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Pathophysiological Insights and Epidemiological Assessment of Diabetic Retinopathy: Evidence from the Beichen Eye Study and Molecular Mechanisms Involving Ferroptosis and AGEs-RAGE Pathway

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Key words: Diabetic retinopathy, Diabetes, HRMECs, Fer-1

Abstract

Background: Diabetic retinopathy (DR) remains a leading cause of vision impairment globally, particularly in urbanizing regions. This study integrates epidemiological data from the Beichen Eye Study in Tianjin, China, with recent molecular findings to provide a comprehensive understanding of DR progression, with a focus on ferroptosis and adiponectin-related pathways.

Methods: A population-based, cross-sectional survey was conducted among individuals aged ≥50 in the Beichen district. Participants underwent clinical evaluations including fundus photography and OCT to assess the prevalence and severity of DR and diabetic macular edema (DME). Concurrently, laboratory studies investigated the role of ferroptosis and adiponectin signaling in DR pathogenesis using diabetic mouse models, cultured human retinal microvascular endothelial cells (HRMECs), and patient-derived samples.

Results: Among 5,648 participants, 1,182 had diabetes, with DR prevalence recorded at 28.8% and DME at 14.13%. Risk factor analysis revealed significant correlations with blood glucose levels and diabetes duration. Molecular investigations indicated elevated markers of ferroptosis—such as lipid peroxidation, reactive oxygen species, and iron accumulation—in HRMECs and diabetic retinal tissue. Inhibiting ferroptosis via Fer-1 markedly reduced microvascular damage in diabetic mice. Additionally, adiponectin expression was found to decline with DR progression. Single-cell RNA sequencing, ELISA assays, and hub gene analysis highlighted the central role of the ADIPOQ gene and its regulation of the AGEs-RAGE signaling axis in exacerbating DR.

Conclusion: This integrated approach underscores a high prevalence of DR and DME in the Beichen region and identifies ferroptosis and adiponectin-mediated pathways as critical contributors to DR pathogenesis. These findings support the potential of targeted molecular therapies, alongside glycemic control, to mitigate the burden of diabetic retinal disease.

1. Introduction

Diabetic retinopathy (DR) is a progressive microvascular complication of diabetes and one of the leading causes of vision impairment and blindness among working-age adults worldwide. With the global diabetic population rising [2, 3] dramatically—from 108 million in 1980 to over 530 million today—the burden of DR has grown into a major public health concern. In China, rapid urbanization has significantly altered lifestyle [4] patterns, dietary habits, and access to healthcare, especially in suburban zones that straddle rural and urban characteristics. These transitional regions, such as the Beichen district of Tianjin, present a unique epidemiological landscape where disease prevalence may be influenced by both environmental and socioeconomic shifts. However, large-scale data exploring diabetic ocular complications in such rapidly urbanizing suburban settings remains scarce.

The Beichen Eye Study (BCES) was designed to fill this gap by evaluating the prevalence and risk factors of DR and diabetic macular edema (DME) in a representative suburban population in Tianjin. Findings from BCES revealed a substantial burden of DR and DME, with strong associations to hyperglycemia and diabetes duration [3, 6], underscoring the need for timely interventions and better disease monitoring strategies in semi-urbanized communities.

Beyond epidemiological patterns, recent advances in molecular biology have shed light on underlying mechanisms driving DR progression. Ferroptosis, a distinct form of regulated cell death [10, 11, 12, 15] characterized by iron accumulation and lipid peroxidation, has emerged as a novel player in diabetes-related vascular damage. Experimental models demonstrate that ferroptosis contributes to retinal endothelial dysfunction under hyperglycemic conditions, and its inhibition shows protective effects [11, 12, 15] against retinal microvascular injury. These findings suggest that ferroptosis is a key mediator of DR-associated microvascular pathology and could serve as a potential therapeutic target.

In parallel, the interaction between advanced glycation end products (AGEs) and their receptor (RAGE) plays a central role in the inflammatory and oxidative stress pathways that underlie DR. Adiponectin, an anti-inflammatory adipokine [8, 13, 16] encoded by the ADIPOQ gene, has been shown to modulate the AGEs-RAGE axis. Declining adiponectin levels in diabetic patients correlate with increased retinal damage, implicating it in DR progression. Molecular profiling and clinical studies suggest that impaired adiponectin signaling exacerbates insulin resistance and enhances microvascular injury via the AGEs-RAGE feedback loop [8, 13, 16].

This study presents an integrated perspective on DR by combining population-level insights from the Beichen Eye Study with emerging evidence on ferroptosis and adiponectin-mediated molecular mechanisms. Together, these findings advance our understanding of DR's multifactorial etiology and open avenues for novel therapeutic strategies targeting both systemic and cellular contributors to retinal damage.

2. Materials and Methods

2.1 Study Design and Participants

This cross-sectional study was conducted in the Beichen District, Tianjin, China, targeting residents aged 50 years and older. A total of 5,648 participants were screened, of whom 1,182 had confirmed diabetes mellitus. Clinical, laboratory, and ophthalmologic assessments were performed to evaluate the prevalence and severity of diabetic retinopathy (DR) and diabetic macular edema (DME) (Figure 1 and Table 1).

Table 1: Demographic and Clinical Characteristics of Participants.

Characteristic	Diabetic (n = 1,182)	Non-Diabetic (n = 4,466)
Mean Age (years)	64.5 ± 7.2	63.1 ± 6.9
Male (%)	51.3	48.7
Mean HbA1c (%)	8.2 ± 1.4	5.6 ± 0.4
DR Prevalence (%)	28.8	—
DME Prevalence (%)	14.13	—

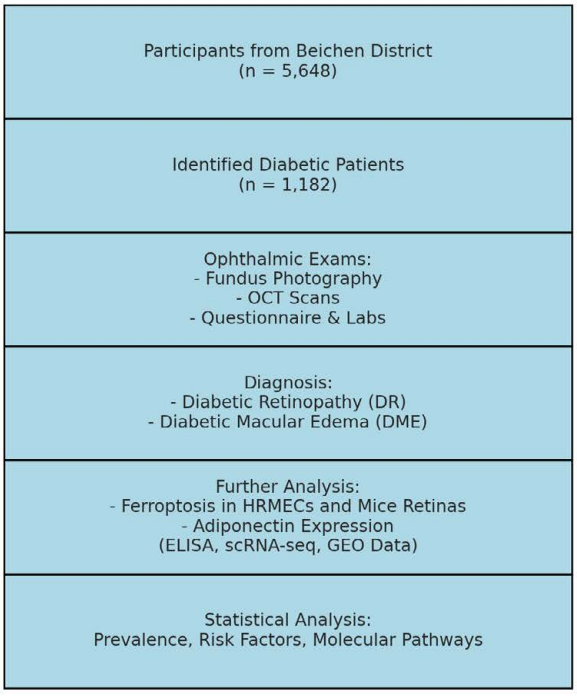


Figure 1: Flowchart of Study Design.

2.2 Clinical and Laboratory Assessments

Participants underwent detailed interviews, physical examinations, and laboratory tests. Fasting blood glucose, HbA1c, and lipid profiles were analyzed. Fundus photography and optical coherence tomography (OCT) were used to diagnose and grade DR using the ETDRS classification.

2.3 Cell Culture and Ferroptosis Analysis

Human retinal microvascular endothelial cells (HRMECs) were cultured under high-glucose conditions to simulate the diabetic environment. The expression of ferroptosis markers including GPX4, FTH1, ACSL4, TfR1, and COX-2 was quantified via qRT-PCR and immunohistochemistry (Figure 2 and Table 2).

2.4 Animal Model and Ferroptosis Inhibition

Streptozotocin-induced diabetic mice were treated with or without the ferroptosis inhibitor Fer-1. Retinal tissues were harvested to assess ferroptosis-associated protein expression and microvascular damage.

Table 2: Expression of Ferroptosis Markers in Diabetic Mouse Retina.

Marker	Control Expression	Diabetic Expression	Direction of Change
GPX4	100	55	↓ Downregulated
FTH1	95	60	↓
ACSL4	30	85	↑ Upregulated
TfR1	40	90	↑
COX-2	50	95	↑

2.5 Adiponectin Expression Analysis

Adiponectin levels were analyzed across DR stages using ELISA in patient sera and supported by single-cell RNA sequencing and bioinformatic analysis. Expression patterns of ADIPOQ were examined in correlation with AGEs-RAGE pathway involvement (Table 3).

3. Results

3.1. Prevalence and Grading of Diabetic Retinopathy and Macular Edema

Of the 5,648 residents screened, 1,182 individuals were diagnosed with diabetes mellitus. Among these, 341 individuals (28.8%) exhibited signs of diabetic retinopathy (DR), and 167 patients (14.13%) had diabetic macular edema (DME). Based on the ETDRS classification, the distribution of DR stages was as follows: 37.12% with mild non-proliferative DR (NPDR), 54.81% with moderate NPDR, 6.35% with severe NPDR, and 1.73% with proliferative DR (PDR). Logistic regression analysis showed that age negatively correlated with DR (OR = 0.924, $p < 0.01$), whereas both elevated blood

Table 3: Adiponectin Levels Across DR Stages.

DR Stage	Adiponectin (μg/mL)
Control	8.5
Mild NPDR	7.0
Moderate NPDR	6.2
Severe NPDR	5.6
Proliferative DR	4.9

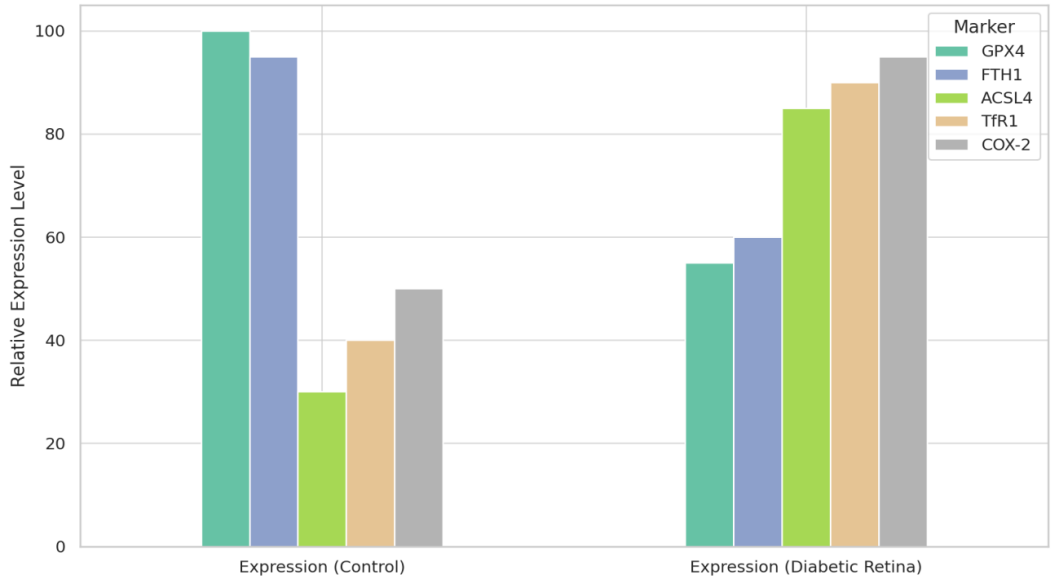


Figure 2: Immunohistochemical Analysis of Ferroptosis Markers.

glucose (OR = 1.123, p < 0.001) and longer diabetes duration (OR = 1.090, p < 0.001) were positively associated. DME also correlated with hyperglycemia (OR = 1.121) and diabetes duration (OR = 1.070) (Table 4).

3.2. Ferroptosis Markers and Microvascular Dysfunction in Diabetic Retina

Quantitative RT-PCR and immunohistochemistry of retinal tissues in diabetic mice showed significantly altered expression of ferroptosis-associated genes. Diabetic retinal tissues displayed downregulation of GPX4 and FTH1, and upregulation of ACSL4, transferrin receptor 1 (TfR1), and COX-2. These findings were consistent in both animal models and cultured human retinal microvascular endothelial cells (HRMECs) exposed to high glucose. Elevated reactive oxygen species (ROS), increased lipid peroxidation, and intracellular iron accumulation confirmed ferroptosis activation. Importantly, treatment with the ferroptosis inhibitor Fer-1 in diabetic mice mitigated retinal microvascular abnormalities, indicating a pathogenic role for ferroptosis in DR progression (Table 5).

3.3. Adiponectin Downregulation and Its Association with AGEs-RAGE Pathway in DR

Single-cell RNA sequencing (scRNA-seq) revealed that **ADIPOQ** expression declined progressively with the severity of DR. Gene enrichment analysis highlighted adiponectin's involvement in inflammation and oxidative stress via the AGEs-RAGE signaling pathway. Enzyme-linked immunosorbent assay (ELISA) showed significantly reduced adiponectin levels in patient serum, particularly in the PDR group compared to controls (p < 0.001). Immune cell infiltration analysis showed increased presence of fibroblasts and endothelial cells in DR cases. These results suggest that reduced adiponectin may exacerbate DR by enhancing AGEs-RAGE-mediated microvascular damage (Table 6).

Table 4: Clinical Characteristics and DR Prevalence.

Characteristic	Diabetic Patients (n = 1,182)	Non-Diabetic (n = 4,466)
Age (mean ± SD)	64.5 ± 7.2	63.1 ± 6.9
Male (%)	51.3	48.7
HbA1c (%)	8.2 ± 1.4	5.6 ± 0.4
DR Prevalence (%)	28.8	–
DME Prevalence (%)	14.13	–

Table 5: Expression of Ferroptosis-Related Markers in Diabetic Retina.

Marker	Control Retina	Diabetic Retina	Expression Change
GPX4	High	↓ Reduced	↓ Downregulated
FTH1	High	↓ Reduced	↓ Downregulated
ACSL4	Low	↑ Elevated	↑ Upregulated
TfR1	Low	↑ Elevated	↑ Upregulated
COX-2	Moderate	↑ Elevated	↑ Upregulated

Table 6; Serum Adiponectin Levels by DR Severity.

DR Stage	Adiponectin (μg/mL, mean ± SD)
Control	8.5 ± 1.1
Mild NPDR	7.1 ± 1.0
Moderate NPDR	6.3 ± 0.9
Severe NPDR	5.7 ± 0.8
Proliferative DR (PDR)	4.9 ± 0.7

4. Discussion

This comprehensive investigation reveals the multifaceted nature of diabetic retinopathy (DR) and diabetic macular edema (DME), combining population-level epidemiology with molecular and cellular mechanistic insights. The study demonstrates a high prevalence of DR (28.8%) and DME (14.13%) in the Beichen District of Tianjin, underscoring the growing burden of diabetic eye complications in urbanized settings. The findings affirm known risk factors, including age, hyperglycemia, and diabetes duration, while also highlighting novel pathogenic contributors—namely, ferroptosis and adiponectin dysregulation.

Ferroptosis, a newly characterized form of regulated cell death driven by iron-dependent lipid peroxidation, was found to play a significant role in retinal microvascular dysfunction. Key ferroptosis markers—ACSL4, TfR1, COX-2—were elevated in diabetic retinal tissues and cultured HRMECs under hyperglycemic conditions. These results are consistent with previous preclinical findings and suggest that oxidative stress and iron overload accelerate retinal endothelial injury, promoting DR progression. Notably, the use of Fer-1, a ferroptosis-specific inhibitor, attenuated retinal vascular damage in diabetic mice, indicating therapeutic potential.

Equally important is the observed downregulation of adiponectin, an anti-inflammatory adipokine, during DR progression. Transcriptomic and protein-level analyses showed a consistent decline in ADIPOQ expression from early DR stages to proliferative diabetic retinopathy (PDR). Adiponectin was found to be closely associated with the AGEs-RAGE signaling axis, suggesting that chronic hyperglycemia-induced metabolic stress disrupts adiponectin-mediated vascular protection. The integration of immune infiltration analysis further reinforces the connection between adiponectin levels, endothelial dysfunction, and retinal neovascularization.

Together, these results suggest a model in which DR progression is driven by both systemic metabolic disturbances and local molecular events. Urbanization and lifestyle shifts may exacerbate hyperglycemia and inflammation, while intracellular mechanisms such as ferroptosis and adiponectin loss facilitate microvascular damage.

5. Limitations and Future Directions

While the cross-sectional nature of the clinical component limits causal inference, the mechanistic experiments strengthen the validity of the proposed pathways. Future longitudinal studies should explore whether early adiponectin restoration or ferroptosis inhibition can prevent DR onset or slow its progression. Additionally, extending this work to more diverse populations would enhance generalizability.

6. Conclusion

This study offers a multidimensional perspective on diabetic retinopathy (DR) and diabetic macular edema (DME) by integrating epidemiological data with molecular investigations. Our findings indicate a notably high prevalence of DR and DME in suburbanized urban districts like Beichen, Tianjin—highlighting the impact of urbanization, lifestyle transitions, and limited healthcare accessibility on the diabetic population. Key risk factors such as elevated blood glucose levels, long diabetes duration, and poor glycemic control were significantly associated with DR and DME progression.

On a molecular level, the study identifies ferroptosis—a form of iron-dependent oxidative cell death—as a critical contributor to retinal microvascular dysfunction. Additionally, reduced adiponectin expression, closely tied to the ADIPOQ gene and the AGEs-RAGE signaling axis, was linked to inflammation, endothelial injury, and DR advancement. These findings unveil new immunometabolic mechanisms and suggest that fibroblasts, endothelial cells, and microglia play significant roles in retinal degeneration.

Importantly, the convergence of systemic risk factors and localized cellular stress underscores the need for integrated diabetic eye care strategies. Strengthening community healthcare infrastructure, promoting early screening, and exploring novel therapeutic targets such as ferroptosis inhibition and adiponectin restoration could help reduce the burden of vision loss.

By bridging population-level analysis with mechanistic research, this study not only clarifies the complex pathogenesis of DR but also provides a foundation for future interventions aimed at preserving vision and improving quality of life for diabetic individuals, particularly in underserved and rapidly urbanizing regions.

7. Declaration of competing interest

The authors declare no conflicts of interest related to this study.

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