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THE ANALYSIS STUDY OF VISUAL IMPAIRMENT AND BLINDNESS DUE TO MACULAR DISEASES: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *DME and AMD are major causes of blindness, affecting the macula and central vision. AMD accounts for 8.7% of global blindness cases. Understanding AMD beyond the retina can provide insights into its pathophysiology, consequences, therapy, and clinical course. Anti-VEGF agents have shown promise in treating AMD, but a definitive treatment remains unidentified.*

Methods: *Following PRISMA 2020 guidelines, this systematic review concentrated on full-text English literature published between 2014 and 2024. Editorials and review articles that appeared in the same journal as the submission were not accepted without a DOI. A number of websites, including ScienceDirect, PubMed, and SagePub, were utilized to gather the literature.*

Result: *The study looked at more than 400 publications using reputable sources including Science Direct, SagePub, and PubMed. After it was decided that eight publications needed greater investigation, a more extensive review of the entire literature was carried out.*

Conclusion: *BCVA is crucial in the treatment of AMD and DME, with targeting VEGF being an effective approach. However, their effectiveness in other forms of AMD is less convincing. Chronic inflammation is a key factor in retinal diseases, including AMD. DME treatment requires a multidisciplinary approach, with anti-VEGF agents being the first-line treatment.*

Keyword: *DME, AMD, blindness, macula, VEGF.*

INTRODUCTION

Age-related macular degeneration (ARMD) is a leading cause of blindness in developed countries, particularly among individuals over 60 years of age. It primarily affects the macula, leading to central vision impairment and hindering activities such as reading and driving. ARMD accounts for 8.7% of global blindness cases.[1] Ophthalmologists experimented with thermal laser and photodynamic therapies in the 1980s, but their results were mixed. Various medications have been used as a result of insights into the pathophysiology of the disease. According to recent research, comprehending AMD outside of the retina may offer important insights into its pathophysiology, effects, treatment, and clinical trajectory.[2] Notably, the development of anti-VEGF agents in the early 2000s has been instrumental in treating choroidal neovascularization and has shown promise in preserving or restoring vision in many cases.[3]

The potential of the following drugs to treat age-related macular degeneration (AMD) is being investigated: Anti-platelet-derived growth factor (anti-PDGF) medication migpleranib prevents PDGF from attaching to PDGF-BB.[4] Many regulatory bodies throughout the world have approved the use of pazopanib, a topical eye drop formulation of a strong and selective multi-targeted receptor tyrosine kinase inhibitor, for the treatment of renal cell carcinoma and soft tissue sarcoma.[5] Lampalizumab (INN), a humanized monoclonal antibody's antigen-binding fragment that binds to complement factor D, is being developed as a treatment for AMD-related geographic atrophy.[6] Atrophic AMD is treated with topical ocular drops containing tandospirone, a partial 5-HT1A receptor agonist; paroxysmal nocturnal hemoglobinuria (PNH) is treated with intravenous infusions of eculizumab, an inhibitor of complement protein C5.[7] Even with these encouraging advancements, an effective long-term treatment for AMD has not yet been found. To find new therapeutic targets, more research into the underlying disease pathways is required. New findings are being made in an effort to better understand the causes, effects, therapies, and clinical development of AMD; therefore, researchers' methods may need to go beyond the retina's immediate environment.[2] Therefore, this review extensively explores the role of pathogenesis, consequences, and treatment in AMD, which is crucial for the management of the disease, offering valuable insights into AMD concerns and expediting the management of this condition.[7]

Diabetic macular edema (DME) is a significant complication of diabetes, frequently leading to vision loss.[8] One of the hallmarks of diabetic macular edema (DME) is the build-up of fluid in the macula, the area of the retina in the center that is responsible for sharp vision.[9,10] The retina swells as a result of the blood-retinal barrier breaking down in the pathophysiology of DME, which is a complex interaction of vascular, inflammatory, and neurodegenerative processes.[10,11] Blurred vision and metamorphopsia, or distorted vision, are two clinical symptoms of DME that significantly impair tasks requiring central vision, like reading and facial recognition.[11]

The worldwide diabetes pandemic is inextricably linked to the prevalence of DME. Globally, millions of people suffer from diabetes today; projections indicate that number will increase to 592 million by 2035.[12] Of these, about one-third may have diabetic retinopathy in some form, and a sizable fraction may advance to diabetic macular edema (DME).[8,13] In addition to the length of diabetes, other risk factors include the existence of systemic diseases like hyperglycemia and hypertension.[13] Within nine years of diagnosis, DME affects approximately 27% of patients with type 1 diabetes; this represents a prevalence of 5.40%. The DME prevalence of type 2 diabetes increases from 3% after five years to 28% after twenty years, with an annual incidence of 0.4%. Overall, depending on the study and population, DME prevalence varies between 4.2% and 7.9% in type 1 diabetes and between 1.4 and 12.8% in type 2 diabetes.[8,13] This increasing frequency of DME highlights the need for effective management strategies that can address its vision-threatening effects. The introduction of anti-vascular endothelial growth factor (VEGF) therapies has, in this context, marked a paradigm shift in the DME management field. A major component in the pathophysiology of DME is the target of these treatments, which have the potential to stabilize affected patients' visual outcomes as well as enhance them.[14]

Developing effective management strategies can be aided by comprehending the connection between macular diseases and visual impairment or blindness. Based on studies done over the previous ten years, this systematic review of the literature sought to investigate the connection between macular diseases and visual impairment or blindness.

METHODS

PROTOCOL

The study's author carefully followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to make sure all rules were followed. In order to present precise and convincing research findings, a methodical approach was employed.

CRITERIA FOR ELIGIBILITY

This paper offers a comprehensive review of studies carried out over the last ten years concerning the relationship between pharmacologic treatments for knee osteoarthritis and long-term pain management. Through thorough data analysis, this program seeks to improve and clarify patient care protocols. The major objective of this thesis is to draw attention to significant topics that are discussed in a variety of literary works.

To ensure that the data used in this analysis were accurate, strict inclusion and exclusion criteria were implemented. For inclusion, any work published in English between 2014 and 2024 is acceptable. Among the exclusion criteria are multiple entries in the same publication, editorials, public reviews, and submissions without a DOI.

SEARCH STRATEGY

The study's keywords include "blindness, blind, macular disease, visual impairment, relationship, macular degeneration, prognosis, effect". For this research, the following Boolean MeSH keywords were entered into the databases: (((“blindness”[MeSH Terms] OR “blind“[All Fields] AND “macular disease”[All Fields]) OR (“visual impairment”[MeSH Terms] OR “visual”[All Fields] AND “macular”[All Fields]) AND (“relationship”[MeSH Terms] OR “effect”[All Fields] OR “outcome”[All Fields] OR “macular degeneration”[MeSH Subheading] OR “prognosis”[All Fields] OR “impairment”[All Fields]))).

DATA RETRIEVAL

Before beginning this thorough investigation, the authors carefully considered the relevance of each article based on its title and abstract. Only studies that met the article's inclusion and goal criteria were accorded greater weight. A clear and consistent pattern emerged after multiple searches. English was the only language in which full-text contributions were accepted. The most rigorous screening process produced content that directly related to the study's topic and satisfied all predetermined inclusion criteria. Research that failed to satisfy these requirements were usually disregarded and their findings were not given much weight. The evaluation contained a wide range of data, including factors, titles, authors, publication dates, locations, and study procedures.

QUALITY ASSESSMENT AND DATA SYNTHESIS

The authors themselves go over each article's title and abstract in detail to determine which ones require further investigation. After that, each document that had been made available for review had to be carefully examined. The evaluation results served as a guide for selecting the review papers. This criterion made it possible to choose papers for further examination more rapidly, which in turn made it possible to evaluate earlier research and the circumstances surrounding its assessment in greater detail.

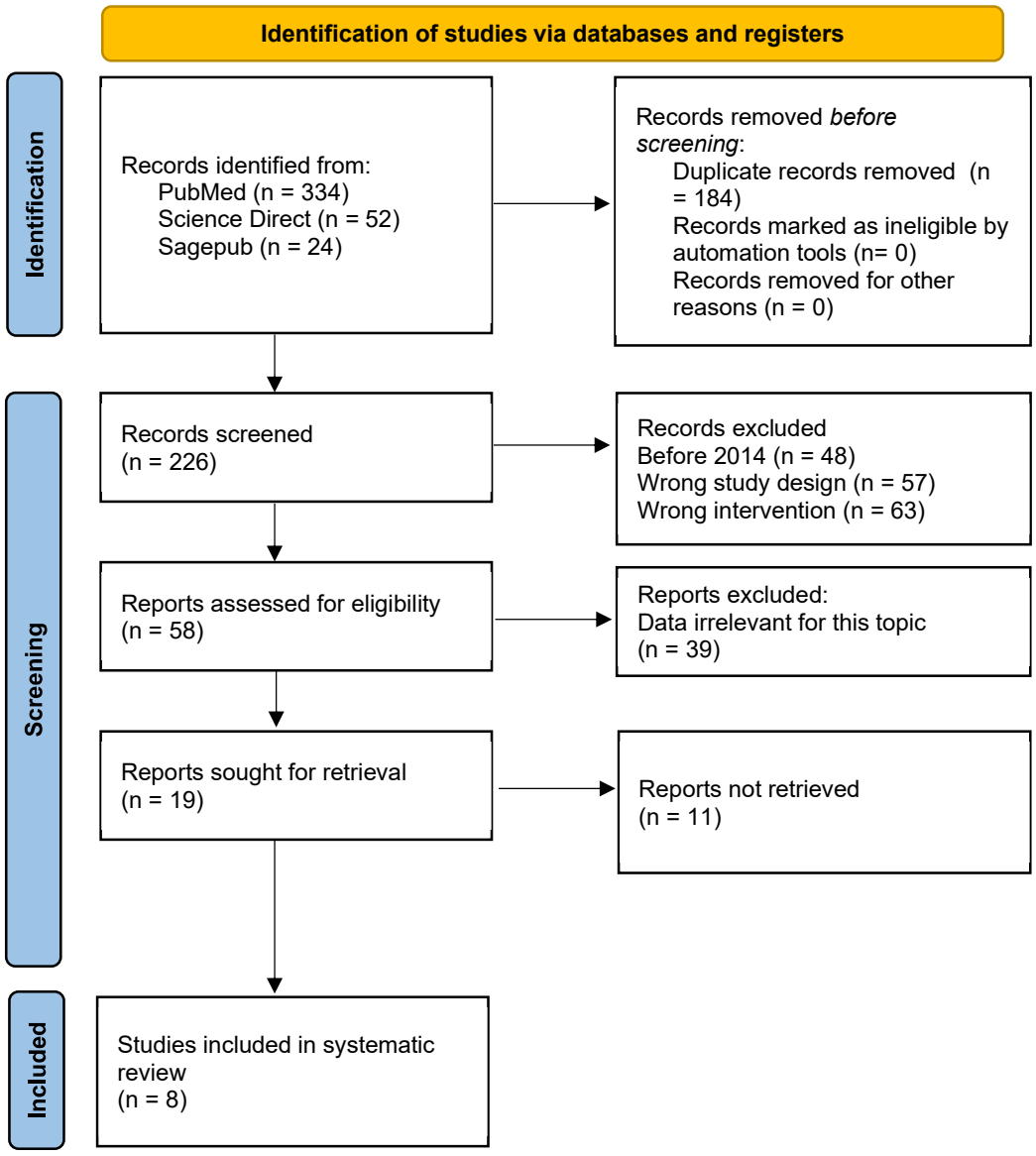

Figure 1. Article search flow chart

RESULT

To begin the investigation, our team painstakingly gathered a sizable collection of papers from reputable sources such as Science Direct, PubMed, and SagePub. Following a thorough three-step screening process, we selected eight papers that were judged to be extremely relevant to our current systematic investigation. After that, we carefully evaluated each report and focused on a small number of subjects for additional research. We have included a quick summary of the evaluated content in Table 1 to assist you in expediting our investigation.

Table 1. The literature included in this study

Author	Origin	Method	Sample	Result
Amini et al.[7] (2023)	Iran	Review	-	AMD, a complex eye disorder, causes irremediable blindness in the elderly. It affects the macula, affecting vision. Factors like aging, genetics, environment, and autoimmune disorders contribute to AMD. Healthy lifestyles, exercise, and personalized genetic

				information can reduce risk and improve visual acuity.
Khoramnia et al.[15] (2023)	Germany	Review	-	The management of diabetic macular oedema (DMO) requires clear guidelines to improve visual outcomes. Despite anti-VEGF therapies enhancing visual acuity, the relationship between these parameters and visual acuity is unclear. Controlling CSFT and managing intraretinal fluid could improve visual outcomes, highlighting the need for clearer guidelines.
Vujosevic et al.[16] (2023)	Italy	Review	-	AMD, a leading cause of blindness, significantly impacts visual quality. Geographic atrophy, the late form of AMD, increases with age, affecting 1 in 5 individuals aged 85 and above. Geographic atrophy poses a significant burden on patients, careers, and health providers.
Cheema & Cheema.[17] (2024)	United Kingdom	Review	-	One of the main causes of vision impairment in diabetics is DME pathogenesis. Anti-vascular endothelial growth factor (VEGF) treatments, including bevacizumab, aflibercept, and ranibizumab, are used in the management of DME. By focusing on VEGF, these treatments lessen macular edema and enhance visual acuity. The goal of future developments in anti-VEGF therapy is to direct clinical practice and enhance patient outcomes.
Cheng & Liu.[18] (2024)	China	Systematic Review	39 studies	The study found that intravitreal injection of bevacizumab + triamcinolone acetonide improved best-corrected visual acuity in patients with DME, while intravitreal dexamethasone was the most effective in improving visual acuity and reducing central macular edema at 6-month follow-up. Both treatments showed significant improvements in visual acuity and edema reduction.
Salvetat et al.[19] (2024)	Italy	Review	-	Diabetic macular edema, a common complication of diabetes, is caused by poor

				glycemic control, hypertension, hyperlipidemia, and genetic predisposition, requiring early diagnosis and management.
Sepah et al.[20] (2024)	USA	Post Hoc Analysis Study	2 studies	In both trials, patients with higher AH IL-6 concentrations had worse visual outcomes. Patients with low AH IL-6 concentrations experienced a mean BCVA change of 2.9 letters, while those with high AH concentrations experienced a mean BCVA change of 4.9 letters.
Yao et al.[21] (2024)	Singapore	Review	-	This review explores the potential of AI in managing diabetic retinopathy and diabetic macular edema, highlighting advancements in disease identification, patient profiling, and management. However, challenges like regulatory compliance and privacy need to be addressed for widespread adoption.

Amini's research highlights the systemic nature of AMD, involving genetic, environmental, autoimmune, and non-autoimmune disorders. Healthy lifestyles, therapeutic strategies, and personalized genetic information are crucial for reducing visual impairment and legal blindness.[7]

Khoramnia's research highlights the need for clear recommendations on retinal fluid management in DMO patients, highlighting the importance of controlling CSFT fluctuations and fluid parameters in decision-making. A more stringent approach and clearer recommendations could improve visual outcomes for patients with DMO.[15]

AMD progression is a significant issue in Asian populations, with European populations showing higher prevalence and incidence rates of GA. Vujosevic's research suggests that genetic variability and environmental factors play a role in this progression. Future studies should explore the drivers of progression to GA across different ancestries and regions, aiming to develop prevention strategies and resource allocation strategies.[16]

The review by Cheema & Cheema emphasizes how anti-VEGF medications can significantly improve DME, the primary cause of visual impairment in diabetics. Important clinical trials that have demonstrated their efficacy include VISTA-DME, VIVID-DME, and RIDE/RISE. But problems like fluctuating patient responses and economic factors still exist, requiring ongoing research and creative thinking in treatment approaches.[17]

Cheng et al. conducted a study involving 39 studies involving 5823 eyes of diabetic macular edema patients and 10 interventions. The study found that IVB + TA had the best effect on improving visual acuity, followed by DEX+LP. DEX was the best in improving best-corrected visual acuity at 6 months of treatment, followed by IVA and DEX+LP. The effects of TA+LP and LP were not ideal.[18]

Salvetat et al. highlighted the complex treatment of Dry Eye Disease (DME) with intravitreal pharmacotherapy, macular laser photocoagulation, and pars plana vitrectomy. However, anti-VEGF agents have higher retinal thickness fluctuations, require a demanding regimen, and have lower systemic safety.[19]

Sepah et al. found that IL-6 concentration in AH was higher than in serum samples at month 2, and a negative correlation between AH and serum IL-6 concentrations was observed. BCVA change improved in patients with low vs high IL-6 concentrations. Higher AH IL-6 concentrations at baseline were associated with worse BCVA outcomes at month 12 in READ-3. Higher AH IL-6 concentrations were associated with lower BCVA gains.[20]

Yao's research highlights the potential of AI algorithms in managing DR and DME, enhancing accuracy in screening, triage, and diagnosis, and enabling AI-driven precision medicine, thereby addressing the global burden of these conditions.[21]

DISCUSSION

Genetic susceptibility significantly impacts the development of AMD, with a total of 103 AMD genes or loci having been identified by the GWAS Catalogue. Among these, CFH and HTRA1 are particularly pivotal in regulating complement activity and influencing AMD, as highlighted in the work of Fritsche et al. (2014).[22] Moreover, a specific single nucleotide polymorphism (SNP) denoted as Y402H has been associated with AMD prevalence in the European population. Mutations in the complement pathway, including CFB and CFI, can either confer protection or increase the risk for AMD. It's important to note that environmental factors, such as smoking, can also impact the onset and progression of AMD. Notably, the APOE gene governs lipid metabolism in the nervous system and retina, while the ARMS2/HTRA1 gene raises the risk of early AMD development and its progression to nAMD and GA, as indicated by studies conducted by Canfield et al. (2017) and Grassmann et al. (2015).[23,24]

Visual acuity is an essential consideration in the treatment of age-related macular degeneration (AMD), and targeting VEGF, a promoter of abnormal blood vessel growth, has proven to be an effective approach. Medications that inhibit VEGF, such as pegaptanib sodium and ranibizumab, have demonstrated similar efficacy in managing AMD. However, their effectiveness in treating other forms of AMD is less convincing.[7] Studies on polypoidal choroidal vasculopathy, including EVEREST I and II, have shown comparable visual acuity outcomes but improved histological findings. In addition, complement inhibition with drugs like aseculizumab and lampalizumab shows promise as a potential therapy for AMD.[25,26] It's worth noting that using standard visual acuity as the primary measure in various studies may not be suitable, especially in cases of geographic atrophy (GA) where the progression of lesions is slow. Further research is warranted to assess the impact of incorporating photodynamic therapy for polypoidal choroidal vasculopathy.[7]

Chronic inflammation is a key factor in retinal diseases, including DME and AMD.[27,28] The correlation between intraocular IL-6 levels and visual acuity (VA) outcomes with ranibizumab treatment in the HARBOR and READ-3 trials was examined. In the HARBOR trial, there was no correlation between AH and serum IL-6 concentrations, suggesting local intraocular secretion. However, in the READ-3 trial, averaged IL-6 concentrations remained relatively stable, suggesting that intraocular IL-6 concentrations were unaffected by anti-VEGF therapy in patients with DME.[20] This suggests that IL-6 may be a therapeutic target, especially in patients with high IL-6 concentrations.[29] The current body of evidence suggests that DME transitions from a permeability-based disease to an inflammation-based multifactorial disease, where inflammatory mediators, including IL-6, may play an important role in mediating underlying macular edema.[20]

The relationship between visual outcomes and retinal thickness in patients with diabetic macular edema disease (DME) is unclear. While CSFT, the most commonly used OCT biomarker, has a correlation with BCVA at baseline and following treatment, the relationship is small to moderate. Recent studies suggest retinal fluid volume may be a more reliable biomarker for monitoring DME. Individual fluid types also impact visual outcomes, with patients treated with ranibizumab, laser photocoagulation, or both having better BCVA than those with IRC > 380 μm.[15] Visual function assessment using fundus images has been explored in recent studies. An ML-based VA measurement model was developed using fundus photos from 79,798 patients with macular diseases. The model showed an average accuracy of 82.4% in estimating four VA levels.[30] Paul et al. employed AI architectures to predict best-corrected visual acuity (BCVA) using fundus photos in center-involved DME (CI-DME) patients. The ResNet50 architecture estimated BCVA with an MAE of 9.66 letters, within two lines on the ETDRS chart.[31] This approach could offer VA estimation for patients unable to participate in chart-based assessments.[21]

The goal of DME management is to address the multifactorial nature of the disease by combining anti-VEGF agents with other treatment modalities such as corticosteroids and laser therapy. In addition to treating inflammation and macular edema, this method lowers vascular permeability. However, the possibility of side effects limits the use of corticosteroids. Alternatively, anti-VEGF and laser therapy can be combined, focusing on immediate reduction of edema and longer-term stabilization. The goal of ongoing research is to identify the safest and most effective methods, maximizing therapeutic benefits while lowering risks and treatment burdens.[17] DME treatment is complex and requires a multidisciplinary approach, with anti-VEGF or steroids being the first-line treatment. However, anti-VEGF agents are associated with higher retinal thickness fluctuations, higher patient compliance, and lower systemic safety.[32,33] CSs offer an alternative therapeutic strategy, but their efficacy and safety require careful patient selection. Alternative therapeutic strategies targeting inflammation, oxidative stress, and neurodegeneration are currently unapproved.[19]

The research revealed that the combination of IVB+TA and glucocorticoids (TA or DEX) significantly enhanced the outcomes of patients with diabetic macular edema at the 3-month follow-up. The combination of IVB and TA showed

significant superiority over other anti-VEGF or glucocorticoid therapies during this 3-month period. The effectiveness of TA alone was comparable to that of anti-VEGF alone, while the combination of IVB and TA demonstrated significant superiority over other anti-VEGF or glucocorticoid treatments. The combination of TA and LP had a notable therapeutic effect on central macular thickness in diabetic macular edema patients, which was statistically different from LP. The outcomes suggested that all regimens, except for the placebo, contributed to improving the best corrected visual acuity and decreasing macular thickness.[18] The efficacy of DEX in enhancing the best corrected visual acuity needs to be reassessed to eliminate bias-related errors and to clarify the actual impact of DEX on BCVA at 3 and 6 months.[34] Future research could focus on patients who show resistance to anti-VEGF drugs during clinical treatment.[18]

CONCLUSION

Genetic susceptibility and environmental factors significantly impact the development of age-related macular degeneration (AMD). Best corrected visual acuity (BCVA) is an essential consideration in the treatment of AMD, and targeting VEGF, a promoter of abnormal blood vessel growth, has proven to be an effective approach. Medications that inhibit VEGF, such as pegaptanib sodium and ranibizumab, have demonstrated similar efficacy in managing AMD. However, their effectiveness in treating other forms of AMD is less convincing. Chronic inflammation is a key factor in retinal diseases, including DME and AMD. The relationship between visual outcomes and retinal thickness in patients with diabetic macular edema disease is unclear, but retinal fluid volume may be a more reliable biomarker for monitoring DME. DME treatment requires a multidisciplinary approach, with anti-VEGF agents being the first-line treatment.

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