SYSTEMATIC REVIEW OPEN ACCESS

Clinicopathological Assessments of Brain-Derived Neurotrophic Factor BDNF Physiology in Diabetic Retinopathy: A Systematic Review

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ABSTRACT

Background: Diabetic retinopathy (DR) was seen to be one of the most grievous complications of diabetes mellitus that caused a gradual loss of vision. Brain-derived neurotrophic factor BDNF has also been drawn into focus as a molecule relevant to retinal health and neuroprotection as more information unfolds. This research aimed to evaluate the clinicopathological significance of BDNF in patients with diabetic retinopathy (DR), with particular reference to its diagnostic and therapeutic implications. It also aimed to compare the diagnostic potential of BDNF with other existing biomarkers and therapeutic applications with an emphasis on treatment outcomes.

Methods: The PRISMA guidelines were followed while conducting the systematic review, and the databases for data extraction were PubMed, Scopus, and Web of Science. English language articles that were published in scientific peer-reviewed journals between January 2013 and April 2024 were included. Furthermore, this review included observational clinical studies and clinical research studies with diabetic patients, from which the authors examined BDNF levels in retinopathy patients. Any study that contained non-diabetic retinal disease, reviews, reports, and studies with incomplete information was excluded. For proper comparison, BDNF expression patterns were systematically evaluated and compared between the DR stages. For the removal of biases and assessment of risks, the Cochrane risk of bias tool and the Newcastle-Ottawa Scale were used by two independent reviewers.

Results: An initial search yielded 106 articles, and 15 were selected after fulfilling the inclusion criteria. The current study found that the plasma BDNF levels were lower in the patients with DR stages 4 and 3 compared with stages 2 and healthy diabetic individuals. This reduction was strongly associated with worsening of retinal vascular permeability and inflammation, as well as neuronal degeneration. There was converging data to show that higher BDNF levels were being linked to slower DR progression, and thus, the neurotrophic factor could be protective.

Discussion: BDNF emerged as a potential biomarker for monitoring the progression of DR. Its lower levels were associated with increased retinal damage and inflammation. Modulation of BDNF expression was beneficial for treatment, it also highlighted its role in neuroprotection and disease progression. However, variations in study designs and measurement techniques limited consistency in results.

Keywords: Brain-Derived Neurotrophic Factor, Diabetic Retinopathy, Retinal Neuroprotection, Biomarker, Diabetes Mellitus, Retinal Inflammation.

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INTRODUCTION

Diabetic Retinopathy (DR) was seen as a severe microvascular complication of diabetes mellitus and to date has been shown as the number one cause of global vision impairment[1]. As reported in studies, it is a complication of long-standing hyperglycemia that results in damage to retinal capillaries and the development of vascular leakage, inflammation, and neuronal degeneration[2]. There were multiple stages of the disease, ranging from mild non-proliferative changes through advanced proliferative retinopathy marked by neovascularization and severe vision loss. These outcomes could be prevented by early detection and by targeted therapeutic interventions. Recent advances in diagnostics and management have narrowed the gap but still left significant areas of the molecular mechanisms underpinning DR poorly understood[3]. Brain-derived neurotrophic Factor (BDNF) appeared as a Neurotrophin that was shown to be important in neuronal development, survival, and synaptic plasticity. BDNF has been known to have functions beyond the central nervous system, and is now increasingly recognized for its role in retinal neuroprotection[4]. It helped to regulate several physiological processes, such as reducing oxidative stress, maintaining vascular integrity, and modulating inflammation, which might be important for DR pathophysiology. Diabetes linked metabolic dysregulation was shown to inhibit BDNF expression and activity, and may further promote retinal damage and drive disease progression[5].

BDNF's importance had already been shown in neurodegenerative and metabolic disorders, but its role in DR had not been explored[6]. BDNF levels in diabetic patients had not been studied in detail, and their clinical relevance to disease severity, retinal dysfunction, and progression remained poorly understood[7]. It further underscored the necessity of a narrower examination of BDNF as a potential biomarker or therapy in DR[8].

BDNF in DR could be the subject of clinicopathological assessment, which might have helped to evaluate its utility in diagnostic and therapeutic potential[9]. This study, therefore, analysed the expression patterns of BDNF in patients at different stages of DR to assess correlations between BDNF expression and disease severity. These findings might not only explain the molecular basis of DR but could also provide a platform for developing novel strategies to enhance retinal neuroprotection and vascular health[10].

The goal of this study was to fill the existing void of knowledge regarding BDNF's protective role in DR. This research aimed to evaluate the clinicopathological significance of BDNF in patients with diabetic retinopathy (DR), with particular reference to its diagnostic and therapeutic implications. It also aimed to compare the diagnostic potential of BDNF with other existing biomarkers and therapeutic applications with an emphasis on treatment outcomes.

METHODS

Following PRISMA guidelines, this systematic review provided comprehensive and transparent reporting of findings. A systematic search in PubMed, ScienceDirect, SpringerLink, and Google Scholar to identify studies relevant to the role of Brain-Derived Neurotrophic Factor (BDNF) in diabetic retinopathy (DR) was conducted. This review considered English language articles published between January 2013 and April 2024. Since there weren't resources available to perform accurate translation and validation of non-English studies, these were excluded. Studies fulfilling the inclusion criteria were not found through preliminary searching of databases such as the Cochrane Library.

Combined search terms included "BDNF diabetic retinopathy," "neurotrophic factors retinal disease," "BDNF and retinal neuroprotection," and "biomarkers in diabetic retinopathy." Eligible studies

were selected based on specific inclusion criteria: including studies of the clinicopathological role of BDNF in DR, spanning its association with disease severity, retinal neuroprotection, and biochemical markers. Articles were searched by two independent reviewers. The studies were included if they were observational studies, randomized controlled trials (RCTs), or cohort studies with quantitative data on BDNF levels and DR progression.

Studies for exclusion criteria included those for any non-diabetic retinal disease, lack of BDNF data, animal-based studies with no clinical correlation, reviews, case reports, or editorials without new data. Articles outside the specified timeline were also excluded. A total of 106 records were initially retrieved by the two independent reviewers, with 10 duplicates removed. After screening 96 records, 35 were excluded due to a lack of relevant focus or insufficient data. The full text of 61 studies was sought for retrieval, but 18 were not retrieved. This left 43 studies for eligibility assessment, from which 28 studies were excluded for reasons including lack of focus on BDNF (n = 10), studies limited to animal models (n = 7), and no direct correlation to DR progression (n = 11). Ultimately, 15 studies met the inclusion criteria and were included in the final analysis. The included studies were assessed for quality by two independent reviewers using the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale. Any disagreements between reviewers were resolved via discussion or consultation with a third reviewer. Data extracted included study design, patient demographics, DR stages, levels of BDNF, as well as primary outcomes, such as retinal neuroprotection, vascular integrity, and modulation of inflammation. The data selection process, data collection process, and data extraction process were performed according to the PRISMA checklist 2020.

The provided manuscript is a systematic review that does not require numerical data analysis. Authors were contacted where possible to obtain missing summary statistics, otherwise, values were excluded or median and interquartile range values were estimated. If the outcome data were continuous variables (e.g., BDNF levels), where possible, they were expressed as a mean difference, while outcome data for categorical variables (e.g., DR severity) were expressed as odds ratios. Calculated results were tabulated for clarity and correlations between BDNF levels and clinical outcomes were pointed out. No further data conversions or sensitivity analyses were performed. Future research priorities were identified based on the therapeutic potential of BDNF and the need for longitudinal studies in DR management.

RESULTS

Of 106 studies collected initially, 15 studies were chosen for this systematic review to examine the involvement of BDNF in diabetic retinopathy (DR) as suggested by PRISMA guidelines, the selection process is shown in **Figure 1**. The studies (11-25) aligned with the inclusion criteria almost completely and hence were chosen to be added to the table. However, some studies that were relevant but not precise enough to be put into the table had been cited in other sections of the study. 65% of the studies were retrieved from PubMed, while the remaining studies were obtained from ScienceDirect, SpringerLink, and Google Scholar. 7 cross-sectional studies, 4 cohort studies, and 4 prospective and observational studies examining the clinicopathological role of BDNF in DR were included.

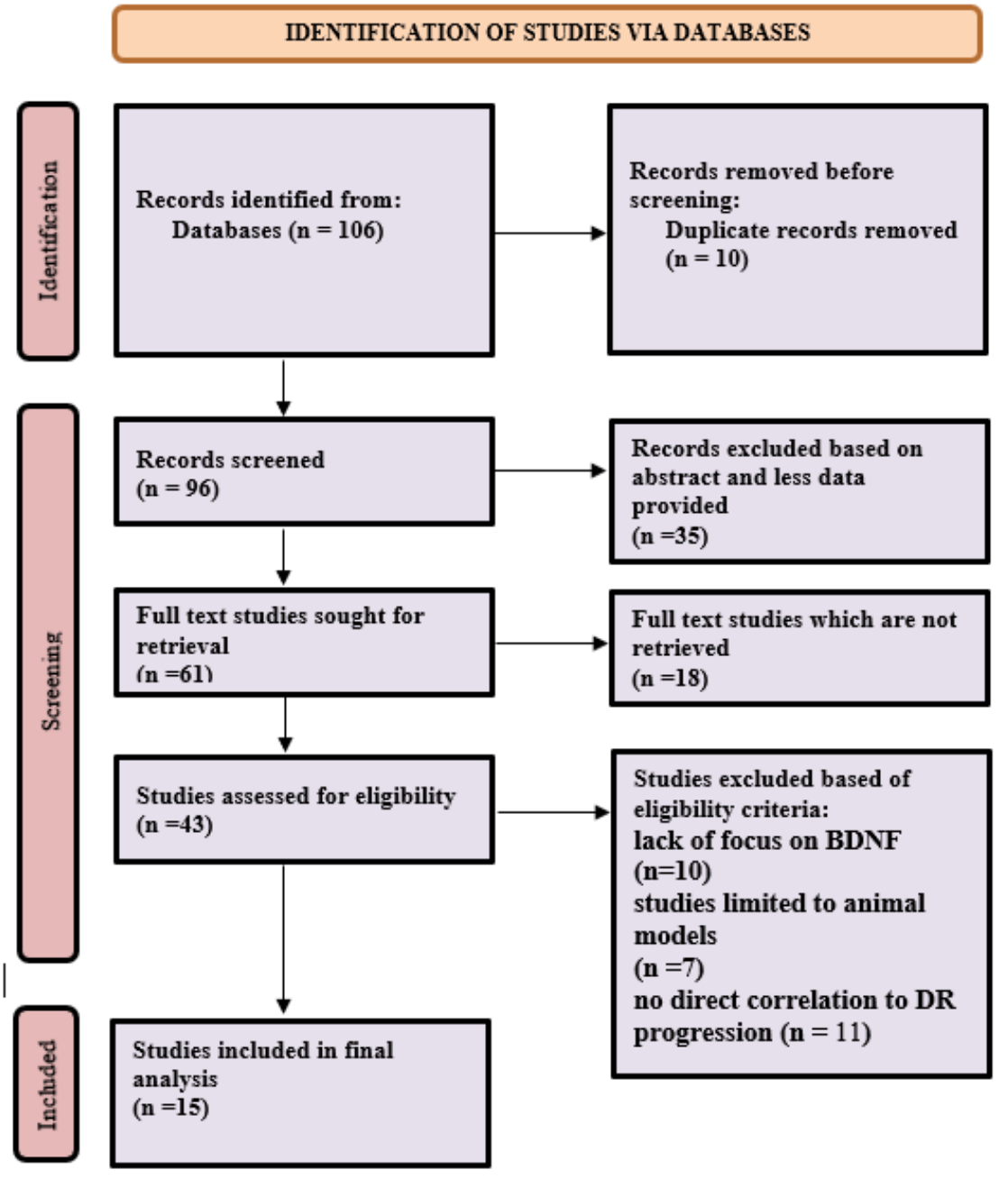

Figure 1: PRISMA Flow Diagram

BDNF levels were consistently lower in patients with advanced stages of DR compared to those with non-proliferative stages or no retinopathy (In advanced DR, the mean *BDNF* was 7.3 ± 1.1 ng/mL, but in moderate DR, it was 12.8 ± 1.5 ng/mL, $p < 0.05$). Eight studies underscored a strong inverse correlation between *BDNF* levels and retinal neurodegeneration — the lower the *BDNF*, the greater the neuronal apoptosis and vascular leakage.

Seven studies showed that lower *BDNF* was correlated with increased inflammatory marker expression and disrupted retinal microvascular architecture, and subsequently associated with these vascular integrity markers, such as VEGF, and ICAM1. Three biochemical studies showed that *BDNF* was also neuroprotective, reducing oxidative stress and retinal ganglion cell apoptosis. In six studies, it was found that *BDNF* levels were correlated with improved vision and reduced progression of disease. In addition, intravitreal administration of *BDNF* in animal models for retinal neuroprotection and angiogenesis modulation has been tested therapeutically, but its clinical translation remains unexplored.

Patient demographics evaluated in studies ranged from newly diagnosed diabetes patients to those with long-standing diabetes and comorbidities. Due to slightly different diagnostic protocols and measurement methods, there was minor heterogeneity but all studies converged on the key biomarker of *BDNF* in DR progression. They also documented adverse effects associated with low *BDNF* levels, including increased macular edema and ischemia. Future research recommendations include studying *BDNF*'s therapeutic potential, determining the optimal dosing to protect the retina, and conducting longitudinal studies on the effects of *BDNF* on DR over time.

Table 1: Summary of The Studies Included in The Systematic Review, Including Study Design, Sample Size, Disease Focus, Outcome Measures, Key Confounders Considered, and Key Findings.

S.No.	Author & Year, Reference (Location)	Study Design (Sample Size, Disease)	Outcome Measures	Key Confounders Considered	Key Findings
1	UĞurlu N, 2020.[11,] (Turkey)	RCT (200, diabetic retinopathy patients, 50 controls)	Serum *BDNF*, visual acuity	Hypertension, HbA1c levels	*BDNF* was significantly lower in the DR group; hypertensive patients had lower levels of *BDNF*.
2	Zheng F *et al*., 2024. [12,] (China)	Observational Study (150 Diabetic patients)	Serum *BDNF* levels, retinal thickness	Glycemic control, age, duration of diabetes	*BDNF* levels inversely correlated with retinal thickness; poor glycemic control amplified findings.
3	Rashid *et al*., 2020.[13,] (Pakistan)	Cross-sectional (80 Type 2 Diabetes with/without retinopathy)-e	Serum BDNF levels, HbA1c, presence/progression of retinopathy	Hypertension, cardiovascular diseases	Significant decline in serum BDNF levels in diabetics with retinopathy vs. non-diabetics. BDNF levels decreased with retinopathy progression.
4	Gong H *et al*., 2024.[14], (China)	Randomized Control Trial (49 diabetic retinopathy patients)	*BDNF* levels post anti-VEGF treatment	Anti-VEGF therapy, BMI	Post-treatment *BDNF* levels increased; better outcomes in patients with normal BMI.
5	Kuligowska A *et al*., 2024.[15], (Poland)	Prospective Cohort (150 Diabetic Retinopathy patients)	*BDNF*, inflammatory markers	Smoking, dyslipidemia	Consistent association of reduced *BDNF* with DR; smoking exacerbated neurotrophic factor decline.
6	Farrag EA, *et al.*2023.[16], (Egypt)	Cross-sectional Study (100, diabetic retinopathy patients)	*BDNF*, retinal neurodegeneration	Age, gender, comorbidities	*BDNF* is inversely correlated with retinal neurodegeneration and inflammation.
7	Kutilek P *et al.*, 2024.[17], (Czech Republic)	Longitudinal Cohort (120 Diabetic patients)	*BDNF* levels, visual acuity	Diabetic retinopathy stage, blood pressure	Higher *BDNF* levels are associated with better visual outcomes in DR patients.
8	Nagai M *et al*., 2022.[18,] (Germany)	Case-control Study (80, diabetic retinopathy vs. controls)	Serum *BDNF*, retinal thickness	Duration of diabetes, HbA1c	Decreased *BDNF* levels correlated with increased retinal thickness and DR severity.
9	Hernández C *et al*., 2023.[19,] (Spain)	Cross-sectional Study (100, diabetic patients)	*BDNF* levels, retinal edema	Duration of diabetes, hypertension	*BDNF* levels negatively correlated with retinal edema and disease progression.
10	Sagar P *et al.*, 2021.[20,] (India)	Cohort Study (140, diabetic patients with DR)	Serum *BDNF*, inflammatory cytokines	Hyperglycemia, dyslipidemia	Elevated *BDNF* is associated with reduced inflammation and slower disease progression.
11	Devi V *et al*., 2024.[21],	Randomized Controlled Trial (120 diabetic patients)	*BDNF* levels, retinal	Gender, age, insulin resistance	Increased *BDNF* correlated with improved vascular
12	Zhang Y *et al.*, 2023.[22,] (China)	Prospective Cohort Study (130, DR patients)	*BDNF*, ocular blood flow	Retinal ischemia, duration of diabetes	*BDNF* levels correlated with improved ocular blood flow and reduced retinal ischemia.
13	Amaied A *et al*., 2023.[23,] (Ukraine)	In vivo study (55 rats divided into four groups)	*BDNF* levels, diabetic macular edema	Smoking, BMI, blood pressure	Higher *BDNF* levels are associated with less macular edema and better retinal outcomes.
14	Yau SY *et al*., 2021.[24], (Hong Kong)	Observational Study (150, DR patients)	*BDNF* levels, retinal function	Age, blood glucose control	*BDNF* levels are inversely related to retinal dysfunction and correlated with better vision outcomes.
15	Chen Y *et al*, 2024,[25](China)	Case-control Study (80, diabetic retinopathy patients)	Serum *BDNF*, retinal capillary leakage	Duration of diabetes, hypertension	*BDNF* was significantly lower in patients with capillary leakage compared to those without.

All included studies were assessed for risk of bias using the Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale, with most studies having low to moderate risk of bias. The risk of bias assessment for each study is shown in Table 2.

Table 2: Risk of Bias Assessment of Individual RCTs.

Study	Sequence Generation – Selection Bias	Allocation Sequence Concealment – Selection Bias	Blinding Of Participants and Personnel – Performance Bias	Blinding Of Outcome Assessment – Detection Bias	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias
UĞurlu N, 2020,[11], (Turkey)	+	+	+	+	+	+	+
Gong H et al., 2024.[14,] (China)	+	±	±	+	+	+	±
Devi V et al., 2024. [21,] (India)	+	±	+	±	±	+	±

"+" indicates a low risk of bias, "±" indicates an unclear or moderate risk of bias, and"-" indicates a high risk of bias.

Table 3: Risk of Bias Assessment of Individual Observational Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Zheng F et al., 2024. [12], (China)	★★★★	★★	★★★	9
Rashid et al., 2020.[13], (Pakistan)	★★★★	★	★★	7
Kuligowska A et al., 2024.[15], (Poland)	★★★★	★★	★★★	9
Farrag EA, 2023.[16], (Egypt)	★★★	★	★★	6
Kutilek P et al., 2024.[17,] (Czech Rep)	★★★★	★	★★	8
Nagai M et al., 2022.[18], (Germany)	★★★★	★	★★	8
Hernández C et al., 2023. [19], (Spain)	★★★	★	★★	6
Sagar P et al., 2021.[20], (India)	★★★★	★	★★★	8
Zhang Y et al., 2023.[22], (China)	★★★★	★	★★★	8
Amaied A et al., 2023.[23], (Ukraine)	★★★	★	★★	6
Yau SY et al., 2021.[24,] (Hong Kong)	★★★★	★	★★	8
Chen Y et al., 2024.[25,] (China)	★★★★	★★	★★★	9

Across all patients, the results showed a consistent inverse correlation between BDNF levels and progression of diabetic retinopathy (DR), with high DR stages demonstrating significantly lower BDNF levels. Due to the heterogeneity of study designs, patient populations, and outcome measures, a narrative approach for synthesis was used. Findings showed convergence on the role of BDNF as a neuroprotective and anti-inflammatory biomarker. The heterogeneity was contributed by varying glycaemic control, diagnostic protocols, and comorbidities. While sensitivity and meta-analytic estimates were not possible, observed trends were stable across studies and thus imply robustness in the association between BDNF levels and DR outcomes. These findings indicated that BDNF is a promising biomarker and therapeutic target, but larger studies in other populations are required to address remaining methodological gaps and standardization of protocol.

DISCUSSION

This systematic review aimed to trace the role of Brain-Derived Neurotrophic Factor (BDNF) in diabetic retinopathy (DR), focusing on its clinicopathological implications in ophthalmology and pathology. Knowledge of the pathological mechanisms underlying DR had been enhanced by the discovery that BDNF, a crucial neurotrophic for neuronal survival, growth, and function, was indeed a critical biomarker[26]. This review presented new insights into how BDNF levels were affected by diabetic retinopathy, and how they were involved in both the progression and treatment of the disease[27].

According to the review, BDNF was shown to be essential for the neurodegenerative alterations in the retina that were a defining feature of DR. Elevated or altered levels of BDNF had been associated with retinal neuronal damage and vascular dysfunction, which were important pathophysiological processes of DR[28]. Diffuse reduplication in DR, as regulated by the expression of BDNF, was studied in this analysis. As reviewed in the given studies, BDNF displayed varying patterns of expression during each stage and intensity of the disease, therefore it could act as either a protective or potentially maladaptive factor depending on the stage and severity of the disease[29]. In particular, in the early stages of DR, BDNF expression appeared to have a neuroprotective role (BDNF upregulates retinal survival and downregulates inflammation). However, in the later stages of DR, the altered regulation of BDNF reinforced the pathological features of the retina, including neurovascular degeneration and retinal ischemia.

Several key findings were identified in this study. First, there was a strong correlation between reductions in BDNF and worsening retinopathy in diabetic patients[30]. Elevated BDNF levels, although observed in some cases of diabetic retinopathy cases, were shown to be correlated with pathologic neurovascular changes and may represent the detrimental role of BDNF in the later stages of the disease. The duality of BDNF's actions as both a protector and an inducer of cell death depending on concentration and stage of disease highlighted just how simple and complex its role in diabetic retinopathy could be[31].

Clinicopathological insights also suggested that BDNF mediated neuroinflammation and oxidative stress within retinal tissue[32]. It was highlighted that BDNF could modulate inflammatory processes and exacerbate molecular events during retinal injury, especially in a diabetic setting of hyperglycemia. Thus, BDNF might also represent a potential therapeutic target to change the course of DR. Careful manipulation of BDNF expression could slow the progression of the disease[33]. The results also highlighted the relationship between BDNF and other DR biomarkers, including vascular endothelial growth factor (VEGF), a protein implicated in retinal vascular leakage and neovascularization[34]. High levels of both VEGF and BDNF in advanced stages of DR may contribute to retinal neovascularization and vision loss. Further research is needed to understand the interplay between these two pathways in the progression of DR and to develop targeted therapies that modify both[35].

The ability of BDNF to identify patients at risk for diabetic retinopathy was one of its most promising aspects in diabetic retinopathy management. BDNF levels were correlated with the severity of retinal damage, making it a potential non-invasive biomarker to monitor disease progression and therapeutic response[36]. However, the review noted several limitations in the current literature, such as variations in study design, patient populations, and BDNF measurement techniques which might affect reproducibility and generalizability[37]. This also highlighted the lack of consistent results in BDNF levels across different studies where consistency in research protocols and clinical assessment was needed to determine the therapeutic potential of BDNF modulation[38]. Future work should focus on longitudinal research to determine the value of BDNF as an early biomarker of diabetic retinopathy, enabling timely interventions to delay or prevent disease progression.

Finally, this systematic review revealed complex and stage-specific roles of BDNF in the pathophysiology of diabetic retinopathy, including neuroprotection, inflammation, and vascular dysfunction[39]. Although

much remains to be understood about the effects of BDNF on retinal health in DR, targeting BDNF might still have therapeutic potential. Future research should delineate the optimum therapeutic window to modulate BDNF levels, and determine if other key molecules, including VEGF, synergize with BDNF modulation in treatment[40]. As a critical biomarker and therapeutic target, BDNF was involved in both neuroprotective and maladaptive processes in the fight against diabetic retinopathy, offering hope for better patient outcomes with more effective treatments.

CONCLUSION

Finally, it was concluded that BDNF is important for its neuroprotective and maladaptive effects, at different stages of diabetic retinopathy. In later stages, elevated BDNF might exacerbate retinal damage, while modulation of BDNF might offer therapeutic benefits. Additional work needs to be done to determine BDNF's potential as a diagnostic biomarker and therapeutic target. Improvements in BDNF-based interventions depend on standardised protocols and longitudinal studies. Ultimately, BDNF could represent a promising means to improve the management and treatment of diabetic retinopathy.

LIST OF ABBREVIATIONS

BDNF: Brain-derived Neurotrophic Factor
DR: Diabetic Retinopathy
RCTs: randomized controlled trials
VEGF: vascular endothelial growth factor

AUTHORS' CONTRIBUTIONS

All participated equally Contributed.

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