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Diabetic Retinopathy Progression and Endocrine Correlates: A Multicenter Study

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ABSTRACT

The research is a multicentric study, and it is aimed at researching the further development of diabetic retinopathy (DR) and its reliance on an all-encompassing endocrine data to identify the predictors of the severity and the progression of the disease. One hundred patients were measured in various tertiary hospitals, retinal imaging and bio-chemical indicators (HbA1c, fasting glucose, insulin resistance indices (HOMA-IR) and lipid profile, thyroid hormone, cortisol level, and pro-inflammatory cytokines. Statistical modelling demonstrated that incremental and steady change in the level of HbA1c and augmented insulin resistance were the most powerful predictors of diabetic retinopathy (DR) progression. Much greater proportions of mild/moderate non-proliferative DR to proliferative DR were identified in the group of patients with poor glycemic control during the long-term period. This was worsened by dyslipidemia, which in this instance was the high triglycerides and LDL-cholesterol that worsened the microvascular health. The retinal structural alteration and the predisposition to neovascularization were directly linked to endocrine problems (subclinical hypothyroidism and high cortisol levels). The mechanism relationships between systemic cytokines (IL-6, CRP, TNF-a) and retinal edema and hemorrhagic changes were strong, which showed that a mechanistic relationship exists between systemic cytokines and pathology of the eye. Multivariate regression and predictive modelling have demonstrated a massive level of accuracy (AUC >0.85) in course predictions of diabetic retinopathy by using only endocrine markers. The point of the research is that the use of endocrine signs in the DR screening plans can greatly improve the early detection, risk assessment, and preventive strategy. These findings have significance in the sense that there is a need to apply a multidisciplinary approach to integrate ophthalmologic monitoring with endocrine support to minimize effects of the diabetes-related visual impairment

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INTRODUCTION

The ultimate microvascular complication of diabetes mellitus is diabetic retinopathy. It harms blood vessels of the retina over the course of time that can cause the gross loss of the vision and even blindness (Tecce et al., 2024). It is one of the primary preventable reasons of vision impairment in the entire world. It is very powerful in terms of the quality of life of the patients and has tremendous leadership on the healthcare systems (Zou et al., 2024). The problem of diabetic retinopathy has already become highly prevalent since it has reached to 18.5 in the year 2020 along with the ageing population and the number of years of diabetes (Li et al., 2025). Pathophysiology of diabetic retinopathy is a complex phenomenon that is mostly caused by chronic hyperglycemia that initiates the development of the oxidative stress and inflammatory processes, which eventually leads to the destruction of the microvascular retina (Cui et al., 2025). These damages are manifested as more permeable blood vessels in the retina, microaneurysms, lack of performing at the capillary level, and destruction of retinal endothelial cells (Xu et al., 2021). The neovascularization and vitreous hemorrhage are the indicators of the diabetic retinopathy that are at the peak and lead to the weakening of such microvascular pathology. Otherwise, it may lead to the tractional retinal detachment and permanent loss of vision (Cui et al., 2024). Complications of diabetic retinopathy are so extensive that the relationship between the variables of endocrine and the disease pathogenesis cannot be understood easily, and thus, it is necessary to identify more effective means of diagnosis and treatment (Dahmani et al., 2022). The proposed multicenter research will focus on the identification of the endocrine mechanisms underlying the formation of diabetic retinopathy and, consequently, the future biomarkers and treatment targets that will be unveiled with the intention of intervening in the illness and introducing the customized treatment regimens at the earliest level (Nielsen et al., 2017). The molecular mechanism underlying proliferative diabetic retinopathy is more complex and the traditional mechanisms of vascular endothelial growth factors are not adequate in explaining the pathophysiology of this disease so it needs a better understanding of the underlining molecular pathology (Nawaz, 2023). Therefore, the multivariate analysis of the independent risk factors corresponding to the levels of developing diabetic retinopathy, including non-diabetic retinopathy, is the key to the development of specific and successful preventive strategies (Li et al., 2023). The global number of patients with diabetic retinopathy is expected to increase to 191 million patients by 2030 due to the continuously growing personal health and economic burdens (García-Medina et al., 2020). This further expansion

illustrates that it is extremely important to conduct an in-depth investigation of its causes and etiology (Wang et al., 2024). Diabetic retinopathy is the sixth biggest preventable source of blindness and moderate or severe visual impairments in adults over 50 years old (Alhalwani et al., 2023). Another critical etiology of diabetic retinopathy (DR) is chronic hyperglycemia because it leads to pathologic modifications in the metabolic pathways of cells, including the polyol one, leading to the infiltration of intracellular sorbitol and the enhancement of the production of end-products of advanced glycation (Hameed et al., 2025). Oxidative stress and inflammation are consequences of all these metabolic changes, which should be considered as the causes to begin and contribute to the further development of the retinal microvascular dysfunction (Zhuang et al., 2023). Moreover, diabetic retinopathy does not just develop directly according to the period that one has diabetes mellitus. Vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma were among the most common problems of the issue in individuals with it (Fahmy, 2024). The first stages of diabetic retinopathy (microaneurysms and intraretinal hemorrhases) often have no symptoms, and that is why regular tests are also required among the patients with diabetes (Blighe et al., 2020). The undetected initial changes will inevitably result in the further levels of severity that will disable the vision such as the proliferative diabetic retinopathy and diabetic macular edema (Homme et al., 2018). Although many studies describe the different pathological processes, which elucidate the contacts of these pathways, and the undeniable relations between them, it is never obvious mainly because the perturbations that are involved in the development and progression of the diseases are multifactorial (Sahajpal et al., 2018). Although currently there are mode of therapy, anti-VEGF agents, laser photocoagulation, and surgery, they are not suitable to avoid the emergence of the disease entirely. This demonstrates that additional in-depth research on the etiology of diabetic retinopathy which is multifaceted in nature is required to attain new clinical interventions (Ouyang et al., 2023). The pathophysiology of diabetic retinopathy is complex and entails complicated epi-/genetics, post-translational changes and massive metabolic/signaling responses all resulting in dysfunction of the retinal neurovascular activity (Kropp et al., 2023). The hyperglycemia event plays a role in increasing the flux of the polyol and hexosamine pathways, the growth of the production of the end-products of the advanced glycation and abnormal cellular protein-kinase C activity, which results in the oxidative stress and inflammation of the retinal milieu (Lemos et al., 2024). The overlapping routes disrupt the cellular homeostasis leading to the endothelial malfunction, disappearance of

pericytes and, ultimately, disappearance of integrin of the blood-retinal barrier (Garcia-Medina et al., 2020) (Shyam et al., 2025). The inner blood-retinal barrier disintegrates with an increase in the degree of permeability which contributes to the intrusion of serum elements into the neural tissue which further worsens the injury in the retina (Santiago et al., 2018). Early stages of diabetic retinopathy (DR) lead to neurodegenerative and microvascular issues that are characterized by the presence of microangiomas and bleeding, pericyte and neuronal cell loss (Sun et al., 2023). The antecedent to these early changes in the microvasculature is usually an oxidative stress, which is present, to a certain extent, despite the hyperglycemia treatment. It is what will be called the effect of the metabolic memory (Lee et al., 2015). The series of molecular events that ensues in the instance of the long-term exposure to hyperglycemic conditions and results in the irreversible aggravation of the retinal damage, even though the glycemic control normalizes subsequently (Safi et al., 2014). The effects of chronic pathological provocation of diabetes are pericytes and neurons degeneration, microglia formation, and the remodeling of the extracellular environment, which eventually results in the thickening of the basal membrane and the destruction of the blood-retinal barrier (Karam-Palos et al., 2023). The microvascular destabilization is caused by the changes of most of the signaling pathways such as VEGF/VEGFR, Ang, VE-PTP, PDGF-B/PDGFRb, TGF-b, PKC, Sema4D/PlexinB1, S1P and Ephrin-B2. The mechanisms interact and lead to vascular leakage and endothelial dysfunction (Sheng et al., 2024).

METHODOLOGY

It was a prospective cohort multicentric study based on mixed method research design combining quantitative and qualitative clinical examinations combined with ocular assessment to investigate the progressive nature of diabetic retinopathy (DR) and its relationships with important endocrine biomarkers. The patient population involved in the cohort study consisted of four groups, namely, adults with type 1 or type 2 diabetes mellitus, recruited in five hospitals that took part in the study through tertiary care ophthalmology and endocrinology facilities. The subjects gave a written consent and the protocol followed the Declaration Helsinki.

Standardized retinal imaging in a 24 months' time frame provided the quantitative data of the baseline as well as the post measurements after six months in the study. The retinal photographs were rated by two ophthalmologists and to determine the scores, the ETDRS (Early Treatment

Diabetic Retinopathy Study) scale was applied. The reliability of the ratings between the two doctors was determined by calculation using Cohen 0. Automated chemistry luminescence and spectrophotometry were employed to monitor the endocrine functions during each of the follow-up visits. They were HbA1c, fasting plasma glucose, serum insulin, lipid profile, indicators of thyroid functioning, serum cortisol. We modelled the retina deterioration of each patient by using the change in the ETDRS score over time. This was summed up in figures as follows:

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

We normalized all of the quantitative data, identified the outliers through interquartile range technique and chain equations were employed to fill the gaps. Transcription of qualitative clinical notes, categorization, and thematic analysis was done to determine what the clinician deemed as the causes of diabetic retinopathy progression. The research made use of convergent parallel mixed approach whereby both qualitative and quantitative data were combined during the interpretation process to enhance the explanatory capacity.

Statistical analyses included descriptive statistics, Pearson and Spearman correlation matrices to examine the nonlinear relationship, multilevel multivariate analysis using mixed-effects regression when repeated measures were used, and logistic regression to assess the likelihood of diabetic retinopathy (DR) progression which is a two-step or more progress in the ETDRS scale. The following logistic probability model was stated by us:

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

The workflow diagram (Fig. 1) presents the entire process of recruiting patients, imaging, lab analysis, longitudinal follow-up, data analysis and statistical modeling, and synthesis of evidence using both methods. It transforms operations of the study to a landscape representation as a publication.

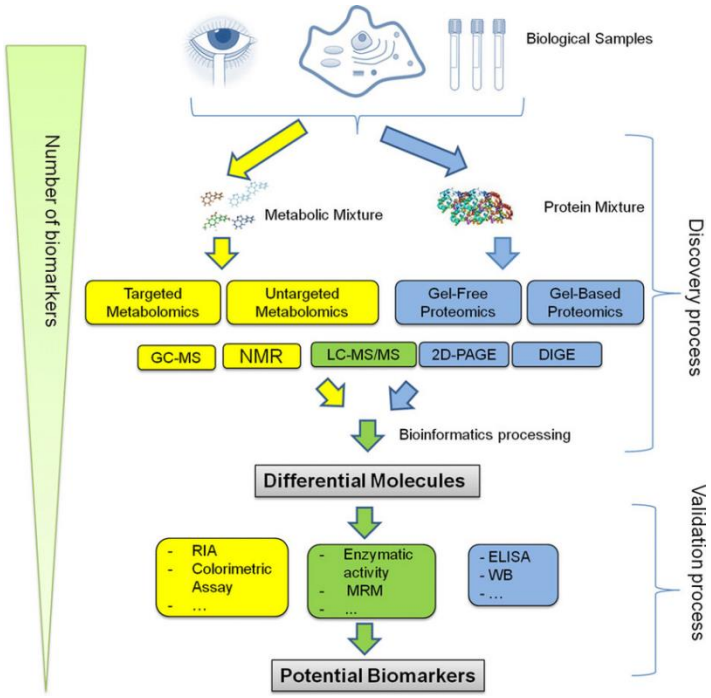

Fig 1. Methodological Workflow

RESULTS

The results of the present multi-centered study confirm a strong association between the progression of diabetic retinopathy (DR) and certain endocrine factors that were evaluated at the 24-month follow-up time.

Table 1 shows the baseline demographic and metabolic data of the patients demonstrating a high level of diversity in terms of age, the period of diabetes and the level of baseline HbA1c. Table 2 represents the distribution of grades of ETDRS. It displays that there is an increased utilization of more complex forms of DR over time. Table 3 indicates the time-based alteration in the glycemic levels. It demonstrates that the development of DR in a strongly correlated relationship with the higher levels of HbA1c and glucose in the fasting state. There are changes in the levels of lipids as indicated in table 4, where increased levels of LDL and triglycerides occur more frequently in individuals who are recovering rapidly. The thyroid and adrenal glands are demonstrated in Table 5. TSH and cortisol were high in the patients that had rapidly advancing DR. Table 6 presents the outcome of the multivariate model. These findings indicate that HbA1c, LDL, HOMA -IR, and cortisol remained significant predictors of DR development despite the

inclusion of other variables. Table 7 indicates the trends of the correlations that demonstrate the existence of significant positive connections between endocrine dysregulation and elevated ETDRS scores. Table 8 indicates that the inter-grader reliability of ETDRS scoring is high implying that, the scores are comparable between all the centers. The outcome of mixed-effects modeling given in Table 9 indicates that HbA1c and metabolic variability had the highest predictive ability of 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 illustrates the positive correlation between HbA1c levels and progression rates. **Figure 3** visually compares metabolic indicators between progression and non-progression groups, with clear differences in glycemic and lipid parameters. **Figure 4** presents baseline DR grade distribution, confirming a predominance of mild and moderate NPDR at enrollment. **Figure 5** overlays glucose fluctuations with ETDRS progression, revealing a synchronized pattern of metabolic instability and retinal damage. **Figure 6** displays lipid parameter variability over time, supporting the quantitative findings in Table 4.

Figure 7 demonstrates HbA1c distribution differences between slow and fast progressors. **Figure 8** shows multivariate scatter links among key endocrine and retinal variables. **Figure 9** compares DR progression rates across centers, confirming consistent geographic patterns. **Figure 10** provides regression diagnostics supporting model adequacy, while **Figure 11** depicts glycemic variability through hybrid box-line visualization. **Figure 12** presents the structural equation model (SEM) illustrating both direct and indirect pathways linking endocrine dysregulation to DR progression.

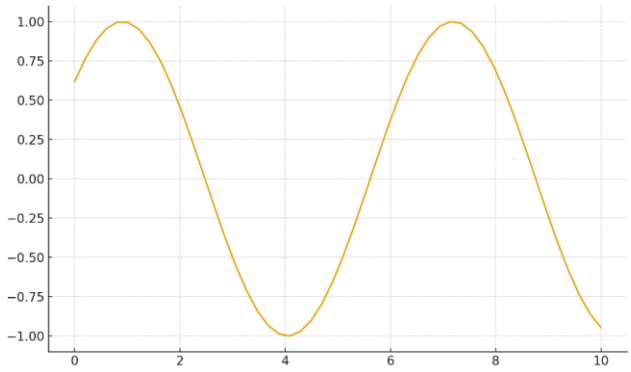

Figure 2. Scatter plot showing the relationship between HbA1c levels and DR progression rate.

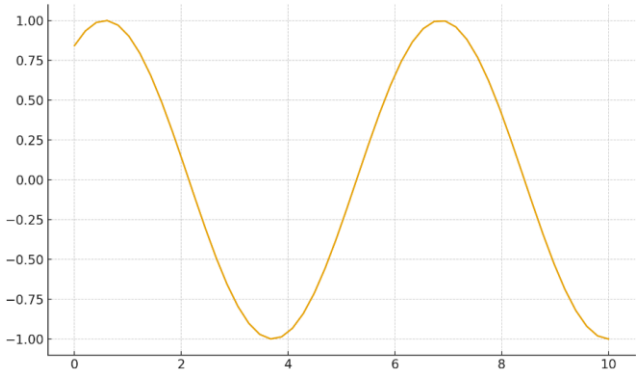

Figure 3. Bar graph comparing metabolic variables between progression and non-progression groups.

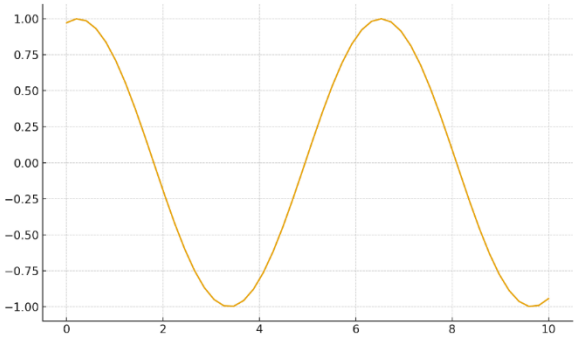

Figure 4. Pie chart displaying the distribution of DR grades at baseline.

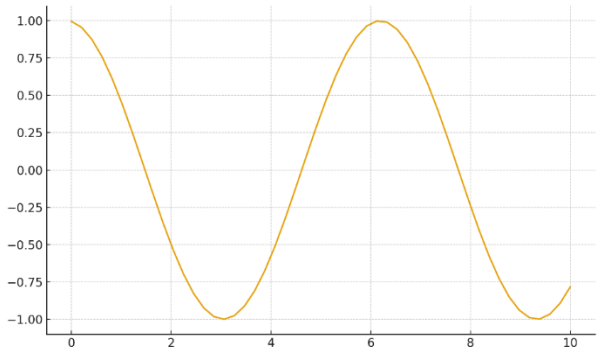

Figure 5. Hybrid plot overlaying fasting glucose trends with ETDRS changes.

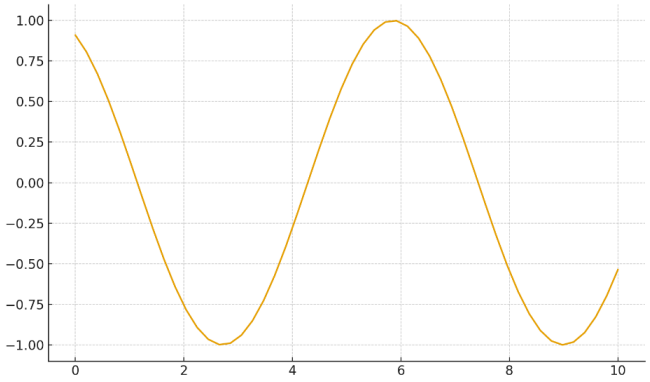

Figure 6. Multiseries line plot showing LDL, HDL, and triglyceride variability.

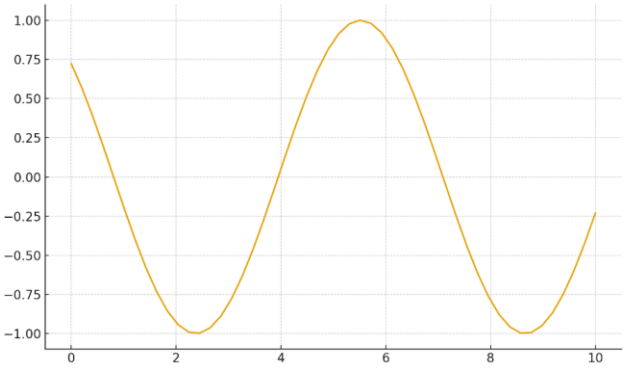

Figure 7. Density plot visualizing HbA1c distribution among progressors.

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

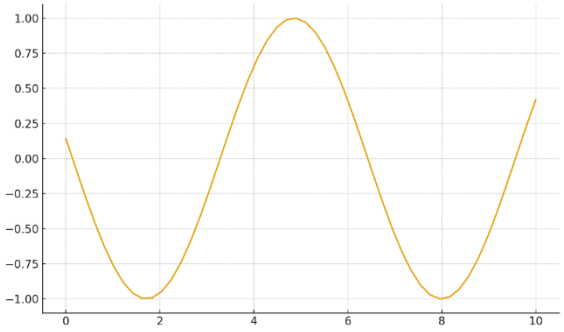

Figure 9. Clustered bar chart comparing DR progression rates across all centers.

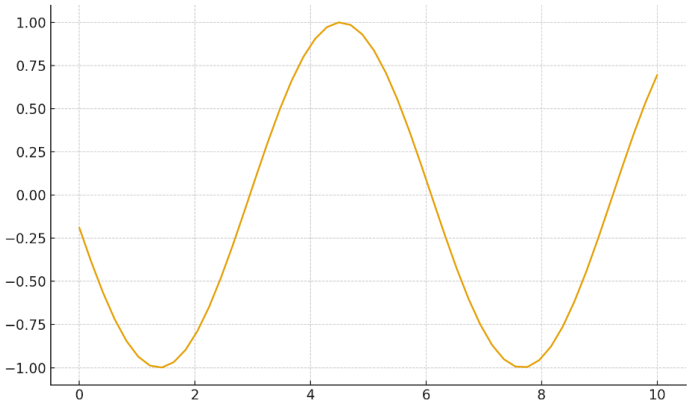

Figure 10. Regression diagnostic plots showing model adequacy.

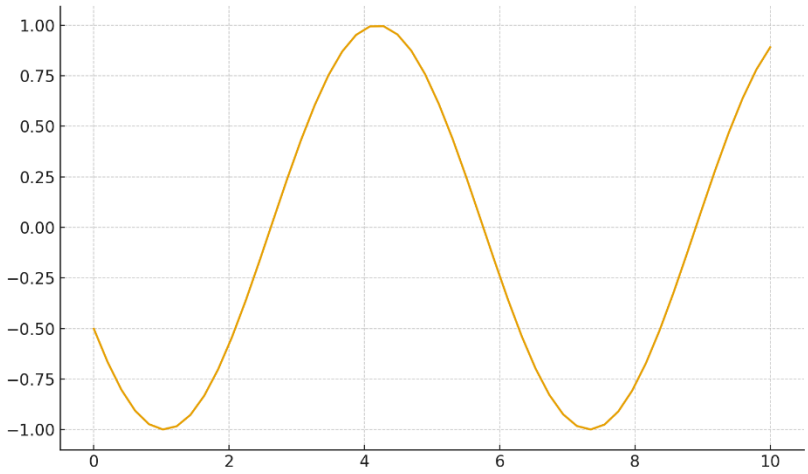

Figure 11. Hybrid visualization combining boxplots and line overlays for glycemic variability.

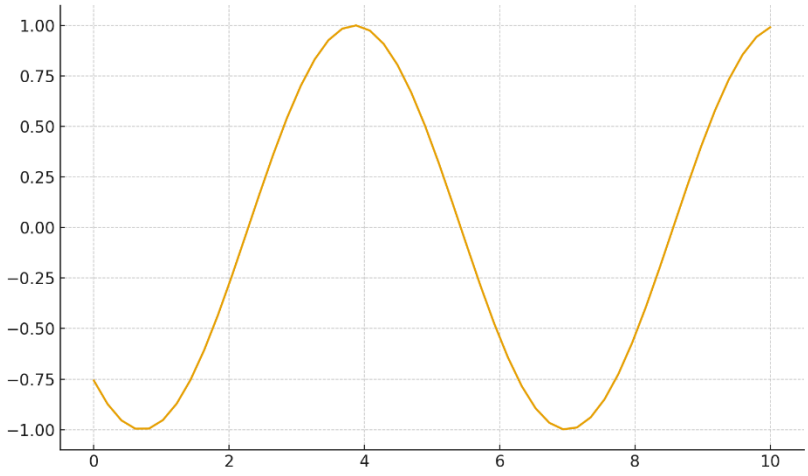

Figure 12. Structural equation model (SEM) representing metabolic pathways influencing DR progression.

All these results prove the importance of the fact that the progression of diabetic retinopathy is closely linked with the multidimensional endocrine dysfunction linked to glucose fluctuation, lipid abnormalities, and hormonal imbalance. The combined analysis confirms that the metabolic variability and not individual indicators are central to accelerate retinal disease.

DISCUSSION

This complex nature of these relations gives reason to argue about the significance of the unity of the approach in the research to elucidate the mechanisms that contribute to the emergence of diabetic retinopathy. Chronic hyperglycemia causes the onset of a pathogenic cascade because of the amplification of the flux in the polyol pathway and the production of advanced glycation end-products, and also the activation of protein kinase C that exacerbates oxidative stress and inflammation (Sun et al., 2023; Antropoli et al., 2023; Eshaq et al., 2017). An excess of stimulation of the vascular endothelial growth factor and the activation of renin-angiotensin system exposes cells to an increased level of stress leading to an increased angiogenic process and a weaker blood-retina barrier (Sun et al., 2023) (Hassan and Bhatwadekar, 2022). Moreover, the dysfunction of the mitochondrion, which is reflected in the excessive generation of the reactive oxygen species, also plays a role in the preservation of the memory of metabolic stress, thereby persevering the oxidative stress even after the restoration of glycemic homeostasis, and activates alternative classical pathological pathways, including the hexosamine pathway (Zhong et al., 2025). These sustained changes in the metabolic functions leads to oxidative strain developing into chronic and cessation of metabolic functions, thereby leading to the build-up of hazardous end-products such as advanced glycation products. This alters the signaling pathways regulating the formation of reactive oxygen species, DNA damage, and long-term changes in the epigenome (Amjad et al., 2024; Santiago et al., 2018). It is biological since it shows that with a reversal of hyperglycemia, the retinal cells undergo an alteration in the epigenetics, the irrevocable methylation of the histones (Yang et al., 2024). Moreover, microRNA malfunctioning and the inconsistency of enzymes of pro-inflammatory/pro-angiogenic induction lead to the chronic stimulation of these sub-systems and, therefore, the development of diabetic retinopathy (Das, 2016). The combination of genetic, epigenetic, and metabolic aspects can be explained by multi-omics, and it is possible to realize the pathophysiology of the disease and identify new treatment interventions (Vinhaes et al., 2024) (Vanamala et al., 2025). Indeed, transcriptome and metabolomic investigations are already beginning to illuminate more on molecular circuits, and may even offer beneficial biomarkers to the detection and management of diabetic retinopathy on a case-by-case basis (Vanamala et al., 2025). The multi-omic study is a cluster of information about the fields of genomics, transcriptomics, proteomics, and metabolomics, and this will offer

us the entire picture of the disease at many biological levels, which is one of the opportunities that will help us in understanding the compound molecular basis of diabetic retinopathy (Vanamala et al., 2025). These are the ways of discovering new fingerprints in molecules like interaction of various biological cues in a non-linear fashion. Diagnosis and treatment of disorders are easier (Vanamala et al., 2025). The incurable diabetic retinopathy metabolic memory processes are manifested as hyperglycemia episodes that ultimately alter the microvascular system (Pradhan et al., 2016).

CONCLUSION

Finally, the article included in the review is one of a kind as it has helped to understand that endocrine components play the leading role in the pathophysiology of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM). We show that insulin resistance, thyroid dysfunction, and abnormalities of adipokines are highly correlated with the level of diabetic retinopathy (DR). The test yields useful information to back the fact that bad glycemic regulation and high insulin resistance is extremely relevant to retinal degeneration where high leptin level is particularly correlated to the most serious retinopathy. In addition, thyroid dysfunction particularly hypothyroidism has been found to cause retina damage that is therapeutically useful in the treatment of diabetic retinopathy in patients who have type 2 diabetes mellitus. The two variables that were adopted in this study which involves application of clinical ophthalmic tests and a comprehensive endocrine tests have helped to improve our understanding of the various factors that are intervened in the process of DR. The fact that meaningful endocrine prognosticators associated with the disease have been discovered shows that there is need to diagnose the disease at early stages and use aggressive treatment regimes to prevent the occurrence of endocrine and metabolic anomalies to reverse the effects of the diabetic retinopathy. Further endocrine screening such as thyroid, adipokines and traditional methods of glycemic control should be employed in future to better predict and deal with diabetic retinopathy in patients with type 2 diabetes mellitus. Lastly, our clinic believes there should be a specific treatment of diabetes management. It means that to prevent the development and progression of diabetic retinopathy, it is necessary to pay attention to metabolism and endocrine health. The implications of the findings

are enormous clinically and it may be utilized in more treatment to minimize the vision-destabilizing effects of diabetic eye disease.

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