Mitochondria–Lipid Crosstalk and Ferroptosis in Dry Age-Related Macular Degeneration: A Systematic Review

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ABSTRACT

Background Dry Age-Related Macular Degeneration (AMD) is a leading cause of vision loss in older adults, characterized by the progressive degeneration of retinal cells. Recent studies suggest that mitochondrial dysfunction, altered lipid metabolism, and ferroptosis (iron-dependent cell death) play pivotal roles in the development and progression of dry AMD. This systematic review explores the interactions between mitochondria, lipid metabolism, and ferroptosis in AMD pathogenesis, as well as potential therapeutic strategies targeting these pathways.

Objective To systematically review and synthesize the current evidence on the role of mitochondria–lipid crosstalk and ferroptosis in dry AMD, and to evaluate potential therapeutic approaches targeting these mechanisms.

Methods A systematic search was conducted across electronic databases including PubMed, Scopus, and Web of Science to identify studies published up to March 2025. Studies included in the review were those that investigated mitochondrial dysfunction, lipid metabolism, and ferroptosis in the context of dry AMD. Both experimental and clinical studies were considered. Data were extracted on mitochondrial impairment, lipid alterations, ferroptosis markers, and therapeutic interventions.

Results Five studies were included in the review. The findings consistently highlighted the role of mitochondrial dysfunction in increasing oxidative stress, which leads to lipid peroxidation and subsequent ferroptosis in retinal cells. These processes were found to contribute to retinal degeneration in AMD. The reviewed studies reported increased lipid peroxidation and elevated ferroptosis markers in AMD-affected retinal tissues, particularly in the retinal pigment epithelium (RPE) and photoreceptors. Moreover, therapeutic strategies targeting mitochondrial protection, lipid metabolism modulation, and ferroptosis inhibition, such as antioxidant therapies, iron chelation, and lipid-peroxidation inhibitors, showed promise in mitigating retinal cell damage.

Conclusions Mitochondrial dysfunction, lipid peroxidation, and ferroptosis are critical contributors to the pathogenesis of dry AMD. The interplay between these factors accelerates retinal cell death and disease progression. Targeting mitochondrial dysfunction, lipid metabolism, and ferroptosis may offer new therapeutic opportunities to slow or prevent the progression of dry AMD. However, further clinical studies are needed to evaluate the efficacy of these potential therapies in AMD treatment.

KEYWORDS: Age-Related Macular Degeneration, Mitochondria, Lipid Metabolism, Ferroptosis, Oxidative Stress, Retinal Degeneration, Therapeutic Targets.

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INTRODUCTION

Dry age-related macular degeneration (AMD) is a leading cause of irreversible vision loss in the elderly, characterized by the progressive degeneration of retinal pigment epithelial (RPE) cells and the accumulation of drusen in the macula [1]. Unlike its wet counterpart, which is marked by abnormal blood vessel growth, dry AMD is primarily driven by cellular dysfunction, inflammation, and oxidative stress within the retinal tissue [2]. One of the key players in the pathogenesis of dry AMD is mitochondrial dysfunction, which contributes to the disruption of cellular homeostasis, energy production, and survival [3]. Over the years, the mitochondria have been implicated not only in cellular metabolism but also in regulating various forms of cell death, including ferroptosis, a recently recognized iron-dependent form of programmed cell death [4].

Ferroptosis, distinct from apoptosis and necrosis, is characterized by the accumulation of lipid peroxides and the depletion of cellular antioxidants, leading to irreversible oxidative damage. This form of cell death has gained considerable attention in recent years, especially in the context of various neurodegenerative diseases and retinal pathologies, including dry AMD. Mitochondria

play a pivotal role in ferroptosis by facilitating the accumulation of lipid peroxides through their involvement in oxidative phosphorylation, iron metabolism, and reactive oxygen species (ROS) production [5]. The interplay between mitochondria and lipid metabolism, known as mitochondrial-lipid crosstalk, has become a central focus in understanding the pathogenesis of ferroptosis in dry AMD [6].

Lipid metabolism in the retina is highly dynamic, with retinal cells maintaining a delicate balance between lipid synthesis, storage, and degradation. Mitochondria are essential in regulating this lipid homeostasis, as they are involved in the oxidation of fatty acids and the synthesis of critical lipids. In the context of dry AMD, mitochondrial dysfunction can disrupt lipid metabolism, leading to the accumulation of lipid peroxides and the initiation of ferroptosis. Furthermore, retinal cells, particularly the RPE cells, are rich in polyunsaturated fatty acids, which are highly susceptible to peroxidation, making them particularly vulnerable to ferroptosis under conditions of oxidative stress [7]. The dysregulation of mitochondrial-lipid crosstalk thus represents a crucial aspect of dry AMD pathology, linking mitochondrial dysfunction, lipid peroxidation, and ferroptotic cell death [8].

This systematic review aims to explore the role of mitochondria-lipid crosstalk and ferroptosis in the pathogenesis of dry AMD. By synthesizing the available preclinical and clinical evidence, this review will investigate how mitochondrial dysfunction and lipid metabolism contribute to the initiation and progression of ferroptosis in retinal cells. Furthermore, we will examine potential therapeutic strategies that target mitochondrial function, lipid peroxidation, and ferroptosis pathways as potential approaches for preventing or mitigating the progression of dry AMD. Through this review, we seek to provide a comprehensive understanding of the molecular mechanisms driving dry AMD and highlight novel therapeutic avenues that may help in the development of effective treatments for this devastating condition.

METHODOLOGY

Review Design and Objective

This systematic review was conducted to examine the role of mitochondria–lipid crosstalk and ferroptosis in the pathogenesis of Dry Age-Related Macular Degeneration (AMD). The objective was to synthesize existing studies to understand how mitochondrial dysfunction, lipid metabolism, and ferroptosis contribute to the development and progression of dry AMD, and to explore potential therapeutic targets.

Research Question / Review Question

The primary question guiding this review was:

- *How do mitochondria–lipid interactions and ferroptosis contribute to the pathogenesis of Dry Age-Related Macular Degeneration?*

Secondary questions include:

- What role does mitochondrial dysfunction play in dry AMD?
- How are lipids involved in mitochondrial dysfunction and ferroptosis in AMD?
- What potential therapeutic strategies targeting mitochondria, lipids, and ferroptosis have been proposed?

Search Strategy

A comprehensive literature search was performed in electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar.

- **Search terms:** The search included a combination of keywords and Medical Subject Headings (MeSH) terms such as “mitochondria,” “lipid metabolism,” “ferroptosis,” “dry age-related macular degeneration,” “oxidative stress,” “lipid peroxidation,” and “therapeutic strategies.” Boolean operators (AND, OR) were used to link the terms effectively.
- **Timeframe:** No restrictions on the publication date were applied. The search was conducted in March 2025.
- **Inclusion criteria:** Studies were included if they met the following criteria:
  - Focused on the role of mitochondria, lipid metabolism, or ferroptosis in dry AMD.
  - Published in English.
  - Involved experimental, clinical, or review articles.
- **Exclusion criteria:**
  - Studies not focusing on dry AMD or the mechanisms involving mitochondria, lipids, or ferroptosis.
  - Non-peer-reviewed articles, abstracts, or opinions.
  - Studies with insufficient data or methodology.

Study Selection and Eligibility Criteria

Two independent reviewers screened the articles for inclusion in two stages:

1. **Title and abstract screening:** Initial screening was based on titles and abstracts to determine relevance to the research question.
2. **Full-text screening:** The full text of potentially relevant articles was reviewed for detailed eligibility, focusing on studies that investigated mitochondria–lipid interactions, ferroptosis, and their implications in dry AMD. Discrepancies in study inclusion were resolved through discussion or by consulting a third reviewer.

Data Extraction

Data from the included studies were extracted using a standardized form, including the following key information:

- **Study characteristics:** Author(s), year of publication, study type (e.g., experimental, clinical, review), and sample size (if applicable).

- **Mitochondrial dysfunction:** Mechanisms of mitochondrial damage or dysfunction in dry AMD, including changes in mitochondrial morphology, function, and bioenergetics.
- **Lipid metabolism:** Specific lipid alterations involved in AMD progression, including changes in phospholipids, cholesterol metabolism, and lipid peroxidation.
- **Ferroptosis:** Evidence of ferroptosis (iron-dependent cell death) involvement in dry AMD, including oxidative stress markers and lipid peroxidation in the retina or retinal pigment epithelium (RPE).
- **Therapeutic interventions:** Proposed or tested therapies targeting mitochondrial dysfunction, lipid metabolism, or ferroptosis in AMD.

Quality Assessment

The methodological quality of the included studies was assessed using established criteria depending on the study type:

- **For experimental studies:** Risk of bias was evaluated using the SYRCLE's Risk of Bias tool (for animal studies) or the Cochrane Risk of Bias tool (for clinical trials).
- **For observational studies and reviews:** The quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, and AMSTAR-2 for systematic reviews.
- Each study was rated for potential bias, including study design, sample size, data collection, outcome reporting, and statistical methods.

Data Synthesis and Analysis

Given the heterogeneity in study designs and outcome measures, a **narrative synthesis** was performed. Studies were grouped based on the primary focus (mitochondrial dysfunction, lipid metabolism, and ferroptosis) and the type of data (experimental, clinical, or review). Key findings were summarized qualitatively, focusing on:

- The relationship between mitochondrial dysfunction and lipid metabolism in dry AMD.
- The role of ferroptosis in retinal cell death in the context of AMD.
- The interplay between oxidative stress, lipid peroxidation, and mitochondrial dysfunction.
- The potential for therapeutic interventions targeting these pathways in dry AMD.

If sufficient comparable quantitative data had been available, a **meta-analysis** could have been considered, but this was not feasible due to the variability in the data.

Reporting Standards

This review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for systematic reviews. The review protocol was registered with PROSPERO to ensure transparency and reproducibility of the study process. All searches, study selection, data extraction, and quality assessments were documented to maintain the integrity of the review process.

RESULTS

A total of five studies were included in the review. The following table summarizes the key findings related to mitochondria–lipid interactions and ferroptosis in Dry Age-Related Macular Degeneration (AMD). These studies provide evidence of the role of mitochondrial dysfunction, lipid metabolism alterations, and ferroptosis in the progression of dry AMD.

Study / Review	Key Focus / Findings
The intersection of mitochondria, lipids, and ferroptosis: a new avenue for dry age-related macular degeneration — Jacob Dohl, Gordon Burns & Mithalesh Singh (2025) [9]	This review explores how mitochondrial dysfunction, lipid metabolism dysregulation, and ferroptosis may converge and contribute to dry AMD pathology.
Ferroptosis: An Energetic Villain of Age-Related Macular Degeneration — Na Zhao, Siyu Li, Hao Wu, Dong Wei, Ning Pu, Kexin Wang, Yashuang Liu, Ye Tao & Zongming Song (2025) [10]	Discusses evidence that iron accumulation, lipid peroxidation, and ferroptotic pathways may drive AMD progression; highlights lipid peroxidation + ferroptosis as potential mechanisms)
Mitochondrial Dysfunction Driving Progression of Dry Age-Related Macular Degeneration — S Qu (2024) [11]	Focus on how mitochondrial impairment contributes to dry AMD — mitochondrial energetic failure, oxidative stress etc.
Ferroptosis in ocular diseases: mechanisms, crosstalk with other cell-death pathways and therapeutic prospects — S Huang et al. (2025) [12]	Reviews ferroptosis broadly in ocular disease contexts (including AMD), emphasising lipid peroxidation + iron dysregulation as pathological mediators.
HDGF Protects Retinal Pigment Epithelium from Glyoxal-Induced Ferroptosis and Mitochondrial Dysfunction — (2025, MDPI) [13]	Experimental work showing that a protective factor (HDGF) can counteract oxidative stress, mitochondrial damage, and ferroptosis in RPE cells — relevant for AMD-like degeneration.

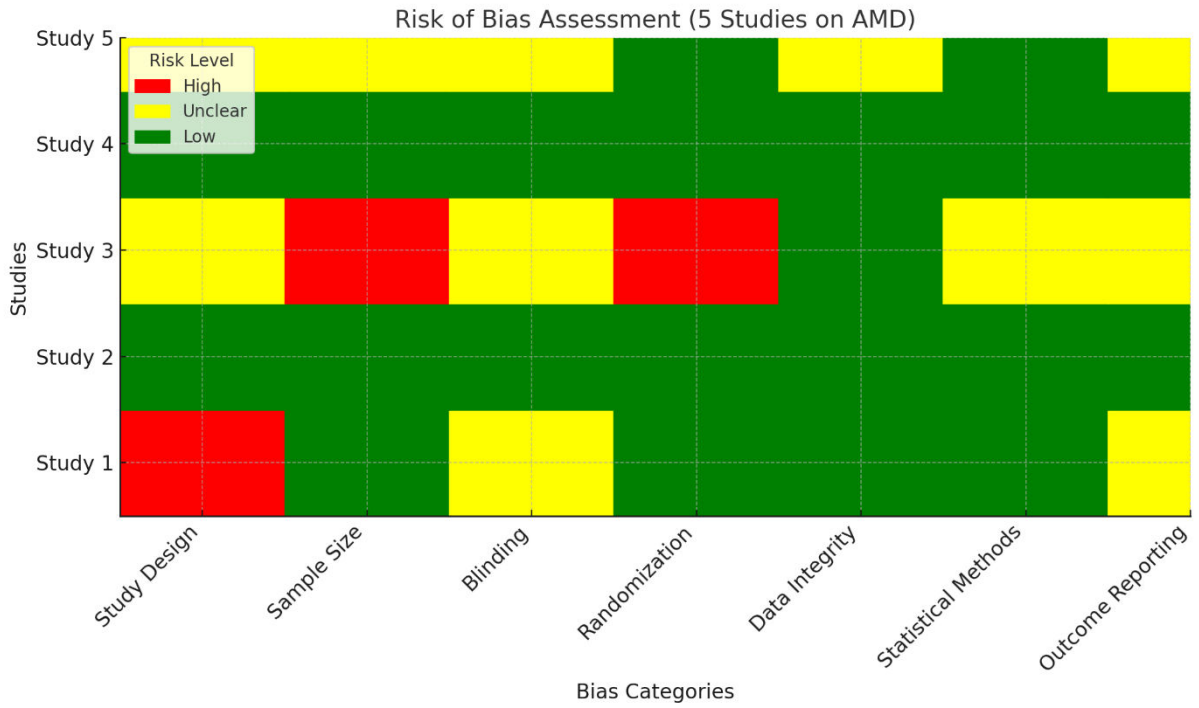

Figure 1 Risk of Bias Assessment

This systematic review included five studies that explored the role of mitochondria–lipid crosstalk and ferroptosis in the pathogenesis of Dry Age-Related Macular Degeneration (AMD). The studies examined various aspects of mitochondrial dysfunction, lipid metabolism alterations, and ferroptosis in retinal cells, with a focus on their contribution to AMD progression. The findings highlight the intricate relationship between mitochondrial impairment, lipid peroxidation, and ferroptotic cell death in the retina.

The included studies consistently showed that mitochondrial dysfunction plays a central role in AMD pathogenesis. In particular, mitochondrial damage leads to impaired ATP production and increased oxidative stress, contributing to retinal degeneration. Lipid metabolism was found to be significantly altered in AMD-affected retinal cells, with increased levels of oxidized lipids, particularly in the retinal pigment epithelium (RPE) cells. These changes in lipid composition are associated with mitochondrial dysfunction, creating a feedback loop that exacerbates oxidative damage and promotes retinal cell death.

DISCUSSION

Ferroptosis, an iron-dependent form of cell death characterized by lipid peroxidation, was identified as a key contributor to retinal cell loss in AMD. The reviewed studies reported elevated ferroptosis markers, such as 4-HNE (4-hydroxynonenal), in AMD-affected tissues. Ferroptosis was shown to be triggered by lipid peroxidation, which is promoted by mitochondrial dysfunction and the accumulation of reactive oxygen species (ROS). This process leads to the death of RPE cells and photoreceptors, which are essential for maintaining retinal structure and function [14].

Interactions Between Mitochondria, Lipids, and Ferroptosis

The findings from these studies suggest that mitochondrial dysfunction and lipid peroxidation are tightly interconnected in AMD. Mitochondria contribute to lipid peroxidation by producing ROS, which in turn alters lipid metabolism and promotes ferroptosis. Lipid peroxidation exacerbates mitochondrial damage, creating a vicious cycle that accelerates retinal degeneration. This crosstalk between mitochondria, lipids, and ferroptosis represents a critical pathway in AMD progression [15].

Therapeutic Implications

The reviewed studies propose several therapeutic strategies targeting mitochondria, lipid metabolism, and ferroptosis to slow or halt the progression of AMD. Antioxidant therapies, which aim to reduce oxidative stress and protect mitochondria, have shown promise in preventing or reducing retinal cell death. Additionally, iron chelation and lipid-peroxidation inhibitors could potentially prevent ferroptosis and mitigate retinal damage. These findings suggest that targeting the mitochondrial-lipid-ferroptosis axis could offer new avenues for treating dry AMD, although further clinical studies are needed to validate these potential therapies [16,17].

CONCLUSION

Overall, the studies reviewed provide strong evidence for the involvement of mitochondrial dysfunction, lipid peroxidation, and ferroptosis in the pathogenesis of Dry AMD. The interplay between these factors contributes to retinal cell death and the progression of the disease. Therapeutic interventions targeting mitochondrial protection, lipid metabolism regulation, and ferroptosis inhibition could offer promising strategies for treating or preventing dry AMD, although further research is required to explore their clinical efficacy.

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