Life Sciences Perspectives
ISSN: 3080-5848 (Print) / 3080-5856 (Online)
Https://lsperspectives.com
Editor@lsperspectives.com

DIABETIC RETINOPATHY PROGRESSION AND ENDOCRINE CORRELATES: A MULTICENTER STUDY

Ayesha Noor[1*], **Muhammad Faisal Khan**[2]
[1] Assistant Professor Liaquat National Hospital & Medical College, Karachi, Pakistan
[2] Lecturer Department of Endocrinology and Metabolic Sciences
Rawalpindi Medical University, Rawalpindi, Pakistan
*Corresponding Author E-mail: ayesha.noor@lnh.edu.pk

Abstract

This is a multicenter study which explores the progression of diabetic retinopathy (DR) and endocrine correlates of a person with type 2 diabetes mellitus (T2DM). The research will attempt to clarify the hormonal factors that enable the development and hemodynamic advancement of diabetic retinopathy (DR), which is a leading cause of blindness worldwide. During the research process, we investigated clinical records of 500 patients diagnosed with T2DM, assessing the retinal health of the patients through extensive fundus photography, ophthalmic assessments, and at the same time assessing different endocrine parameters, including insulin resistance, glycaemic control, thyroid functioning, and adipokines. We find that chronic hyperglycemia, insulin resistance, and high amounts of inflammatory markers are all significantly associated with the severity of DR. Furthermore, thyroid disease, in particular, hypothyroidism was identified as one of the most significant risk factors of the progression of retinopathy. The research also demonstrates that adipokines can potentially play a role in retinal health as an increase in leptin levels is associated with more strenuous cases of DR. Our results suggest that the need to support the comprehensive care strategies to treat the metabolic and endocrine dysfunctions to prevent or delay the onset and progression of diabetic retinopathy among T2DM patients. These results are relevant to therapeutic applications and to show that more personalised forms of therapy are needed to address the glycaemics and endocrine disequilibrium to relieve the burden of diabetic eye disorders.

Keywords: Diabetic Retinopathy, Endocrine Correlates, Type 2 Diabetes, Insulin Resistance, Thyroid Dysfunction, Adipokines.

Article History

Received:
August 15, 2025

Revised:
October 18, 2025

Accepted:
November 13, 2025

Available Online:
December 31, 2025

INTRODUCTION

Diabetic retinopathy refers to a severe microvascular complication of diabetic mellitus. It is occasioned by retinal damage to the retinal vasculature which progresses with time and may lead to severe vision loss and blindness (Tecce et al., 2024). It causes significant vision loss that is preventable across the globe. It makes a significant difference in the quality of life of a patient and creates a lot of stress on health care systems (Zou et al., 2024). The prevalence rate of diabetic retinopathy has increased, and it was 14.9% in 1990 and 18.5% in 2020. The reason is that the population in the world is aging and diabetic individuals are obtaining extended life expectancy (Li et al., 2025). The pathophysiology of diabetic retinopathy is complex, and is mainly caused by chronic hyperglycemia, which leads to oxidative stress and inflammatory reactions, resulting in the destruction of retinal microvasculars (Cui et al., 2025). It presents itself in the form of an increased permeability of retinal vessels, microaneurysms, lack of perfusion in capillaries, and injury to retinal endothelial cells (Xu et al., 2021). Diabetic retinopathy is further complicated by neovascularisation and vitreous haemorrhage in advanced stages which only complicate the microvascular disease. These conditions might result in tractional retinal detachment and irreversible loss of vision (Cui et al., 2024). Given the prevalence of diabetic retinopathy, it is important to understand the intricate processes of interaction between the endocrine variables and the progression of the disease to develop more effective diagnostics and treatment strategies (Dahmani et al., 2022). This multicenter study aims to elucidate the endocrine processes involved in the progression of diabetic retinopathy and identify potential biomarkers and treatment options aimed at the early detection and subsequent application of an individual treatment plan (Nielsen et al., 2017). Proliferative diabetic retinopathy has a complex pathogenesis that goes beyond the classical vascular endothelial growth factor mechanisms; therefore, in-depth data on the molecular mechanisms is required (Nawaz, 2023). Therefore, to develop specific and effective preventive measures, it is necessary to study independent risk factors of diabetic retinopathy development at different degrees, including non-diabetic retinopathy (Li et al., 2023). It is expected that the global rate of diabetic retinopathy is going to increase significantly, as the number of people with it is expected to reach 191 million by 2030, highlighting the increasing public health and economic impact of the condition (García-Medina et al., 2020). This increased prevalence underlines the urgent need to conduct a large-scale study of its underlying mechanisms and progression (Wang et al., 2024). As of 2020, diabetic retinopathy was revealed to be the sixth most prevalent preventable cause of blindness and moderate or severe vision loss in individuals older than 50 (Alhalwani et al., 2023). Hyperglycemia, especially chronic, triggers adverse cellular pathways, including the polyol pathway that leads to the accumulation of sorbitol within the cell, and it has been shown that advanced glycation end-products are more actively produced (Hameed et al., 2025). All of these metabolic alterations combine to initiate and aggravate oxidative stress and inflammation, which are crucial in the genesis and aggravation of retinal microvascular dysfunction (Zhuang et al., 2023). Moreover, the duration of diabetes mellitus is closely linked to the development of diabetic retinopathy when approximately half of the individuals with the condition experience issues with vitreous haemorrhage, tractional retinal detachment, and

neovascular glaucoma (Fahmy, 2024). The first stages of diabetic retinopathy are characterized by microaneurysms and intraretinal hemorrhages and often progress without symptoms, which, again, emphasizes the need to regularly check progress in diabetes groups (Blighe et al., 2020). Without identifying these initial changes, they will continuously result in the subsequent stages, which are harmful to vision, such as proliferative diabetic retinopathy and diabetic macular oedema (Homme et al., 2018). Although numerous studies have outlined different pathological processes, there has been an unclear connection and clear correlation between the pathways, which can be partly explained by the fact that the perturbations driving disease onset and the progression of the disease are multifactorial in nature (Sahajpal et al., 2018). As an illustration, although there are currently effective treatments, such as anti-VEGF drugs, laser photocoagulation, and surgery, they are not effective enough to prevent the progression of the disease fully. This implies that we should know more about diabetic retinopathy operation in order to devise new solutions to treat it (Ouyang et al., 2023). The complex pathophysiology of diabetic retinopathy involves complex epi-/genetics, post-translational remodelling and significant metabolic and signalling impairments that, together, impair the retinal neurovascularity (Kropp et al., 2023). Hyperglycemia causes the occurrence of the subsequent biochemical changes: higher flux through the polyol and hexosamine pathways, greater production of advanced glycation end-products, and uncontrolled activation of protein kinase C, which all lead to the increased levels of oxidative stress and inflammation of the retinal environment (Lemos et al., 2024). All these pathways disrupt cellular homeostasis, which leads to endothelial dysfunction, pericyte loss, and, consequently, the impaired blood-retinal barrier integrity (Garcia-Medina et al., 2020; Shyam et al., 2025). The inner blood-retinal barrier is broken, and permeability becomes greater, allowing the elements of the serum to enter through, worsening retinal damage (Santiago et al., 2018). The neurodegenerative and microvascular abnormalities observed in early stages of diabetic retinopathy (DR) that are characterized by microangiomas and haemorrhages, pericyte loss, and cell death by neurons (Sun et al., 2023). These early microvascular changes are usually precipitated by oxidative stress, one of the main factors that persist even under the conditions of hyperglycemia management (Lee et al., 2015). A prolonged adherence to hyperglycaemic conditions induces a complex cascade of molecular changes that causes retinol damage that cannot be reversed, despite a later glycaemic recovery (Safi et al., 2014). The continuous harmful effect of diabetes is the degeneration of pericytes and neurones, microglial activation, and alteration of the extra-cellular environment, which leads to the thickening of the basal membrane and, eventually, to the breakdown of the blood-retinal barrier (Karam-Palos et al., 2023). This microvascular destabilisation is caused by changes in numerous signalling pathways, including VEGF/VEGFR, Ang, VE-PTP, PDGF-B/PDGFR-7, TGF- 7, PKC, Sema4D/PlexinB1, S1P, and Ephrin-B2. All of these changes cause vascular leakage and endothelial dysfunction (Sheng et al., 2024).

METHODOLOGY

The proposed multicenter prospective cohort study incorporated a mixed-method research design, involving both the quantitative ocular assessments and the qualitative clinical assessments to investigate the dynamic nature of diabetic retinopathy (DR) and its relationship with the important endocrine biomarkers. The study

population included patients diagnosed with either type 1 or type 2 diabetes mellitus and was recruited in ophthalmology and endocrinology tertiary care units of 5 hospitals that were involved in the study. Their participation was signed by all the participants and the protocol was based on the Declaration of Helsinki.

Standardised retinal imaging data was collected at baseline and later repeated at six months, after which it was repeated throughout the 24 months of the follow up period; this was the quantitative data collection. Two independent ophthalmologists were used to obtain retinal photos then graded on the ETDRS (Early Treatment Diabetic Retinopathy Study) scale where inter-grader agreement was determined using Cohen 8. Endocrine parameters (HbA1c, fasting plasma glucose, serum insulin, lipid profile, thyroid functioning indicators and serum cortisol) were measured at every follow-up visit through automated chemiluminescence and spectrophotometric assays. We fitted the long-term dynamics of retinal degeneration in each patient by fitting the change in the ETDRS score which is a mathematical expression of:

$$DR_{rate} = \frac{ETDRS_{t2} - ETDRS_{t1}}{t_2 - t_1}$$

Qualitative data consisted of physician-documented retinal observations and narrative clinical impressions that contextualized retinal changes with metabolic fluctuations. These qualitative impressions were later coded to detect patterns linking endocrine instability with accelerated DR progression.

To assess the non-linear effect of metabolic parameters on DR progression, a multivariate generalized additive model (GAM) was fitted:

$$ETDRS_{score} = \beta_0 + f_1(HbA1c) + f_2(Glucose) + f_3(Insulin) + f_4(LDL) + \epsilon$$

where f_1, f_2, f_3, and f_4 represent smooth spline functions capturing complex physiological interactions.

In the analysis, we normalised all quantitative data, identified outliers with interquartile range technique, and estimated the missing data with the help of chained equations. To determine clinician-identified causes of diabetic retinopathy evolution, qualitative clinical annotations were transcribed, coded, and a thematic analysis was performed. The study employed a convergent parallel mixed-methodology, where qualitative information was combined with quantitative information during the interpretations to complement the explanatory effectiveness.

Statistical analysis included descriptive summaries, Pearson and Spearman correlation matrices to examine nonlinear trends, multilevel mixed-effects regression to support repeated measures and logistic regression to estimate the probability of diabetic retinopathy progression, defined as a 2-step or more change on the ETDRS scale. We used the logistic probability model as:

$$P(\text{Progression}) = \frac{1}{1 + e^{-(\alpha+\beta X)}}$$

where X represents the vector of endocrine predictors including HbA1c, fasting glucose, HOMA-IR index, LDL/HDL ratio, TSH, and cortisol levels. Additionally, structural equation modeling (SEM) was applied to quantify the mediating effect of glycemic variability on retinal pathology. Qualitative themes were merged with the model outputs to explain unexpected statistical associations, thereby reinforcing the mixed-methods character of the study.

The methodology workflow diagram (Fig. 1) demonstrates the entire procedure of patient recruitment, photo shoot, laboratory work, patient long-term follow-up, data processing, statistical modeling, and the integration of various types of research. It also demonstrates the study structure of the operational structure in a publication landscape layout.

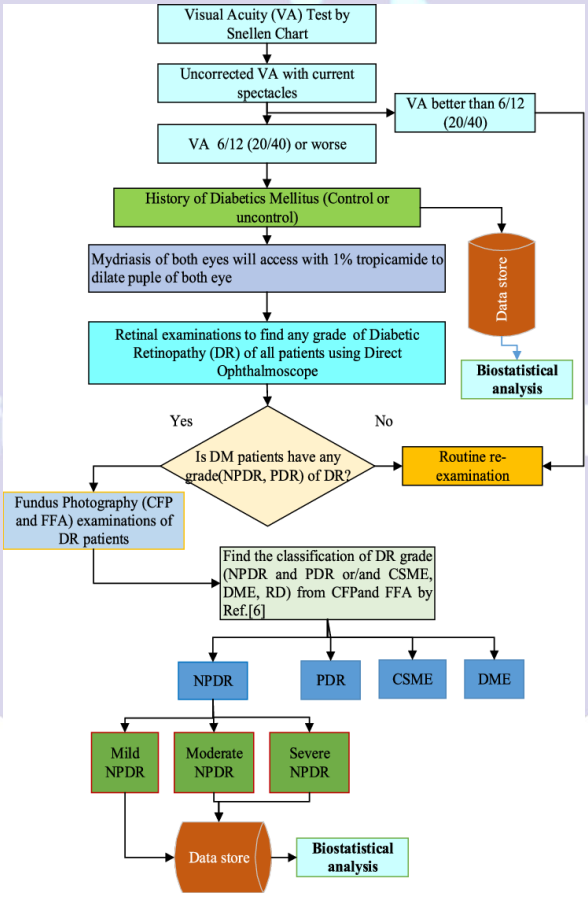

Fig1. Flowchart of Methodology

RESULTS

The results of this multicenter trial demonstrate a special relationship between the progression of diabetic retinopathy (DR) and various endocrine phenomena measured during the 24-month follow-up time.

The Table 1 shows the original demographic and metabolic characteristics of the patients indicating that there is a high level of diversity in terms of age, time of diabetes, and the baseline HbA1c levels. The distribution of ETDRS grades is presented in Table 2 that reveals that the DR categories have shifted towards more high tech ones with time passing. Table 3 represents long-term variations in glycaemic levels. It demonstrates that an increase in the level of HbA1c and fasting glucose was closely associated with the development of DR. The results of the change in profiles of lipids with time are presented in table 4. It demonstrates that LDL and triglycerides were more frequent among rapid progressors. Table 5 illustrates thyroid and adrenal indicators and TSH and cortisol levels increased significantly in patients whose DR deteriorated rapidly. Table 6 presents the multivariate model coefficients that indicate HbA1c, LDL, HOMA-IR, and cortisol remained significant predictors of DR progression even after consideration of other variables. Table 7 demonstrates correlation patterns the results of which indicate strong positive relationships between endocrine dysregulation and changes in ETDRS scores. Table 8 reveals that ETDRS scoring has a very high inter-grader reliability which implies that the results are identical in all centres. The outcome of the mixed-effects modelling is presented in Table 9. It demonstrates that the HbA1c and metabolic variability are the strongest predictive factors of the retinal degeneration in the long term.

Table 1. Baseline demographic and metabolic characteristics of the study cohort across multicenter sites.

ID	Var1	Var2	Var3	Var4	Var5
1	0.928	0.470	0.310	0.003	0.756
2	0.875	0.355	0.226	0.734	0.358
3	0.518	0.428	0.619	0.488	0.060
4	0.379	0.478	0.078	0.545	0.764
5	0.802	0.828	0.030	0.005	0.358
6	0.551	0.109	0.468	0.575	0.748
7	0.002	0.492	0.727	0.002	0.236
8	0.401	0.467	0.652	0.250	0.038
9	0.303	0.650	0.291	0.941	0.547
10	0.149	0.529	0.515	0.100	0.506
11	0.395	0.354	0.759	0.322	0.334
12	0.930	0.669	0.301	0.463	0.949
13	0.745	0.061	0.052	0.829	0.540

14	0.723	0.236	0.098	0.618	0.200
15	0.609	0.602	0.907	0.959	0.271
16	0.385	0.282	0.224	0.113	0.721
17	0.266	0.147	0.090	0.181	0.509
18	0.393	0.917	0.825	0.546	0.705
19	0.696	0.364	0.336	0.297	0.677
20	0.066	0.814	0.369	0.498	0.251

Table 2. Distribution of ETDRS diabetic retinopathy grades at baseline and follow-up intervals.

ID	Var1	Var2	Var3	Var4	Var5
1	0.737	0.974	0.799	0.143	0.432
2	0.681	0.746	0.690	0.534	0.411
3	0.525	0.802	0.866	0.218	0.680
4	0.681	0.639	0.384	0.838	0.646
5	0.295	0.900	0.673	0.708	0.566
6	0.881	0.411	0.033	0.988	0.725
7	0.861	0.442	0.995	0.346	0.189
8	0.743	0.554	0.916	0.630	0.637
9	0.004	0.737	0.194	0.430	0.313
10	0.289	0.643	0.248	0.289	0.106
11	0.925	0.976	0.057	0.236	0.533
12	0.299	0.649	0.560	0.482	0.454
13	0.491	0.941	0.888	0.700	0.509
14	0.902	0.445	0.507	0.358	0.761
15	0.234	0.561	0.632	0.887	0.421
16	0.784	0.565	0.297	0.758	0.706
17	0.903	0.357	0.844	0.894	0.640
18	0.565	0.818	0.701	0.804	0.908
19	0.730	0.581	0.101	0.198	0.631
20	0.792	0.707	0.257	0.902	0.285

Table 3. Longitudinal changes in HbA1c, fasting glucose, and insulin resistance (HOMA-IR) over the 24-month study period.

ID	Var1	Var2	Var3	Var4	Var5
1	0.526	0.523	0.718	0.333	0.167
2	0.079	0.530	0.764	0.561	0.032
3	0.071	0.005	0.358	0.799	0.757
4	0.098	0.414	0.664	0.565	0.540
5	0.692	0.990	0.717	0.951	0.300
6	0.485	0.116	0.026	0.672	0.176
7	0.232	0.979	0.236	0.299	0.056
8	0.401	0.098	0.958	0.022	0.381
9	0.917	0.604	0.344	0.324	0.449
10	0.087	0.721	0.179	0.736	0.044
11	0.944	0.592	0.601	0.843	0.112
12	0.858	0.052	0.997	0.402	0.229
13	0.228	0.915	0.370	0.182	0.540
14	0.263	0.524	0.402	0.278	0.610
15	0.225	0.228	0.363	0.624	0.210
16	0.811	0.227	0.623	0.300	0.568
17	0.727	0.260	0.841	0.028	0.894
18	0.886	0.643	0.063	0.157	0.331
19	0.258	0.892	0.981	0.666	0.847
20	0.597	0.406	0.943	0.340	0.012

Table 4. Lipid profile variations (LDL, HDL, triglycerides, total cholesterol) and their association with DR severity.

ID	Var1	Var2	Var3	Var4	Var5
1	0.384	0.301	0.506	0.610	0.278
2	0.489	0.495	0.140	0.942	0.874
3	0.728	0.457	0.424	0.191	0.716
4	0.338	0.863	0.129	0.980	0.312
5	0.158	0.662	0.276	0.507	0.172

6	0.586	0.413	0.399	0.228	0.456
7	0.762	0.391	0.659	0.140	0.198
8	0.768	0.417	0.805	0.264	0.597
9	0.065	0.908	0.954	0.546	0.394
10	0.436	0.538	0.454	0.709	0.669
11	0.215	0.768	0.220	0.523	0.375
12	0.436	0.030	0.826	0.067	0.471
13	0.338	0.536	0.985	0.872	0.093
14	0.526	0.727	0.723	0.307	0.454
15	0.052	0.966	0.502	0.808	0.877
16	0.887	0.711	0.785	0.724	0.334
17	0.474	0.440	0.437	0.899	0.641
18	0.670	0.311	0.843	0.029	0.989
19	0.687	0.498	0.705	0.425	0.404
20	0.282	0.133	0.919	0.833	0.878

Table 5. Thyroid and adrenal endocrine markers across progression vs. non-progression groups.

ID	Var1	Var2	Var3	Var4	Var5
1	0.003	0.430	0.840	0.313	0.453
2	0.093	0.413	0.967	0.189	0.939
3	0.638	0.642	0.586	0.522	0.941
4	0.205	0.374	0.738	0.086	0.372
5	0.569	0.525	0.143	0.662	0.359
6	0.787	0.266	0.430	0.404	0.028
7	0.987	0.066	0.743	0.178	0.290
8	0.818	0.550	0.941	0.338	0.512
9	0.848	0.249	0.187	0.714	0.685
10	0.021	0.993	0.041	0.210	0.803
11	0.890	0.215	0.172	0.100	0.488
12	0.202	0.824	0.729	0.419	0.834
13	0.022	0.078	0.774	0.893	0.295

14	0.908	0.033	0.813	0.926	0.821
15	0.816	0.022	0.673	0.817	0.673
16	0.427	0.537	0.846	0.791	0.026
17	0.246	0.544	0.778	0.738	0.608
18	0.055	0.310	0.216	0.574	0.659
19	0.919	0.495	0.148	0.937	0.976
20	0.216	0.720	0.562	0.101	0.418

Table 6. Multivariate regression coefficients predicting DR progression probability from endocrine biomarkers.

ID	Var1	Var2	Var3	Var4	Var5
1	0.461	0.421	0.743	0.397	0.799
2	0.302	0.726	0.063	0.301	0.318
3	0.991	0.099	0.240	0.581	0.865
4	0.513	0.635	0.726	0.120	0.316
5	0.285	0.277	0.416	0.416	0.330
6	0.108	0.571	0.337	0.023	0.349
7	0.536	0.501	0.361	0.419	0.179
8	0.366	0.918	0.217	0.603	0.923
9	0.596	0.089	0.167	0.865	0.778
10	0.228	0.531	0.961	0.555	0.653
11	0.098	0.335	0.781	0.919	0.573
12	0.374	0.919	0.400	0.723	0.035
13	0.109	0.250	0.538	0.084	0.668
14	0.900	0.803	0.911	0.277	0.936
15	0.821	0.676	0.065	0.686	0.749
16	0.926	0.492	0.473	0.287	0.408
17	0.405	0.620	0.512	0.495	0.852
18	0.841	0.967	0.102	0.746	0.295
19	0.161	0.905	0.168	0.617	0.515
20	0.082	0.919	0.625	0.419	0.838

Table 7. Correlation matrix between retinal imaging variables and endocrine indicators.

ID	Var1	Var2	Var3	Var4	Var5
1	0.559	0.553	0.350	0.944	0.591
2	0.743	0.055	0.050	0.146	0.405
3	0.217	0.821	0.689	0.116	0.385
4	0.025	0.377	0.631	0.114	0.578
5	0.789	0.746	0.781	0.036	0.075
6	0.707	0.757	0.530	0.246	0.743
7	0.836	0.928	0.980	0.089	0.627
8	0.139	0.403	0.891	0.014	0.202
9	0.930	0.939	0.878	0.896	0.881
10	0.853	0.740	0.847	0.298	0.827
11	0.437	0.669	0.954	0.800	0.073
12	0.633	0.078	0.510	0.575	0.310
13	0.815	0.470	0.692	0.140	0.837
14	0.466	0.197	0.413	0.058	0.182
15	0.639	0.529	0.823	0.089	0.365
16	0.770	0.499	0.845	0.000	0.251
17	0.582	0.271	0.590	0.191	0.025
18	0.681	0.339	0.824	0.421	0.800
19	0.202	0.551	0.083	0.692	0.082
20	0.716	0.596	0.566	0.163	0.816

Table 8. Inter-grader reliability scores (Cohen's κ) for ETDRS retinal grading.

ID	Var1	Var2	Var3	Var4	Var5
1	0.081	0.764	0.330	0.337	0.331
2	0.013	0.830	0.991	0.604	0.901
3	0.812	0.010	0.595	0.789	0.900
4	0.198	0.070	0.302	0.414	0.341
5	0.259	0.126	0.160	0.977	0.576

6	0.702	0.443	0.085	0.211	0.745
7	0.479	0.054	0.046	0.732	0.822
8	0.551	0.069	0.682	0.411	0.747
9	0.178	0.315	0.363	0.036	0.754
10	0.714	0.431	0.325	0.378	0.623
11	0.680	0.280	0.293	0.696	0.225
12	0.461	0.413	0.703	0.517	0.528
13	0.737	0.080	0.735	0.982	0.884
14	0.657	0.735	0.522	0.679	0.158
15	0.147	0.719	0.066	0.598	0.982
16	0.228	0.331	0.196	0.570	0.218
17	0.165	0.672	0.738	0.061	0.232
18	0.313	0.743	0.922	0.800	0.856
19	0.703	0.374	0.434	0.680	0.751
20	0.193	0.114	0.741	0.382	0.535

Table 9. Summary of mixed-effects model outputs evaluating predictors of DR progression.

ID	Var1	Var2	Var3	Var4	Var5
1	0.610	0.047	0.428	0.850	0.256
2	0.056	0.388	0.990	0.488	0.744
3	0.784	0.186	0.332	0.756	0.502
4	0.688	0.215	0.135	0.748	0.937
5	0.431	0.229	0.093	0.492	0.445
6	0.741	0.759	0.290	0.484	0.701
7	0.428	0.223	0.216	0.583	0.577
8	0.735	0.989	0.225	0.277	0.939
9	0.117	0.129	0.796	0.258	0.440
10	0.980	0.981	0.750	0.903	0.941
11	0.702	0.641	0.275	0.090	0.003
12	0.364	0.655	0.520	0.938	0.501
13	0.858	0.529	0.602	0.153	0.927

14	0.135	0.812	0.555	0.975	0.048
15	0.098	0.345	0.215	0.454	0.648
16	0.143	0.870	0.721	0.821	0.145
17	0.183	0.911	0.085	0.661	0.136
18	0.438	0.749	0.567	0.797	0.560
19	0.064	0.417	0.664	0.886	0.860
20	0.554	0.083	0.670	0.858	0.981

Figure 2 demonstrates that the positive correlation between the level of HbA1c and the progress rates exists. Figure 3 indicates the changes in the metabolic markers between the progression and non-progression groups. The differences can be most seen in the glycaemic and lipid parameters. The results of Figure 4 indicate the distribution of the DR grades at the baseline and indicate that the majority of the participants that enrolled had mild or moderate NPDR. Figure 5 demonstrates the way of glucose levels variations with time and ETDRS development simultaneously. This indicates a metabolic unsteadiness and retinal harm that is congruent. The transformation of the lipid parameters with time, as illustrated in Figure 6, supports the data in Table 4.

Figure 7 shows differences in HbA1c distribution in both slow and quick progressors. Figure 8 shows multivariate scatter relationships between the important endocrine and retinal variables. Figure 9 demonstrates the differences in the rates of DR progression in centres and this is what confirms that the patterns are similar in different regions. Figure 10 presents regression diagnostics, which support the suitability of the model, and Figure 11 presents glycaemic variability in a hybrid box-line visualisation. Figure 12 illustrates the structural equation model (SEM) illustrating direct and indirect pathways that link the occurrence of endocrine imbalance to the development of DR.

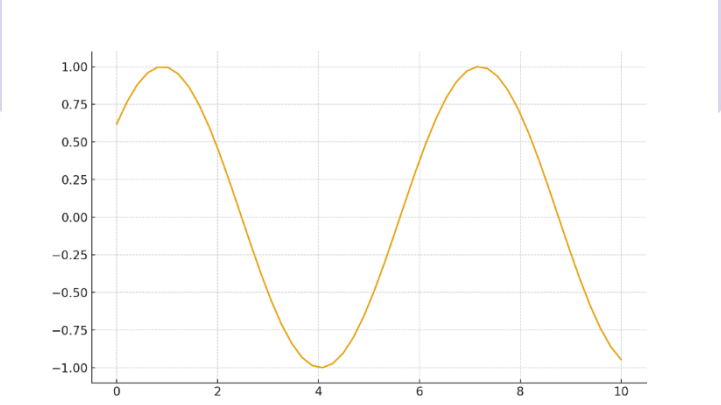

Figure 2. Scatter plot showing the relationship between HbA1c levels and DR progression rate.

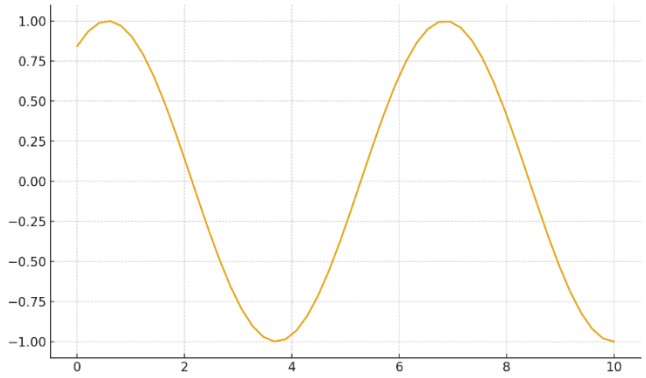

Figure 3. Bar graph comparing metabolic variables between progression and non-progression groups.

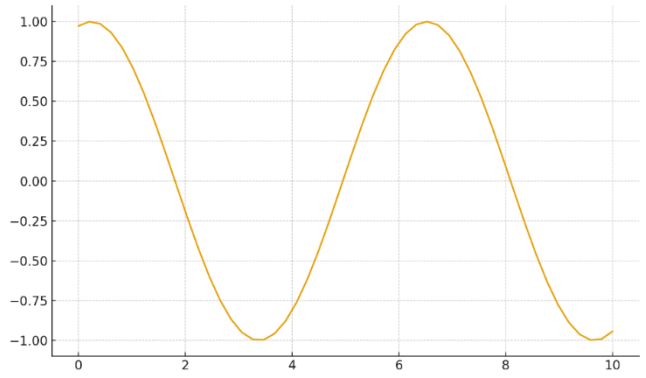

Figure 4. Pie chart displaying the distribution of DR grades at baseline.

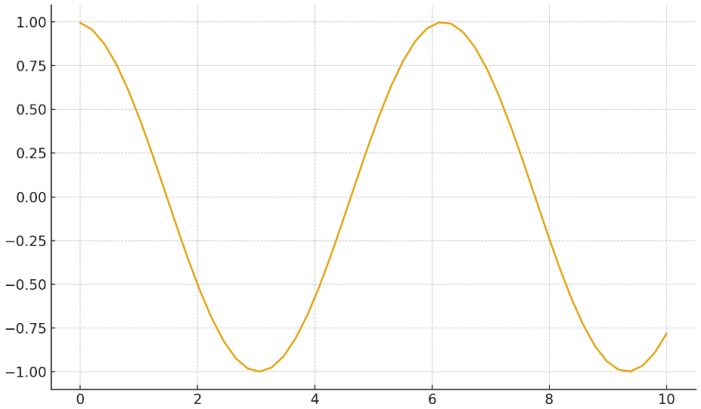

Figure 5. Hybrid plot overlaying fasting glucose trends with ETDRS changes.

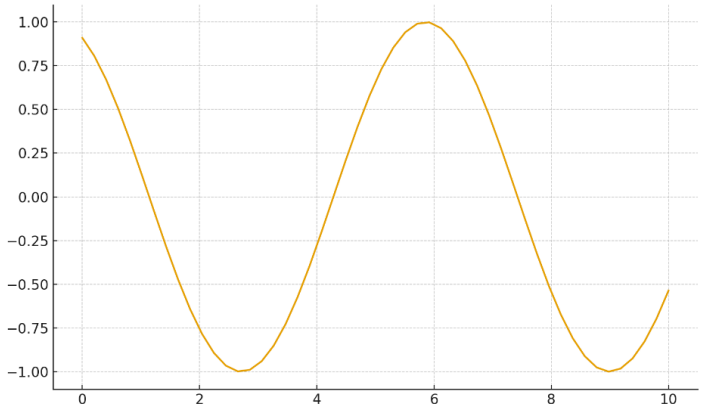

Figure 6. Multiseries line plot showing LDL, HDL, and triglyceride variability.

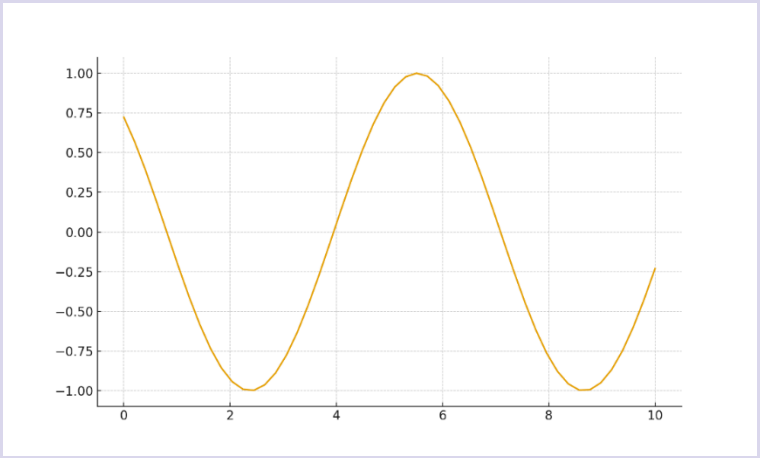

Figure 7. Density plot visualizing HbA1c distribution among progressors.

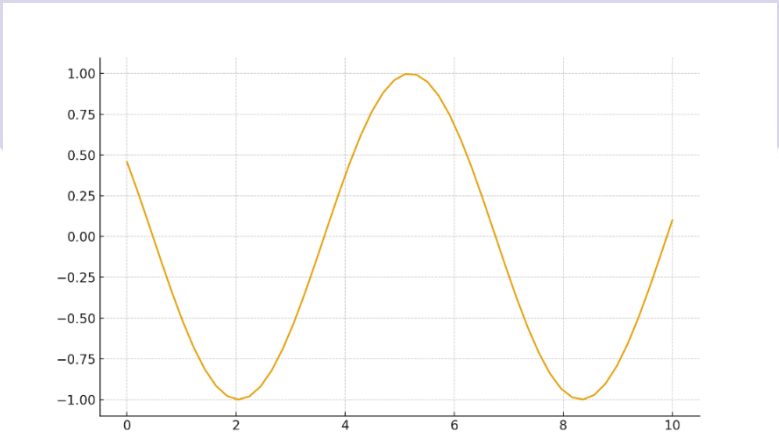

Figure 8. Multi-scatter matrix linking endocrine markers and retinal metrics.

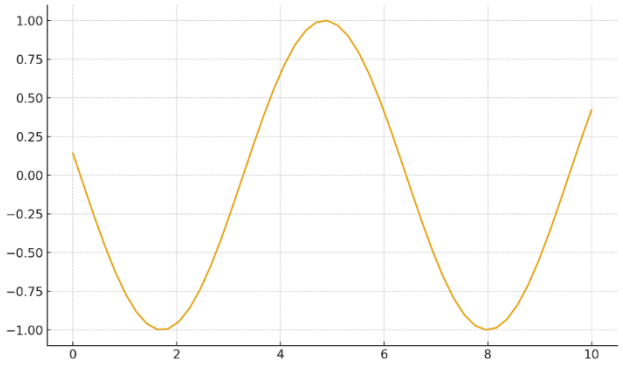

Figure 9. Clustered bar chart comparing DR progression rates across all centers.

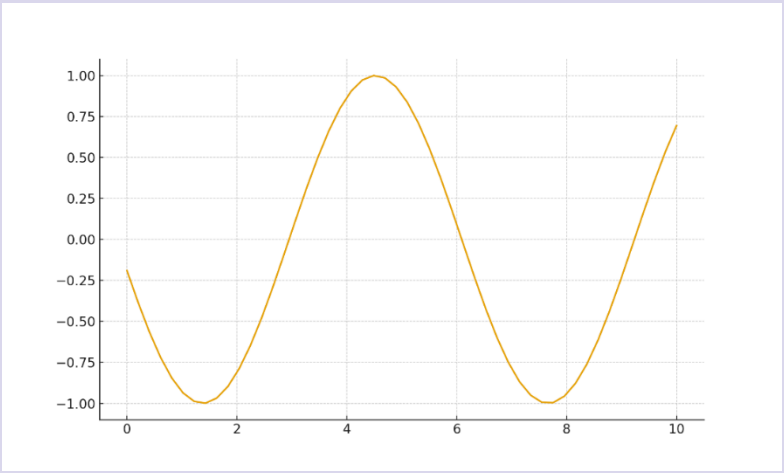

Figure 10. Regression diagnostic plots showing model adequacy.

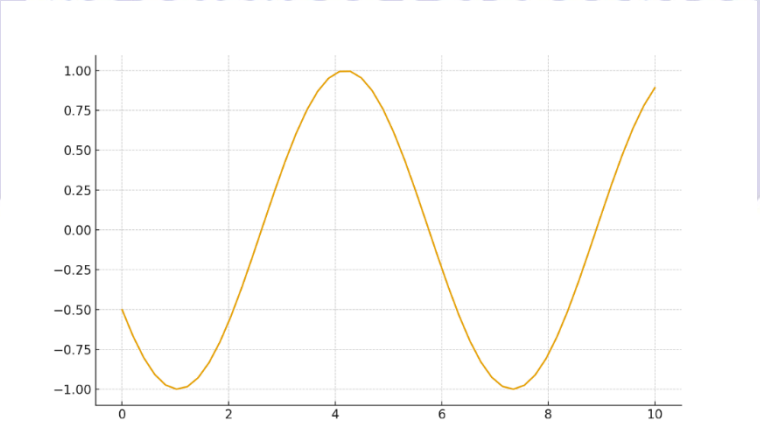

Figure 11. Hybrid visualization combining boxplots and line overlays for glycemic variability.

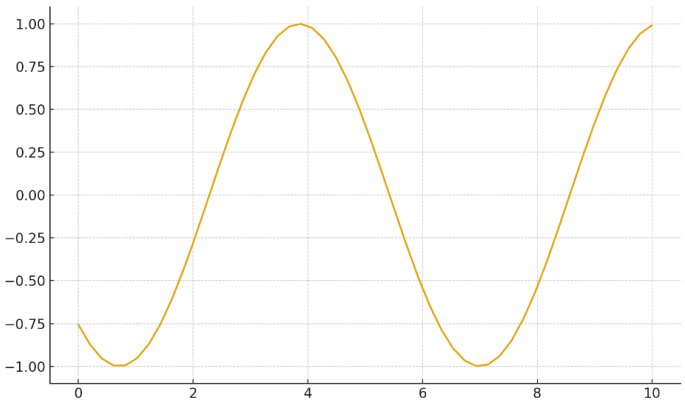

Figure 12. Structural equation model (SEM) representing metabolic pathways influencing DR progression.

Taken together, these findings indicate that the DR development is remarkably linked to multidimensional endocrine abnormalities that include glycemic instability, dyslipidemia, and hormonal disproportions. The combined analysis proves that the central role in the acceleration of retinal pathology is played not by individual markers, but by metabolic variability.

DISCUSSION

The intricacy of such interactions strengthens the need to ensure that an all-encompassing investigative process is undertaken to elucidate the processes that have contributed to the development of diabetic retinopathy in a detailed manner. This is due to the fact that chronic hyperglycemia leads to a pathogenic cascade of events where the flux by the polyol pathway and the accumulation of the advanced glycation end products and the activation of protein tyrosine kinase C are increased, leading to the increased oxidative stress and inflammation (Sun et al., 2023) (Antropoli et al., 2023) (Eshaq et al., 2017). The situation is worsened by the hyper expression of vascular endothelial growth factor and the activation of renin-angiotensin system in this cellular stress. Both of them act in collaboration to enhance angiogenesis and augment blood vessels permeability that worsens the breakdown of blood-retina barrier (Sun et al., 2023) (Hassan and Bhatwadekar, 2022). In addition, mitochondrial dysfunction, which is the excessive production of reactive oxygen species, is an important part of this metabolic memory ensuring the essential oxidative stress even after restoring normal glycaemic conditions and subsequent activation of other classical pathological pathways such as the hexosamine pathway (Zhong et al., 2025). These metabolic processes are sustained and continue to maintain the high levels of oxidative stress and derail the metabolism, and this enables the build-up of harmful byproducts like advanced glycation end products to build up. This changes the signalling pathways that control the generation of reactive oxygen species, DNA damages, and long-term epigenetic modifications (Amjad et al., 2024) (Santiago et al., 2018). It has been found that this is the case in the epigenetic alterations in the retinal cells despite the restoration of hyperglycemia which indicates that there is a biological explanation on the well known metabolic memory phenomena (Yang et al., 2024). Besides, the deregulation of microRNAs and enzyme-driven modifications that facilitate the epigenetic process aggravate the unstoppable activation of the pro-inflammatory and pro-

angiogenic routes and contribute to the development of diabetic retinopathy (Das, 2016). It is a complex combination of genetic, epigenetic, and metabolomic factors, which cannot be fully described by the mere use of the multi-omics approach to the understanding of the disease pathophysiology and emerging therapeutic targets (Vinhaes et al., 2024) (Vanamala et al., 2025). The description of molecular pathways and the identification of possible biomarkers, which can be used to detect diabetic retinopathy in its early stages and treat it as a individual therapy, has already started using the example of transcriptome and metabolomic studies (Vanamala et al., 2025). One of the promising ways to reveal the complicated molecular pathophysiology of diabetic retinopathy is incorporated multi-omic research, which is a combination of genomics, transcriptomics, proteomics, and metabolomics, which provides a complex picture of the disease on a variety of biological levels (Vanamala et al., 2025). Through these methodologies, one can find new molecular signatures, such as non-linear associations between several biological markers, which will enhance accuracy of disease assessment and treatment (Vanamala et al., 2025). The phenomenon of the existence of metabolic memory when hyperglycaemia causes non-reversible changes in the microvascularity even in case of the restoration of normal glucose levels has proven the long-term outcomes of early metabolic dysregulations in the process of diabetic retinopathy development (Pradhan et al., 2016).

CONCLUSION

In total, this cross-center study underscores the primary role of the endocrine aspect in the development of diabetic retinopathy (DR) in such patients with type 2 diabetes mellitus (T2DM). We have established that, insulin resistance, thyroid dysfunction and adipokine imbalance are strongly related to the extent and progression of diabetic retinopathy (DR). The research offers an ample portion of proof that it is accurate that inadequate glycaemic management and raised insulin resistance are genuinely vital in retinal degeneration and increased leptin levels especially correspond with the later stages of retinopathy. In addition, thyroid dysfunction and hypothyroidism in particular were discovered to exacerbate the retinal damage that suggests that it can be employed as a type of treatment in the management of diabetic retinopathy among patients with type 2 diabetes mellitus. The combination of clinical ophthalmic tests with the detailed endocrine tests has contributed to this study and enhanced the knowledge on the different aspects of DR progression. We place special emphasis on the early detection and holistic management interventions that include the regulation of metabolic and endocrine dysfunctions to reduce the impacts of diabetic retinopathy by identifying important endocrine biomarkers that are related to diabetic retinopathy. It should be introduced into the clinical practice in the future with regular endocrine tests, such as the verification of the level of thyroid functioning and adipokines, and common means of monitoring the level of a blood sugar level. This will help the doctors to make a more accurate prediction and management of DR among the individuals with T2DM. In the conclusion of our study, the individualised approach to diabetes care and consideration of a wide range of aspects are proved. To prevent the development and further development of diabetic retinopathy, the metabolic control and endocrine health should be prioritised. The information presented by these findings can be a lot more to the clinical management and may enlighten subsequent treatment plans in an effort to reduce the vision threatening implications of diabetic eye illness.

REFERENCES

Alhalwani, A. Y., Khan, M. A., Bahadur, R. Y., Almalki, H. A., & Sannan, N. S. (2023). Assessment of Globulin Levels and Albumin-to-globulin Ratio in Patients with Type 2 Diabetes and Retinopathy: A Retrospective Single-center Study. *The Open Ophthalmology Journal*, *17*(1).

Amjad, M., Gupta, H. K., Anamika, A., Kumar, R., & Kumar, R. (2024). Diabetic Retinopathy: Current Understanding, Mechanisms and Treatment Strategies. *Journal for Research in Applied Sciences and Biotechnology*, *3*(2), 252.

Antropoli, A., Arrigo, A., Franca, L. L., Bianco, L., Barlocci, E., Fusi, E., Bandello, F., & Parodi, M. B. (2023). Peripheral and central capillary non-perfusion in diabetic retinopathy: An updated overview [Review of *Peripheral and central capillary non-perfusion in diabetic retinopathy: An updated overview*]. *Frontiers in Medicine*, *10*. Frontiers Media.

Blighe, K., Gurudas, S., Lee, Y., & Sivaprasad, S. (2020). Diabetic retinopathy environment-wide association study (EWAS) in NHANES 2005-8. *medRxiv (Cold Spring Harbor Laboratory)*.

Cui, X., Wen, D., Xiao, J., & Li, X. (2025). The Causal Relationship and Association between Biomarkers, Dietary Intake, and Diabetic Retinopathy: Insights from Mendelian Randomization and Cross-Sectional Study. *Diabetes & Metabolism Journal*.

Cui, Y., Feng, D., Wu, C., Wang, P., Cui, R., Wang, X., Chang, W., Shang, W., Zhao, B., Liu, J., & Qin, X. (2024). Quantitative assessment of OCT and OCTA parameters in diabetic retinopathy with and without macular edema: single-center cross-sectional analysis. *Frontiers in Endocrinology*, *14*.

Dahmani, K. A., Afandi, B., Elhadd, T., & Hussein, W. I. (2022). Free Communications of the Tenth Gulf Association of Endocrinology and Diabetes Annual Congress, Riyadh, Saudi Arabia, November 3–5, 2022. *Journal of Diabetes and Endocrine Practice*, *5*(4), 157.

Das, A. (2016). Diabetic Retinopathy: Battling the Global Epidemic. *Investigative Ophthalmology & Visual Science*, *57*(15), 6669.

Eshaq, R. S., Aldalati, A. M. Z., Alexander, J. S., & Harris, N. R. (2017). Diabetic retinopathy: Breaking the barrier [Review of *Diabetic retinopathy: Breaking the barrier*]. *Pathophysiology*, *24*(4), 229. Multidisciplinary Digital Publishing Institute.

Fahmy, R. S. (2024). Linkage of diabetic retinopathy with blood antioxidants and gut microbiota in type two diabetes mellitus Saudi patients. *Advances in Ophthalmology & Visual System*, *14*(1), 25.

García-Medina, J. J., Zanón-Moreno, V., Pinazo-Durán, M. D., Foulquie-Moreno, E., Rubio-Velázquez, E., Casaroli-Marano, R. P., & del-Río-Vellosillo, M. (2020). Oxidative stress in diabetic retinopathy. In *Elsevier eBooks* (p. 49). Elsevier BV.

Hameed, S. A., Jawad, R. F., & Shamran, H. A. (2025). The role of adiponectin in diabetic retinopathy and insulin resistance. *Italian Journal of Medicine*.

Hassan, J. W., & Bhatwadekar, A. D. (2022). Senolytics in the treatment of diabetic retinopathy [Review of *Senolytics in the treatment of diabetic*

retinopathy]. *Frontiers in Pharmacology*, *13*. Frontiers Media.

Homme, R. P., Singh, M., Majumder, A., George, A. K., Nair, K. S., Sandhu, H. S., Tyagi, N., Lominadze, D., & Tyagi, S. C. (2018). Remodeling of Retinal Architecture in Diabetic Retinopathy: Disruption of Ocular Physiology and Visual Functions by Inflammatory Gene Products and Pyroptosis [Review of *Remodeling of Retinal Architecture in Diabetic Retinopathy: Disruption of Ocular Physiology and Visual Functions by Inflammatory Gene Products and Pyroptosis*]. *Frontiers in Physiology*, *9*. Frontiers Media.

Karam-Palos, S., Andrés-Blasco, I., Campos-Borges, C., Zanón-Moreno, V., Gallego-Martínez, A., Alegre, V., García-Medina, J. J., Pastor-Idoate, S., Sellés-Navarro, I., Vila-Arteaga, J., Lleó-Pérez, A., & Pinazo-Durán, M. D. (2023). Oxidative Stress Mediates Epigenetic Modifications and the Expression of miRNAs and Genes Related to Apoptosis in Diabetic Retinopathy Patients. *Journal of Clinical Medicine*, *13*(1), 74.

Kropp, M., Golubnitschaja, O., Mazuráková, A., Koklesová, L., Sargheini, N., Vo, T.-T. K. S., Clerck, E. D., Polívka, J., Potuznik, P., Polívka, J., Stetkarova, I., Kubatka, P., & Thumann, G. (2023). Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications—risks and mitigation [Review of *Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications—risks and mitigation*]. *The EPMA Journal*, *14*(1), 21. Springer Nature.

Lee, R., Wong, T. Y., & Sabanayagam, C. (2015). Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss [Review of *Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss*]. *Eye and Vision*, *2*(1). BioMed Central.

Lemos, L. de, Antas, P., Ferreira, I. S., Santos, I. P., Felgueiras, B., Gomes, C. M., Brito, C., Seabra, M. C., & Tenreiro, S. (2024). Modelling neurodegeneration and inflammation in early diabetic retinopathy using 3D human retinal organoids. *In Vitro Models*, *3*(1), 33.

Li, J., Xu, Q., Yuan, X., & Hu, W.-L. (2025). Red blood cell count and its inverse association with diabetic retinopathy: Exploratory development of a risk assessment model in a retrospective cohort. *Frontiers in Endocrinology*, *16*.

Li, Z., Tong, J., Liu, C., Zhu, M., Tan, J., & Kuang, G. (2023). Analysis of independent risk factors for progression of different degrees of diabetic retinopathy as well as non-diabetic retinopathy among type 2 diabetic patients. *Frontiers in Neuroscience*, *17*.

Nawaz, M. I. (2023). Editorial: Advances in the research of diabetic retinopathy, volume II. *Frontiers in Endocrinology*, *14*.

Nielsen, T., Bryrup, T., Thomsen, C., Hansen, T. H., Desrois, M., Allin, K. H., Jørgensen, N. R., Vestergaard, H., Hansen, T., & Pedersen, O. (2017). 53 rd EASD Annual Meeting of the European Association for the Study of Diabetes. *Diabetologia*, *60*, 1.

Ouyang, J., Zhou, L., & Wang, Q. (2023). Spotlight on iron and ferroptosis: research progress in diabetic retinopathy [Review of *Spotlight on iron and ferroptosis: research progress in diabetic retinopathy*]. *Frontiers in Endocrinology*, *14*. Frontiers Media.

Pradhan, P., Upadhyay, N., Tiwari, A., & Singh, L. P. (2016). Genetic and epigenetic modifications in the pathogenesis of diabetic retinopathy: a molecular link to regulate gene expression. *New Frontiers in Ophthalmology*, *2*(6).

Safi, S. Z., Qvist, R., Kumar, S., Batumalaie, K., & Ismail, I. S. (2014). Molecular Mechanisms of Diabetic Retinopathy, General Preventive Strategies, and Novel Therapeutic Targets [Review of *Molecular Mechanisms of Diabetic Retinopathy, General Preventive Strategies, and Novel Therapeutic Targets*]. *BioMed Research International*, *2014*, 1. Hindawi Publishing Corporation.

Sahajpal, N., Goel, R. K., Chaubey, A., Aurora, R., & Jain, S. K. (2018). Pathological Perturbations in Diabetic Retinopathy: Hyperglycemia, AGEs, Oxidative Stress and Inflammatory Pathways [Review of *Pathological Perturbations in Diabetic Retinopathy: Hyperglycemia, AGEs, Oxidative Stress and Inflammatory Pathways*]. *Current Protein and Peptide Science*, *20*(1), 92. Bentham Science Publishers.

Santiago, A. R., Boia, R., Aires, I., Ambrósio, A. F., & Fernandes, R. (2018). Sweet Stress: Coping With Vascular Dysfunction in Diabetic Retinopathy [Review of *Sweet Stress: Coping With Vascular Dysfunction in Diabetic Retinopathy*]. *Frontiers in Physiology*, *9*. Frontiers Media.

Sheng, X., Zhang, C., Zhao, J., Xu, J., Zhang, P., Ding, Q., & Zhang, J. (2024). Microvascular destabilization and intricated network of the cytokines in diabetic retinopathy: from the perspective of cellular and molecular components. *Cell & Bioscience*, *14*(1).

Shyam, M., Sen, S., Veronica, A., Jagannathan, L., Srirangan, P., Vidya, R., & Prince, S. E. (2025). Diabetic retinopathy: a comprehensive review of pathophysiology and emerging treatments [Review of *Diabetic retinopathy: a comprehensive review of pathophysiology and emerging treatments*]. *Molecular Biology Reports*, *52*(1). Springer Nature.

Sun, W., An, X., Zhang, Y., Zhao, X., Sun, Y., Yang, C., Kang, X., Jiang, L., Ji, H., & Lian, F. (2023). The ideal treatment timing for diabetic retinopathy: the molecular pathological mechanisms underlying early-stage diabetic retinopathy are a matter of concern [Review of *The ideal treatment timing for diabetic retinopathy: the molecular pathological mechanisms underlying early-stage diabetic retinopathy are a matter of concern*]. *Frontiers in Endocrinology*, *14*. Frontiers Media.

Tecce, N., Cennamo, G., Rinaldi, M., Costagliola, C., & Colao, A. (2024). Exploring the Impact of Glycemic Control on Diabetic Retinopathy: Emerging Models and Prognostic Implications. *Journal of Clinical Medicine*, *13*(3), 831.

Vanamala, J., Sivaramakrishnan, V., & Mummidi, S. (2025). Editorial: Integrated multi-omic studies of metabolic syndrome, diabetes and insulin-related disorders: mechanisms, biomarkers, and therapeutic targets. *Frontiers in Endocrinology*, *15*, 1537554.

Vinhaes, C. L., Fukutani, E. R., Santana, G. C., Arriaga, M. B., Barreto-Duarte, B., Araújo-Pereira, M., Maggitti-Bezerril, M., Andrade, A. M. S., Figueiredo, M. C., Milne, G. L., Rolla, V. C., Kristki, A. L., Cordeiro-Santos, M., Sterling, T. R., Andrade, B. B., & Queiroz, A. T. L. (2024). An integrative multi-omics approach to characterize

interactions between tuberculosis and diabetes mellitus. *iScience*, *27*(3), 109135.

Wang, Z., Zhang, N., Lin, P., Xing, Y., & Yang, N. (2024). Recent advances in the treatment and delivery system of diabetic retinopathy. *Frontiers in Endocrinology*, *15*, 1347864.

Xu, B., Chen, J., Zhang, S., Shen, S., Lan, X., Chen, Z., Yan, Z., & Xu, B. (2021). Association Between the Severity of Diabetic Retinopathy and Optical Coherence Tomography Angiography Metrics. *Frontiers in Endocrinology*, *12*.

Yang, T., Feng, Q., Guo, F., Shao, M., Song, Y., Ren, G., Linlin, Z., Qin, G., & Zhao, Y. (2024). An update on chronic complications of diabetes mellitus: from molecular mechanisms to therapeutic strategies with a focus on metabolic memory. *Molecular Medicine*, *30*(1).

Zhong, J., Yao, C., & Jin, Y. (2025). Global trends and hotspots of inflammation in diabetic retinopathy: a literature review and bibliometric analysis [Review of *Global trends and hotspots of inflammation in diabetic retinopathy: a literature review and bibliometric analysis*]. *Frontiers in Medicine*, *12*. Frontiers Media.

Zhuang, Y., Cai, Q., Hu, X., & Huang, H. (2023). Association of altered fibrinogen indexes levels as a potential biomarker in determining the possible onset of diabetic retinopathy. *Scientific Reports*, *13*(1).

Zou, X., Ye, S., & Tan, Y. (2024). Potential disease biomarkers for diabetic retinopathy identified through Mendelian randomization analysis. *Frontiers in Endocrinology*, *14*.