in ESI-)	Amino acid metabolism, lipid metabolism, and their interplay with gut microbiota. pSS vs. HC ↑: 13 metabolites, L-histidine, phenylglyoxylic acid, homovanillic acid ↓: 20 metabolites, 5-methoxyindoleacetic acid

al., 2012). Besides, bioinformatic analyses have identified TNF-α and IL-6 as pivotal genes in scleritis, suggesting that oxidative stress and arachidonic acid metabolism as potential therapeutic targets (Yan et al., 2023).

4.3 Uvea and uveitis

The uvea supports ocular homeostasis through oxidative phosphorylation, aerobic glycolysis, the pentose phosphate pathway, and the kynurenine pathway, which also modulates immune function and vascular tone (Hayreh & Hayreh, 2023; TeSlaa et al., 2023; Wang et al., 2023; Wilson, 2017).

Uveitis, as the fourth leading cause of acquired blindness, can arise from both infectious and non-infectious etiologies, with the latter being more prevalent (Burkholder & Jabs, 2021). Uveitis can be subdivided into anterior, intermediate, posterior, and pan uveitis based on the primary anatomical site of inflammation (Jabs et al., 2005).

Anterior uveitis (AU) can manifest as an isolated ocular disease or coexist with systemic conditions, most notably HLA-B27-positive spondyloarthritis (SpA) (Onal et al., 2006). Locally, aqueous humor metabolomics has revealed alterations in branched-chain amino acid biosynthesis, ascorbate metabolism, and the TCA cycle, with ketoleucine identified as a key biomarker of disease activity in HLA-B27-related AU (Verhagen et al., 2019). Systemic metabolic disruptions include perturbations in amino acid, carbohydrate, and lipid metabolism (Guo et al., 2014). Fecal metabolomics has emphasized the role of gut dysbiosis in AU pathogenesis, with specific alterations of short-chain fatty acids (SCFAs) and kynurenine pathway metabolites distinguishing AU from non-AU SpA patients (Essex et al., 2024; Huang et al., 2018).

Panuveitis, often associated with Behçet disease (BD) and Vogt-Koyanagi-Harada (VKH) disease, carries a relatively poor prognosis due to the irreversible damage to macula and optic nerve (Burkholder & Jabs, 2021). Serum metabolomics has demonstrated high diagnostic accuracy for both conditions (AUC = 0.83 for BD and 0.73 for VKH) (Shimizu et al., 2020).

In BD, biomarker panels in urine, serum, and sweat achieved remarkable AUC values of 0.974, 0.998, and 0.947, respectively (Ahn et al., 2017, 2018; Cui et al., 2021). Among these, a consistent decrease in L-citrulline, involved in the urea cycle and nitric oxide (NO) synthesis, indicates dysregulated oxidative stress and immune response in BD, supported by concomitant alterations in glutathione metabolism (Mak et al., 2017). Additionally, sphingosine-1 phosphate (S1P) and EtherLPE 18:2 were identified as key biomarkers correlated with disease activity (Park et al., 2023). In VKH, serum metabolomics identified diagnostic biomarkers (e.g., D-mannose, L-lysine, stearic acid, sarcosine) with AUC values greater than 0.9, alongside dysregulations in aminoacyl-tRNA biosynthesis, lysine degradation, and glycine, serine and threonine metabolism (Chen et al., 2020; Cui et al., 2020). Notably, shared metabolic pathways between BD and VKH, particularly in aminoacyl-tRNA biosynthesis, suggest overlapping immunopathological mechanisms despite their distinct clinical presentations (Xu et al., 2021) (Table 2).

4.4 Orbit and thyroid eye disease

Thyroid Eye Disease (TED) is the most prevalent orbital disease in adults (Bahn, 2010). It is an organ-specific autoimmune condition, driven by autoantibodies to thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) (Krieger et al., 2016; Kumar et al., 2004). Recent metabolomic studies have revealed significant metabolic disruptions in TED.

In tears, elevated Ornithine decarboxylase (ODC) activity and increased polyamine synthesis (e.g., putrescine and spermine) suggest tissue remodeling in active TED, potentially mediated by TSHR autoantibodies (Billiet et al., 2022; Zusman & Burrow, 1975).

In orbital tissues, TED exhibits profound metabolic remodeling, particularly in lipid metabolism. Enhanced triacylglycerol (TAG) biosynthesis, fatty acid uptake, and disruptions in cholesterol and choline metabolism, contribute to de novo adipogenesis and inflammation (Huang et al., 2022; Zhang et al., 2020). Energy metabolism is also affected, with a shift from oxidative phosphorylation to glycolysis and increased oxidative stress, as evidenced by changes in purine and glutathione metabolism (Du et al., 2023; Zhang et al., 2021).

Beyond ocular involvement, TED has broader systemic implications. TED has been linked to elevated sphingosine-1-phosphate (S1P) levels, a key sphingolipid involved in inflammatory signaling and tissue remodeling (AUC > 0.8) (Byeon et al., 2018), and disruptions in steroid hormone biosynthesis (Shi et al., 2023). Regarding amino acid metabolism, coordinated changes in fumarate, proline, phenylalanine, and glycerol were observed across orbital tissues and plasma (Ji et al., 2018). A serum biomarker panel consisting of glycine, glycerol 3-phosphate, estrone sulfate, CPS1, GP1BA, and COL6A1 achieved high predictive accuracy for TED (AUC = 0.933) (Shi et al., 2023). Moreover, upregulation of the kynurenine pathway, a key branch of tryptophan metabolism related to Th1 immune responses, further highlights systemic immune dysregulation in TED (Ueland et al., 2023).

Additionally, the gut-ocular axis involvement is evidenced by altered biosynthesis of unsaturated fatty acids and elevated levels of SCFAs, highlighting gut dysbiosis

Table 2 Detailed information of metabolomics studies on uveitis

Author, Year	Disease	Sample types	Number of Cases	Methodology (Identified Metabolites)	Key Pathways and Major Differential Metabolites
(Verhagen et al., 2019)	AU	AH	Total: 70 30 HLA-B27-AAU, 18 idiopathic AAU, and 22 cataract controls	Targeted DIMS, LC-MS/MS (147 in the discovery cohort and 127 in the replication cohort)	Branched-chain amino acid (BCAA) metabolism, ascorbate and aldarate metabolism, the tricarboxylic acid (TCA) cycle, and serine biosynthesis. HLA-B27-AAU vs. idiopathic AAU ↑: Ketoleucine, malic acid, citric acid, aconitic acid, valine, leucine ↓: 2-Ketogultaric acid, succinic acid, fumaric acid, tryptophan, tyrosine, ascorbic acid
(Guo et al., 2014)	AU	Plasma	Total: 21 12 AU and 9 HCs	Targeted UPLC–MS (33 altered)	Starch and sucrose metabolism, phenylalanine metabolism, pyruvate metabolism, purine metabolism, tyrosine metabolism, and Vitamin B6 metabolism. AU vs. HC ↑: 13 metabolites, D-Erythrose 4-phosphate, 1-Methylnicotinamide, succinic acid, linoleic acid, S-Lactoylglutathione, trimethylamine N-oxide ↓: 20 metabolites, ceramide, chenodeoxycholic acid sulfate, D-Glutamine, niacinamide, 3-(3,4-Dihydroxyphenyl) lactic acid
(Huang et al., 2018)	AU	Fecal microbiota	Total: 60 30 AU and 30 HCs	Untargeted GC-MS	Linoleic acid and short-chain fatty acid metabolism. AU vs. HC ↑: 6-deoxy- D-glucose, linoleic acid, N-Acetyl- beta-D-mannosamine, shikimic acid, azelaic acid, isomaltose, palmitoleic acid
(Ahn et al., 2018)	BD	Serum	Total: 90 45 BD and 45 HCs	Untargeted GC/TOF-MS (104)	Linoleic acid metabolism, glycine, serine, and threonine metabolism, taurine and hypotaurine metabolism. BD vs. HC ↑: decanoic acid, fructose, tagatose ↓: linoleic acid, oleic acid
(Ahn et al., 2017)	BD	Urine	Total: 85 44 BD and 41 HCs	Untargete GC/TOF MS (110)	Sugar metabolism, the pentose phophate pathway, fatty acid metabolism, purine metabolism, and amino acid metabolism. BD vs. HC ↑: guanine, 3-hydroxypyridine, pyrrole-2-carboxylate ↓: L-citrulline, isothreonate, sedoheptuloses, mannose, galactonate, hypoxanthine, gluconic acid lactone
(Cui et al., 2021)	BD	Sweat	Total: 38 20 BD cases and 18 HCs	UHPLC-Q TOF-MS (175)	Phosphatidylethanolamine biosynthesis, ammonia recycling, fatty acid biosynthesis, homocysteine degradation and methionine metabolism. BD vs. HC ↓: l-citrulline, urocanic acid, 2-oxoadipic acid, cholesterol 3-sulfate
(Park et al., 2023)	BD	Plasma and PBMCs	Total: 141 Plasma: 40 BD,17 disease controls and 18 HCs PBMCs: 29 BD cases, 19 disease controls, and 18 HCs	Untargeted GC-TOF MS (92 in plasma), untargeted UPLC Orbitrap-MS based lipidomics (345 lipids in PBMCs)	Plasma: Carbohydrate, fatty acid, and phosphatidylethanolamine metabolism. PBMCs: EtherLPE and LPC metabolism. Sphingosine-1-phosphate (S1P) and EtherLPE O-18:2

Table 2 (continued)

Author, Year	Disease	Sample types	Number of Cases	Methodology (Identified Metabolites)	Key Pathways and Major Differential Metabolites
(Cui et al., 2020)	VKH	Sweat	Total: 60 30 VKH cases and 30 HCs	Untargeted UHPLC-TOF-MS (175)	Amino acid metabolism. VKH vs. HC ↑: 4-methoxycinnamic acid, Val-His, palmitic acid ↓: choline, urocanic acid, tyramine, L-Phenylalanine, L- Leucine, L-Tryptophan, D-Proline, gamma-L-Glutamul-Lvaline, betaine, DL-Indole-3-lactic acid, L-Isoleucine, His-Pro, L-Serine, L-Citrulline
(Chen et al., 2020)	VKH	Plasma	Total: 85 55 VKH cases (28 active and 27 inactive) and 30 HCs	Untargeted UHPLC-MS/MS	Aminoacyl-tRNA biosynthesis, lysine degradation and glycine, serine and threonine metabolism. Active VKH vs. HC ↑: DL-Phenylalanine, L-Lysine, L-NG-Monomethyl arginine, L-Isoleucine, Sarcosine, Gln-Asn, D-Mannose, Glycine, Pseudouridine ↓: Trans-Dehydroandrosterone, Indoleacrylic acid, stearic acid, Indole-2-carboxylic acid, coumarin, acetohexamide Inactive VKH vs. HC ↑: L-Lysine, L-NG-Monomethyl arginine, Sarcosine, D-Mannose, Glycine, 1-Myristoyl-sn-glycero-3-phosphocholine, Diethanolamine ↓: Trans-Dehydroandrosterone, acetohexamide
(Shimizu et al., 2020)	BD and VKH	Serum	Total: 70 19 BD, 15 VKH, and 16 HCs	Untargeted LC/TOF-MS (78)	BD vs. HC ↑: Aspartate, glutamate, proline, pyruvate, malate ↓: Thiamine VKH vs. HC ↓: Nicotinamide
(Xu et al., 2021)	BD and VKH	AH	Total: 45 15 VKH, 15 BD and 15 senile cataract controls	Untargeted UPLC-Q-TOF/MS (29 altered in BD vs. controls and 28 altered in VKH vs. controls)	Aminoacyl-tRNA biosynthesis, pantothenate and CoA biosynthesis, D-arginine and D-ornithine metabolism and phenylalanine metabolism. BD & VKH vs. controls: ↑: Palmitic acid, oleic acid, asymmetric dimethylarginine, L-lysine, D-ornithine, D-pipecolic acid, L-methionine, creatinine, V L-pipecolic acid, and gamma-Glutamyllysine ↓: N-acetylhistidine

and its role in immune modulation *via* Th17/Treg balance (Biscarini et al., 2023; Gong et al., 2019; Zeng et al., 2019; Zhang et al., 2024b) (Table 3).

5 Shared metabolic findings in OID

OID exhibit overlapping metabolic disruptions that bridge localized inflammation with systemic immune responses. Key pathways disrupted in OID include energy metabolism, where glycolysis and purine metabolism fuel immune activation and tissue repair, highlighting its role in infectious OID for rapid pathogen clearance (Shrestha et al., 2023; Zhang et al., 2021). Lipid metabolism alterations, particularly in arachidonic acid and phosphatidylcholine pathways, drive pro-inflammatory mediator production and tissue remodeling in non-infectious OID (Hirakata et al., 2019a, 2019b; Li et al., 2023; Yan et al., 2023). Amino acid metabolism, notably the kynurenine pathway dysregulation, modulates immune privilege and osmotic stress adaptation (Guo et al., 2014; Ma et al., 2024; Wang et al., 2023). Common pathways, such as oxidative stress regulation through glutathione metabolism and oxidative phosphorylation, are critical for mitigating inflammation-induced tissue damage and maintain redox balance across OID subtypes (Du et al., 2023). Additionally, systemic influences, such as microbiota-derived short-chain fatty acids, underscore the gut-eye axis's role in modulating immune responses (Biscarini et al., 2023; Yang et al., 2022). These interconnected pathways demonstrate the specific metabolic reprogramming that underpins the distinct pathophysiological features of OID.

6 Pitfalls and future directions

Although metabolomics has established itself as a vital tool for advancing the understanding of ocular immune diseases, there are still many challenging issues that need to be addressed.

Sample heterogeneity and source bias are inherent challenges in metabolomics, as factors such as age, lifestyle, diet, systemic diseases, and medications can confound metabolomic profiles. While methodological adjustments like propensity score matching (PSM) in case-control studies and randomized controlled trials (RCTs) can address these issues, current studies are often constrained by small sample sizes and non-standardized protocols, limiting statistical power, generalizability, and reproducibility. Expanding studies to large-scale, diverse populations and incorporating longitudinal sampling are essential to improve clinical applicability and to capture dynamic metabolic changes linked to disease progression or treatment. Future studies should also prioritize standardized sampling and analytical methods to enhance data interpretability.

Technological limitations, particularly the insufficient sensitivity, specificity, and accuracy of current MS platforms, also pose challenges. Advancing high-throughput MS can aid in detecting low-abundant metabolites, while integrating metabolomics with imaging techniques may enable high-resolution mapping of localized metabolic changes (Unsihuay et al., 2021). Furthermore, advancements in data analysis tools, particularly those leveraging bioinformatics, artificial intelligence and machine learning, will be critical for identifying complex patterns in metabolomics data. On one hand, integrating data from multiple biofluids and tissues to explore systemic-ocular interconnections can uncover robust biomarkers and therapeutic opportunities targeting both local inflammation and systemic disease drivers. On the other hand, integrating metabolomics with other omics technologies enables holistic data synthesis across diverse biological dimensions, providing a comprehensive view of biological systems and the underlying disease mechanisms. Together, such integrative approaches hold promise for refining personalized medicine.

Moreover, clinical translation remains a major challenge, as no OID biomarkers have yet achieved clinical validation. To bridge this translational gap, interdisciplinary collaborations among researchers, clinicians, and biomedical engineers should be established to validate candidate biomarkers and develop clinical tools, such as diagnostic kits, facilitating precision medicine paradigms.

Ultimately, addressing current limitations and prioritizing translational research will enable metabolomics to revolutionize the understanding of OID, transforming molecular insights into practical applications and advancing diagnostics, therapies, and patient outcomes.

7 Conclusion

Ocular Immune Diseases (OID) are highly heterogeneous, with intricate etiologies and poorly elucidated pathogenesis. Early diagnosis is challenging due to nonspecific symptoms and systemic associations, while current treatments remain suboptimal, leading to unfavorable prognoses. Metabolomics provides key insights into OID pathogenesis, linking ocular inflammation with systemic immune dysregulation. Key metabolic pathways implicated in OID include energy metabolism for immune activation, lipid metabolism driving chronic inflammation, amino acid metabolism modulating immune responses, and oxidative stress mitigating tissue damage. Metabolic biomarkers, such as purine metabolites in infectious OID and lipid mediators in non-infectious OID, facilitate early diagnosis, subtype classification and

Table 3 Detailed information of metabolomics studies on thyroid eye disease (TED)

Author, Year	Sample types	Number of Cases	Methodology (Identified Metabolites)	Key Pathways and Major Differential Metabolites
(Billiet et al., 2022)	Tear	Total: 65 21 active TED, 24 inactive TED, and 20 dry eye controls	Targeted LC-MS (188)	Polyamine metabolism and Urea Cycle. Active TED vs. inactive TED ↑: Two short-chain acylcarnitines, propionylcarnitine, butyrylcarnitine, spermine ↓: Ornithine, glycine, serine, citrulline, histidine
(Du et al., 2023)	OAT	Total: 12 7 inactive TED and 5 HCs	Targeted LC-MS (149)	Purine metabolism, beta-alanine metabolism, and glutathione metabolism. TED vs. HC ↑: Uric acid, oxidized glutathione ↓: Taurine
(Huang et al., 2022)	OAT	Total: 23 11 TED cases and 12 HCs	Untargeted LC-MS (3038, with 593 altered)	Cholesterol metabolism, choline metabolism, and fat digestion and absorption. TED vs. HC ↑: 367 metabolites, triglyceride,1D-myo-Inositol 3-phosphate, phosphocholine ↓: 226 metabolites, lidocaine, 5β-cholestane, monoethylglycylxylidide, pentadecylic acid, 3'-deoxystreptomycin
(Ji et al., 2018)	OAT and Plasma	Total: 79 21 GD, 26 TED, and 32 HCs	Untargeted GC-TOF-MS (90)	TED vs. HC OAT: ↑: Proline, fumarate, phenylalanine ↓: Glycerol Plasma: fumarate, proline, phenylalanine, glycerol
(Shi et al., 2023)	Serum	Total: 60 30 TED, and 30 HCs	Untargeted LC-MS (75 altered)	Glycine, serine, and threonine metabolism, and steroid hormone biosynthesis. TED vs. HC ↑: 20 metabolites ↓: 55 metabolites glycine, glycerol 3-phosphate, estrone sulfate
(Ueland et al., 2023)	Serum	Total: 200 64 GD, 36 TED, and 100 HCs	Targeted LC-MS (34)	Kynurenine pathway. TED/GD vs. HC ↑: kynurenine, quinolinic acid, 3-hydroxykynurenine
(Byeon et al., 2018)	Plasma and urine	Total: 86 23 GD, 31 TED, and 32 HCs	nUPLC-ESI-MS/MS based lipidomics (389 plasma and 273 urinary lipids)	Sphingolipid metabolism and lipid signaling pathways. TED/GD vs. HC Plasma: ↑: S1P, LPC, TG Urine: ↑: LPC, LPE Plasma+Urine: ↓: Ceramides
(Biscarini et al., 2023)	Fecal microbiota	Total: 146 59 GD, 46 TED, and 41 HCs	NMR	SCFA production and immune modulation. TED vs. HC ↑: Short-chain fatty acids (SCFAs), specifically butyrate and propionate
(Zhang et al., 2024b)	Fecal microbiota	Total: 59 30 TED and 29 HCs	Untargeted LC-MS (2234, with 184 altered)	Unsaturated fatty acids biosynthesis. TED vs. HC ↑: 63 metabolites, 4-Methyl-5-thiazoleethanol, Thiamine, Ellagic acid ↓:121 metabolites, Lignoceric Acid, Erucic acid, Arachidic Acid, Docosanoic Acid

personalized treatment strategies. By unveiling the intricate metabolic landscape of OID, metabolomics holds great promise for precision diagnostics and therapeutics, ultimately improving clinical outcomes.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest All authors declare that they have no conflicts of interest to disclose.

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