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K.O. Usenko*
Bogomolets National Medical University, Kyiv, Ukraine
https://orcid.org/0000-0001-9907-6109

D.I. Yevstifeiev
Bogomolets National Medical University, Kyiv, Ukraine
https://orcid.org/0009-0002-4166-6397

G.V. Zaychenko
Bogomolets National Medical University, Kyiv, Ukraine
https://orcid.org/0000-0002-3506-4800

V.M. Hanyuk
Bogomolets National Medical University, Kyiv, Ukraine
https://orcid.org/0000-0001-6368-2916

Retinal neurodegeneration mirrors systemic metabolic phenotypes: Divergent cytomorphometric signatures of sird-like atrophy versus sidd-like edema in experimental diabetes

Background. Diabetic retinopathy (DR) is increasingly recognized as a heterogeneous neurovascular disorder, yet preclinical models often fail to distinguish between the distinct pathophysiological clusters of type 2 diabetes. Recent clinical evidence demonstrates that patients with different metabolic phenotypes, specifically Severe Insulin-Resistant Diabetes (SIRD) versus Severe Insulin-Deficient Diabetes (SIDD), exhibit divergent patterns of retinal complications. However, the specific cytomorphometric signatures that distinguish these phenotypes at the cellular level remain poorly characterized.
Aim: to determine whether specific systemic metabolic phenotypes, SIRD versus SIDD, induce distinguishable cytomorphometric signatures of retinal neurodegeneration in experimental models.
Materials and Methods. Male Wistar rats were stratified into three metabolic models: (1) Chronic High-Fat Diet (HFD, 180 days) mimicking the SIRD phenotype; (2) HFD combined with low-dose streptozotocin (STZ, 30 days post-induction) mimicking the SIDD phenotype; and (3) HFD with supplemental glucose loading. Systemic phenotyping included longitudinal profiling of lipids, liver function, and protein status. Retinal cytoarchitecture was quantified using a computational pathomics pipeline (QuPath/StarDist) with deep learning-based segmentation of >90,000 nuclei, analyzed via Bayesian hierarchical modelling.
Results. The HFD model exhibited a "lipotoxicity-first" trajectory where dyslipidemia and hepatic steatosis preceded hyperglycemia. This SIRD-like phenotype was characterized by progressive retinal atrophy, specifically an 18-46% reduction in Inner Nuclear Layer neuronal density, accompanied by nuclear hyperchromasia indicative of epigenetic condensation. In contrast, the HFD+STZ model, characterized by acute hyperglycemia and significant hypoproteinemia, exhibited a paradoxical 1.54-fold increase in Ganglion Cell Layer density and thickening. This SIDD-like signature reflected cytotoxic edema driven by osmotic and oncotic failure, confirmed morphologically by severe irregular karyomegaly and profound chromatin dissolution (hypochromasia).

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*Corresponding author (*usenko1205@gmail.com*)

Conclusions. Retinal neurodegeneration is not a monolithic process but mirrors specific systemic metabolic trajectories. Chronic insulin resistance (SIRD) drives progressive atrophy via lipotoxicity, while insulin deficiency (SIDD) precipitates acute edema driven by hemodynamic oncotic failure. These findings establish retinal morphometry as a sensitive biomarker for systemic metabolic phenotyping, supporting a precision medicine approach to diabetic retinopathy.
Keywords: diabetic retinopathy, computational pathology, SIRD/SIDD phenotypes, retinal neurodegeneration, cytotoxic edema, lipotoxicity.

BACKGROUND

Diabetic retinopathy (DR) has traditionally been viewed through a glucocentric lens as a microvascular complication driven primarily by chronic hyperglycemia [1-3]. However, a fundamental paradigm shift is underway, supported by clinical evidence indicating that DR is a complex neurovascular disorder wherein neurodegeneration frequently precedes clinically detectable vascular lesions [4-7].

Recent experimental evidence supports this neurodegenerative paradigm. Our previous work demonstrated that multikinase inhibition with sorafenib effectively reduces retinal glial activation in experimental diabetic retinopathy [8], while blockade of cellular protein kinases significantly reduces retinal apoptosis [9] and modulates S100 protein expression in the diabetic retina [10]. These findings collectively suggest that neuronal and glial dysfunction represent early, targetable events in diabetic retinopathy pathogenesis.

While optical coherence tomography (OCT) has enabled the detection of early retinal layer alterations [11], the patterns of structural damage vary significantly among patients, suggesting that hyperglycemia alone cannot account for the full spectrum of retinal pathology. This variability aligns with the emerging understanding of type 2 diabetes (T2D) as a highly heterogeneous disease [12-14]. The landmark stratification by Ahlqvist et al. identified distinct clusters of diabetes with unique pathophysiological profiles, distinguishing Severe Insulin-Resistant Diabetes (SIRD) from Severe Insulin-Deficient Diabetes (SIDD) [15]. Crucially, these clusters exhibit divergent complication risks: the insulin-resistant SIRD phenotype is strongly associated with nephropathy and non-alcoholic fatty liver disease (NAFLD) yet shows a paradoxical lower risk of proliferative retinopathy compared to the insulin-deficient SIDD phenotype, which is prone to rapid neurovascular decline [16, 17].

This clinical heterogeneity exposes a critical "translational misalignment" in preclinical research. Experimental studies often employ animal models interchangeably, failing to distinguish between the slow, lipotoxicity-driven neurodegeneration characteristic of insulin resistance and the acute osmotic stress driven by beta-cell failure [18, 19]. Consequently, the distinct cytomorphometric signatures of these metabolic phenotypes remain poorly characterized. Clinical OCT studies have recently demonstrated that patients with metabolic syndrome or pre-diabetes exhibit retinal thinning (atrophy) prior to the onset of frank diabetes [20, 21], whereas uncontrolled insulin-deficient states may present with subclinical retinal thickening (edema) driven by osmotic and oncotic imbalances [22, 23]. This suggests that morphometric changes in retinal nuclear architecture are not merely local ocular phenomena but may serve as sensitive biomarkers of systemic metabolic toxicity, reflecting hepatic-retinal or renal-retinal crosstalk [24].

In this study, we aimed to bridge the gap between systemic metabolic phenotypes and retinal cytoarchitecture by applying a computational pathomics approach. We hypothesized that different experimental models of T2D, chronic high-fat diet (mimicking SIRD) versus streptozotocin-induced decompensation (mimicking SIDD), induce fundamentally distinct morphological signatures in the retina. By utilizing deep learning-based segmentation and Bayesian hierarchical modelling, we sought to quantify these differences at single-cell resolution, establishing a rigorous framework to differentiate the progressive atrophy of insulin resistance from the acute edematous stress of insulin deficiency.

Aim: to determine whether specific systemic metabolic phenotypes, SIRD versus SIDD, induce distinguishable cytomorphometric signatures of retinal neurodegeneration in experimental models.

MATERIALS AND METHODS

Experimental Design

All experimental procedures were approved by the Commission on Bioethical Expertise and Ethics of Scientific Research of the Bogomolets National Medical University (Kyiv, Ukraine) and were strictly conducted in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes. Male Wistar rats were housed under standard laboratory conditions with a 12-hour light/dark cycle and ad libitum access to water. To rigorously recapitulate the distinct pathophysiology of human T2D clusters and their temporal progression, we utilized a specific diet-induced stratification strategy with precisely defined time-points for intervention and analysis.

Control animals were maintained on standard laboratory chow (PK 120-1, "REZON-1", Ukraine), providing 3295 kcal/kg with 6.3% fat content throughout the study. The SIRD-like phenotype was induced via a chronic High-Fat Diet (HFD) protocol. Animals were

fed a custom high-calorie mixture consisting of crushed standard chow (55.6%), melted pork lard (33.3%), and crystalline fructose (11.1%, ADM® Crystalline Fructose C; Amylum Bulgaria EAD, Bulgaria), providing a total caloric density of 4204 kcal/kg. This specific macronutrient composition was designed to induce systemic insulin resistance, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease (MASLD) [25]. To capture the progressive nature of metabolic injury, animals in this group were maintained on the diet for total durations of 120, 150, and 180 days.

A second experimental cohort was established to recapitulate the "hedonic hyperphagia" phenotype, a maladaptive behavioural hallmark of metabolic syndrome where patients exhibit a specific drive for hyperpalatable, nutrient-dense combinations of lipids and simple carbohydrates [26]. To simulate this supranutritional conditioning, supplemental glucose loading (20 g/kg body weight mixed into the diet) was initiated on day 120 of the chronic HFD protocol. To rigorously dissect the temporal kinetics of this loading, the cohort was stratified into two time points: early-stage exposure (assessed at day 150, after 30 days of loading) and late-stage exposure (assessed at day 180, after 60 days). This longitudinal design allowed for the precise discrimination between retinal neurodegeneration driven by chronic background lipotoxicity versus the structural remodeling exacerbated by cumulative osmotic stress and glucotoxicity.

To model the SIDD-like phenotype, a subset of HFD-conditioned animals received a low-dose injection of streptozotocin (STZ, 25 mg/kg i.p.; Sigma-Aldrich, Co, China) at day 150 of the dietary protocol. Animals were fasted for 16 hours pre-injection and provided 5% glucose solution for 24 hours post-injection. The STZ was dissolved in cold 0.1 M citrate buffer (pH 4.5) to ensure stability. Unlike standard high-dose STZ models of Type 1 diabetes, this "two-hit" protocol superimposed beta-cell failure upon established metabolic syndrome, precipitating acute decompensation characterized by severe hyperglycemia (≥17.5 mmol/L) and ketoacidosis-like symptoms (altered consciousness, polyuria, polydipsia, glucosuria, and ketonuria) [27, 28]. The severity of the combined insult was evidenced by a 53.3% mortality rate within the first week post-STZ injection. The remaining animals (n = 14) in this group were euthanized 30 days post-injection (study day 180).

Biochemical and Metabolic Assessment

To validate the systemic metabolic phenotypes and establish correlations with retinal pathology, a comprehensive biochemical assessment was performed at study termination (day 180). Animals were euthanized under deep thiopental anesthesia, and blood serum was analyzed using a Cobas c311 automated analyzer (Roche Diagnostics, Germany). The analyte panel included markers of glycemic control (glucose), lipid metabolism (total cholesterol, triglycerides, LDL, HDL, VLDL), liver function (ALT, AST, total and direct bilirubin), and renal/protein status (total protein, albumin, urea, creatinine).

Computational Pathomics Pipeline

Following euthanasia, eyes were immediately enucleated, fixed in 4% paraformaldehyde for 24 hours, processed through a standard ascending alcohol series (70-100%), cleared in xylene, and embedded in paraffin. Serial sections were cut at 5 μm thickness using a rotary microtome, deparaffinized, rehydrated, and H&E-stained following standard protocols. Stained slides were digitized at 40× magnification (0.286 μm/pixel resolution). This resolution provided sufficient detail to distinguish individual nuclear boundaries and internal chromatin architecture.

For quantitative analysis, 3-5 non-overlapping regions of interest (ROI) were carefully selected from the central retina of each animal, capturing the full thickness of the neural retina while avoiding the optic nerve head and peripheral sectioning artifacts. Initial morphometric assessment involved manual measurement of retinal layer thickness (μm) for the Ganglion Cell Layer (GCL), Inner Nuclear Layer (INL), and Outer Nuclear Layer (ONL). Measurements were performed perpendicular to the retinal surface at multiple points within each ROI using QuPath (v.0.4.3) tools.

To quantify neuronal population dynamics, we developed an automated pipeline using the StarDist deep learning plugin integrated into QuPath. StarDist utilizes a star-convex object detection neural network specifically designed for dense nuclei segmentation, effectively handling overlapping cells that confound traditional algorithms. Based on the automated counts, we calculated a functional correlate of neuronal loss termed "linear density," defined as the number of nuclei divided by the ROI length (mm). This metric normalizes cell counts to the tangential extent of the tissue section, correcting for potential confounds such as differential tissue shrinkage or oblique sectioning angles. Decreased linear density directly reflects neuronal atrophy and cell loss, providing a more biologically interpretable readout than raw counts.

For each of the >90,000 segmented nuclei, precise geometric parameters were extracted to assess cellular stress. Nuclear Area (μm^2) served as a proxy for cellular stress responses, where increased area (karyomegaly) may reflect hydropic degeneration, osmotic swelling, or chromatin decondensation, while decreased area indicated pyknosis. Nuclear shape was assessed using Circularity, a dimensionless descriptor calculated as $4\pi \times \text{Area}/\text{Perimeter}^2$. Values deviating from 1.0 indicate nuclear envelope deformation, a hallmark of necrotic swelling or mechanical compression. Additionally, maximum and minimum nuclear diameters were analyzed to detect elongation, with significant

deviations between axes indicating mechanical stress or pathological blebbing.

To evaluate epigenetic remodeling and nuclear health, we analyzed chromatin staining patterns using Hematoxylin Mean Intensity as a marker of chromatin compaction. To account for image staining variability, intensity values were standardized using Z-score transformation, calculated as $Z = (x - \mu)/\sigma$, where x is the raw intensity value, μ is the image mean, and σ is the image standard deviation. High Z-scores (hyperchromasia) indicate condensed heterochromatin associated with metabolic memory or apoptosis, while low Z-scores (hypochromasia) suggest euchromatin or edematous dilution. Finally, Hematoxylin Standard Deviation (StDev) was calculated to quantify texture heterogeneity, where high StDev values indicate punctate, marginated chromatin characteristic of early apoptotic stress.

Statistical analysis

The density model structure was:

$$\eta_{ij} = \beta_0 + \beta_{Group} \cdot X_{ij} + f(TRL_{ref}) + u_{ID},$$
$$Y_{ij} \sim NegBin(\mu_{ij}, \phi).$$

This included fixed effects for experimental condition β_{Group}, a B-spline smoothing function for total retinal layer thickness $f(TRL_{ref})$ to adjust for tissue geometry, and a random intercept u_{ID} for each animal to account for within-animal correlation. This hierarchical structure accommodated the multi-level data (nuclei > ROI > layer > animal).

Bayesian inference used Markov Chain Monte Carlo sampling with the No-U-Turn Sampler via NumPyro. Four chains ran for 2500 iterations (1000 warmup), yielding 6000 posterior samples. Weakly informative priors were used. Model convergence was confirmed by $\hat{R} < 1.01$, ESS > 1000, trace plots, and posterior predictive checks.

For continuous nuclear morphometric parameters (area, diameter, intensity), Bayesian hierarchical Gaussian models were used:

$$Y_{ijk} \sim N(\mu_{ijk}, \sigma^2).$$

Circularity was Logit-transformed. Statistical outliers ($Q_1 - 1.5 \times IQR$ or $Q_3 + 1.5 \times IQR$) were removed prior to modelling.

Group differences were quantified using posterior distributions of estimated marginal means and pairwise contrasts. Statistical significance was determined probabilistically: an effect was considered meaningful if the 95% Highest Density Interval (HDI) of the difference excluded zero. Trends were reported if the 95% HDI slightly overlapped zero, but the directional probability was >90%.

Systemic metabolic/biochemical parameters (e.g., body weight, glycemia) were analyzed using conventional frequentist methods: one-way ANOVA followed by Tukey's post-hoc test. Data are presented as mean ±SEM, with $p < 0.05$ considered significant.

RESEARCH RESULTS

Validation of SIRD and SIDD-like Models

Quantitative biochemical profiling confirmed that the experimental stratification successfully induced three distinct metabolic phenotypes, characterized by divergent temporal dynamics of glucotoxicity versus lipotoxicity (Tables 1 and 2). Data presented as Mean ± SEM measured at study termination (180 days). $p < 0.05$ vs Control. Abbreviations: HFD, High-Fat Diet; STZ, Streptozotocin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

Table 1. Systemic Metabolic and Hepatic Function Parameters at Study Termination (180 days)

Parameter	Control (n = 20)	SIRD-like (HFD) (n = 20)	SIDD-like (HFD+STZ) (n = 14)
Systemic Markers			
Body Weight (g)	326.00 ± 18.00	426.00 ± 22.00	304.00 ± 16.00
Glucose (mmol/L)	5.66 ± 0.36	7.59 ± 0.36	21.93 ± 1.21
Protein Metabolism			
Total Protein (g/L)	70.80 ± 0.58	64.17 ± 0.51	62.90 ± 0.38
Albumin (g/L)	40.30 ± 0.31	42.00 ± 0.27	41.60 ± 0.18
Urea (mmol/L)	7.50 ± 0.17	6.03 ± 0.09	5.42 ± 0.11
Creatinine (mmol/L)	58.50 ± 1.43	37.00 ± 1.44	38.20 ± 1.22
Hepatic Function			
ALT (U/L)	64.50 ± 3.45	117.30 ± 6.51	115.70 ± 5.29
AST (U/L)	88.50 ± 5.20	112.00 ± 6.85	107.20 ± 7.01
Total Bilirubin (μmol/L)	2.11 ± 0.15	1.60 ± 0.12	1.85 ± 0.14
Direct Bilirubin (μmol/L)	0.72 ± 0.06	0.73 ± 0.05	0.83 ± 0.03
Indirect Bilirubin (μmol/L)	1.38 ± 0.25	0.87 ± 0.18	1.07 ± 0.16

Table 2. Comparative Lipid and Glycemic Profiles Across Experimental Models

Parameter	Control	HFD (SIRD-like)	HFD+STZ (SIDD-like)	HFD+Glucose
Glycemic Control				
Glucose (mmol/L)	5.66 ± 0.36	7.60 ± 0.57	21.93 ± 1.21	7.73 ± 0.49
Lipid Profile				
Total Cholesterol (mmol/L)	1.30 ± 0.06	2.48 ± 0.12	2.52 ± 0.12	2.58 ± 0.23
Triglycerides (mmol/L)	0.69 ± 0.04	0.78 ± 0.03	0.84 ± 0.04	0.83 ± 0.07
HDL (mmol/L)	0.91 ± 0.05	1.30 ± 0.07	1.60 ± 0.08	1.35 ± 0.12
LDL (mmol/L)	0.25 ± 0.02	0.43 ± 0.02	0.33 ± 0.02	0.44 ± 0.03
VLDL (mmol/L)	0.22 ± 0.02	0.46 ± 0.02	0.37 ± 0.02	0.48 ± 0.04

Data presented as Mean ± SEM. $p < 0.05$ vs Control. Abbreviations: HFD, High-Fat Diet; STZ, Streptozotocin; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; VLDL, Very Low-Density Lipoprotein.

The Chronic HFD model recapitulated the key features of the SIRD cluster. Longitudinal analysis revealed a specific "lipotoxicity-first" trajectory. Significant dyslipidemia was established as early as day 120, with total cholesterol rising to 2.00 ± 0.18 mmol/L (vs. 1.30 ± 0.12 mmol/L in controls, $p < 0.05$), at a time point when fasting glucose remained statistically comparable to controls (6.25 ± 0.59 mmol/L). Overt hyperglycemia in this group developed slowly, reaching statistical significance only by day 180 (7.60 ± 0.57 mmol/L, $p < 0.05$) (Table 2). By study termination, these animals exhibited a profound anabolic phenotype with a 31% increase in body weight (426 ± 22 g vs. 326 ± 18 g, $p < 0.05$) (Table 1). Furthermore, this group displayed biochemical evidence of liver injury consistent with metabolic dysfunction-associated steatotic liver disease (MASLD), including a nearly 2-fold elevation in ALT activity (117.3 ± 6.5 U/L vs 64.5 ± 3.5 U/L) and histological signs of steatohepatitis (Table 1).

The HFD+STZ model reproduced the SIDD (Severe Insulin-Deficient Diabetes) phenotype. The induction of beta-cell failure at day 150 precipitated a rapid catabolic shift. By day 180 (30 days post-STZ), these animals exhibited severe hyperglycemia (21.93 ± 1.21 mmol/L) and a cessation of weight gain (304 ± 16 g) (Table 1). Crucially, this metabolic decompensation was accompanied by significant hypoproteinemia, with total serum protein dropping to 62.9 ± 0.4 g/L compared to 70.8 ± 0.6 g/L in controls ($p < 0.05$) (Table 1). This reduction in circulating protein, occurring in the context of severe osmotic stress (glucose >20 mmol/L) and urea reduction (5.42 mmol/L vs 7.50 mmol/L), establishes a compromised oncotic status favouring retinal fluid extravasation.

The HFD+Glucose model demonstrated the additive effect of dietary glycemic load on lipid metabolism. While glucose loading (initiated at day 120) did not significantly exacerbate fasting hyperglycemia compared to HFD alone (7.73 ± 0.49 mmol/L vs 7.60 ± 0.57 mmol/L) (Table 2), it accelerated the atherogenic lipid profile. Total cholesterol in the glucose-loaded group reached 2.59 ± 0.22 mmol/L by day 150, significantly higher than the non-loaded HFD group at the same time point (2.10 ± 0.15 mmol/L, $p < 0.05$). This confirms that excess dietary carbohydrate in the context of insulin resistance preferentially shunts into lipid synthesis pathways, worsening dyslipidemia.

Differential Patterns of Retinal Neurodegeneration

Quantitative computational analysis of over 90,000 automatically segmented retinal nuclei revealed that the mode and tempo of retinal injury are strictly model-dependent, distinguishing chronic lipotoxicity-driven atrophy from acute hyperglycemia-driven edematous stress. These divergent morphological phenotypes mirror the systemic metabolic stratification established through biochemical profiling.

The SIRD-Like Phenotype: Progressive Inner Retinal Degeneration and Chronic Atrophy

The chronic high-fat diet models, maintained for 120, 150, and 180 days in the absence of severe hyperglycemia, recapitulated a gradual neurodegenerative phenotype. The INL emerged as the primary anatomical substrate of metabolic injury, demonstrating time-dependent neuronal loss. Comparing HFD duration effects using linear neuronal density as the functional outcome metric, the transition from day 120 to day 150 produced a significant 18.3% reduction in INL neuronal population (estimated fold-difference: 0.817, 95% CrI [0.738, 0.904], $p < 0.001$). By day 180, the cumulative atrophic remodeling stabilized at approximately 15.8% below baseline (fold-difference: 0.842, 95% CrI [0.762, 0.931], $p = 0.001$). In contrast, both the GCL and ONL demonstrated relative structural preservation during this timeframe, with no statistically significant reductions in linear density ($p > 0.05$ across all HFD-only comparisons).

Nuclear morphometric analysis revealed that the chronic HFD models induced a distinctive cellular phenotype. GCL nuclei in the 180-day HFD group exhibited progressive enlargement, with mean nuclear cross-sectional area increasing from the control baseline of 43.4 μm^2 to 52.9 μm^2, representing a statistically significant 21.9% expansion ($p < 0.001$). Critically, this

karyomegaly occurred while nuclear circularity remained largely preserved (mean circularity: 0.874 vs control 0.843), and the aspect ratio of maximum to minimum diameter stabilized near 1.72.

The most striking nuclear signature of chronic HFD exposure was pan-retinal hyperchromasia, manifest as significantly increased standardized hematoxylin intensity across all three retinal layers. Comparing HFD at 180 days to earlier timepoints revealed progressive chromatin condensation, with Z-scores for hematoxylin mean intensity rising significantly in the GCL (increase of 0.185, $p = 0.008$), INL (increase of 0.294, $p < 0.001$), and ONL (increase of 0.187, $p = 0.008$). This hyperchromatic nuclear phenotype was further characterized by increased chromatin texture heterogeneity, particularly pronounced in photoreceptors, where hematoxylin standard deviation increased by 18.5% ($p < 0.001$).

Thus, neurodegeneration in the SIRD-like phenotype manifested as: (1) reduced INL neuronal linear density with accompanying karyomegaly, and (2) hyperchromasia of nuclei across all retinal layers.

The SIDD-Like Phenotype:
Cytotoxic Swelling and Hydropic Degeneration

The superimposition of streptozotocin-induced be ta-cell failure upon established metabolic syndrome precipitated a fundamentally distinct retinal response compared to the atrophic changes seen in the HFD-only group. In the HFD+STZ model, the retina exhibited signs of severe fluid dysregulation consistent with acute metabolic decompensation. The GCL, rather than exhibiting thinning, demonstrated paradoxical thickening and a significant 1.54-fold increase in apparent linear density compared to HFD controls (95% CrI [1.09, 2.17], $p = 0.017$). This "pseudo-expansion" occurred exclusively in the context of severe hyperglycemia (21.93 mmol/L) and hypoproteinemia (62.9 g/L), consistent with cytotoxic edema, the swelling of retinal ganglion cell (RGC) somata and Müller cell processes which expands tissue volume and artificially inflates linear density counts.

To verify this interpretation, we examined nuclear size parameters. Indeed, individual nuclear areas were significantly enlarged, suggesting cellular swelling rather than true neuronal proliferation or preservation. The INL similarly exhibited an elevated apparent density (fold-difference: 1.46, $p < 0.0001$), further confirming the generalized nature of this edematous response.

Nuclear morphometry revealed a phenotype of severe structural alteration distinct from the lipotoxicity-driven changes observed in the HFD model. GCL nuclei in the HFD+STZ group exhibited profound irregular karyomegaly, with mean nuclear areas increasing to 57.7 μm^2 (+33% vs control, $p < 0.001$). Unlike the isotropic expansion observed in HFD models, this swelling was accompanied by significant shape distortion (heterotropic expansion), evidenced by a decline in mean circularity to 0.832 ($p = 0.002$) and a reduction in maximum nuclear diameter.

Crucially, the chromatin signature flipped from the hyperchromasia of chronic lipid stress to profound hypochromasia, with standardized hematoxylin intensity Z-scores dropping into negative territory across all layers (e.g., GCL Z-score decrease of 0.195, $p < 0.001$). This loss of staining density implies nuclear dilution due to osmotic water influx and chromatin decondensation, confirming that the tissue "thickening" represents pathological hydropic degeneration rather than neuronal preservation.

Thus, hydropic degeneration in the SIDD-like phenotype manifested as: (1) apparent thickening of retinal layers with artificially elevated linear density, (2) heterotropic karyomegaly with loss of nuclear circularity, and (3) profound hypochromasia of nuclei across all layers.

Glucose Loading as a Positive Control for Maximal Osmotic Toxicity

The supplemental glucose-loaded groups exhibited the most extreme morphological perturbations. The INL demonstrated the most profound reduction in neuronal linear density among all groups, with HFD 180 days + Glucose (last 60 days) showing a 31.7% decline relative to HFD 120 days alone (fold-difference: 0.683, $p = 0.001$). Nuclear area measurements revealed maximal karyomegaly, with GCL nuclei expanding to a mean of 65.7 μm^2 (+51.4% vs control baseline; $p < 0.001$). Nuclear shape analysis demonstrated corresponding maximal circularity loss (0.812 vs 0.843; $p < 0.001$).

The chromatin condensation state exhibited the most severe hypochromasia, with standardized hematoxylin Z-scores dropping to extreme negative values across all layers (GCL: -0.47; INL: -0.47; ONL: -0.76; $p < 0.001$). This was coupled with maximal reduction in texture heterogeneity (hematoxylin standard deviation decreased by 23.6% in photoreceptors, $p < 0.001$).

Thus, maximal osmotic toxicity in the glucose-loaded model manifested as: (1) severe INL neuronal loss, (2) extreme karyomegaly with marked loss of nuclear circularity, and (3) profound hypochromasia representing maximal chromatin dilution.

Photoreceptor Resilience Despite Severe Chromatin Stress

The ONL, containing photoreceptor cell bodies, maintained statistically stable linear density across all groups ($p > 0.05$ for all pairwise comparisons), with no experimental condition inducing measurable photoreceptor loss within the 180-day study timeframe. This preservation occurred despite photoreceptors displaying the most extreme chromatin condensation changes, particularly in glucose-loaded models where ONL Z-scores reached -0.76, representing the lowest chromatin density values recorded in the entire dataset.

DISCUSSION

This study provides the first experimental evidence that retinal neurodegeneration in type 2 diabetes is not a monolithic process driven solely by hyperglycemia, but rather a heterogeneous pathology reflecting specific systemic metabolic phenotypes. By stratifying experimental models into chronic lipotoxicity (SIRD-like) and acute decompensation (SIDD-like) clusters, we identified divergent cytomorphometric signatures, progressive atrophy versus acute edema, that mirror the underlying systemic metabolic derangements. Our findings challenge the traditional "glucocentric" paradigm of diabetic retinopathy, demonstrating that significant retinal neuronal loss occurs during the pre-diabetic phase of insulin resistance and dyslipidemia, long before the onset of overt hyperglycemia. This "Systemic-Retinal Coupling" framework suggests that the retina may function as a sensitive biological sensor of systemic metabolic toxicity, where the mode of cellular injury is dictated by the specific balance between lipid burden, oncotic pressure, and osmotic stress.

The progressive inner retinal atrophy observed in the HFD model supports the emerging concept that neurodegeneration precedes vasculopathy in insulin-resistant states [29]. Our longitudinal data revealed that INL neuronal loss temporally corresponded with early dyslipidemia and hepatic steatosis (day 120) rather than hyperglycemia, which only manifested significantly at day 180. This supports a "lipotoxicity-first" mechanism, where the inflamed, steatotic liver likely acts as a remote generator of neurotoxic signals [30], such as fetuin-A and oxidative stress mediators, that compromise the blood-retina barrier and mitochondrial function [31].

The selective vulnerability of the INL observed in this model likely reflects the exceptionally high metabolic demands of bipolar and amacrine interneurons for synaptic transmission. While retinal neurons do not directly respond to insulin for glucose uptake (glucose enters via GLUT1 transporters independently of insulin), insulin acts as a potent neurotrophic factor and anabolic signal in the retina, promoting cell survival and synaptic maintenance through the PI3K/Akt pathway [32]. We propose that this atrophic phenotype is driven by the disruption of these insulin-mediated survival pathways; in insulin-resistant states, downstream disinhibition of GSK3β promotes tau hyperphosphorylation and cytoskeletal instability, leading to synaptic retraction and apoptosis [33].

Crucially, the pan-retinal hyperchromasia identified in these nuclei suggests a coordinated epigenetic response, specifically, the formation of facultative heterochromatin via histone deacetylation. This "chromatin locking" may represent the morphological basis of "metabolic memory," establishing a transcriptionally silent state that persists even after metabolic parameters fluctuate, and mechanistically explains why retinal thinning in pre-diabetic or metabolic syndrome patients is irreversible [34].

In stark contrast to the atrophic remodeling of the SIRD phenotype, the transition to insulin deficiency in the HFD+STZ model precipitated a fundamental reversal of the retinal morphometric signature from atrophy to acute edema. The paradoxical thickening of the GCL and the "pseudo-increase" in linear neuronal density observed in this group constitute pathognomonic evidence of cytotoxic edema, driven by concurrent failure of osmotic and oncotic regulation.

We propose that this phenotype is the functional result of a "Renal-Retinal Oncotic Axis" failure. Our biochemical data confirmed significant hypoproteinemia in these animals, likely resulting from catabolic protein wasting and hepatic dysfunction. This reduction in plasma oncotic pressure removes the critical "brake" on fluid filtration, favoring extravasation into the retinal interstitium even before frank blood-retina barrier breakdown occurs. Concurrently, the severe hyperglycemia (≥21 mmol/L) overwhelms the retinal glycolytic capacity, shunting glucose into the polyol pathway. The resulting intracellular accumulation of sorbitol creates a potent osmotic gradient that drives water into Müller glial cells, causing them to swell and mechanically expand the retinal layers.

This hydropic degeneration was morphologically captured at the single-cell level as severe, irregular karyomegaly accompanied by profound hypochromasia. Unlike the condensed chromatin of the atrophic phenotype, this "washed-out" nuclear signature reflects the physical dilution of DNA by osmotic water influx and likely the early stages of parthanatos-associated chromatinolysis. Clinically, this finding offers a cellular explanation for the "subclinical edema" and retinal thickening frequently observed in diabetic patients with poor glycemic control (elevated HbA1c), warning that such thickening on OCT may mask underlying neurodegeneration under a facade of preserved tissue volume.

Clinical Translation and Precision Medicine Implications

Our experimental findings provide a mechanistic validation for the divergent retinal complication profiles observed in human diabetes clusters. The association of the HFD model with progressive atrophy mirrors clinical OCT studies in metabolic syndrome and pre-diabetes, where thinning of the ganglion cell-inner plexiform layer (GC-IPL) and retinal nerve fiber layer (RNFL) is frequently detected prior to the onset of frank vasculopathy [20, 21]. We propose that the "INL thinning" observed in our SIRD-like rats is the histological equivalent of "Disorganization of Retinal Inner Layers" (DRIL), a clinical biomarker predictive of neurodegeneration.

Conversely, the high-risk profile of the SIDD cluster, characterized by the highest rates of proliferative

retinopathy and macular oedema [16], is recapitulated by the fulminant edematous response in our HFD+STZ model. The "GCL thickening" we identified aligns with clinical reports of subclinical retinal thickening in patients with poor glycemic control (HbA1c > 8%) and renal compromise, suggesting that such thickening on OCT should be re-evaluated not as tissue preservation, but as a warning sign of impending neurovascular decompensation.

By establishing these specific morphometric signatures, our study offers a rationale for precision medicine in ophthalmology: patients with the SIRD phenotype may benefit from early neuroprotective screening to detect "silent" atrophy, while those with the SIDD phenotype require aggressive management of oncotic and osmotic pressure to prevent edematous collapse.

Limitations and Future Directions

While this study establishes a rigorous framework for phenotyping diabetic retinal neurodegeneration, several limitations warrant consideration. First, our cross-sectional design provided high-resolution histological snapshots at specific time-points but lacked the temporal continuity of longitudinal in vivo imaging. Future studies should integrate longitudinal Optical Coherence Tomography (OCT) and Angiography (OCTA) in the same animals to map the precise onset of retinal thinning relative to the development of hepatic lipidosis and dyslipidemia.

Second, although the observed cytomorphometric signatures (karyomegaly, hyperchromasia) are morphologically consistent with specific cell death pathways such as apoptosis and parthanatos, we did not perform immunohistochemical or proteomic validation of specific markers (e.g., cleaved caspase-3, PARP-1, or phosphorylated tau). Investigating these molecular targets using spatial transcriptomics will be essential to definitively link the observed nuclear phenotypes to specific signaling cascades.

Third, our study utilized exclusively male rats to minimize hormonal variability; given the known sexual dimorphism in metabolic syndrome and diabetic complications, future work must explicitly compare male and female responses to determine if these vulnerability patterns are conserved.

Despite these limitations, our findings open new avenues for precision medicine in diabetic retinopathy. The identification of phenotype-specific retinal signatures suggests that "one-size-fits-all" neuroprotective strategies may be insufficient. Future research should evaluate whether pharmacotherapies targeting insulin resistance (e.g., PPAR-gamma agonists, GLP-1 receptor agonists) are more effective in preventing the "atrophic" SIRD-like retinopathy, while agents targeting oncotic pressure and vascular permeability (e.g., SGLT2 inhibitors) are superior for the "edematous" SIDD-like phenotype. Ultimately, translating these computational pathomic markers into clinical AI algorithms for OCT analysis could enable the non-invasive identification of systemic metabolic clusters through the eye, facilitating earlier and more targeted interventions.

CONCLUSIONS

This study establishes computational pathomics as a powerful framework for deciphering the heterogeneity of diabetic retinal neurodegeneration, demonstrating that retinal morphology is strictly coupled to specific systemic metabolic phenotypes. By applying deep learning-based segmentation to distinct rat models of type 2 diabetes, we identified two divergent pathological trajectories that mirror human clinical clusters.

First, the chronic HFD model (SIRD-like phenotype) induces progressive inner retinal atrophy and epigenetic chromatin condensation, driven by a "lipotoxicity-first" mechanism independent of severe hyperglycemia. This confirms that neurodegeneration precedes vasculopathy in insulin-resistant states and highlights the liver-retina axis as a critical therapeutic target.

Second, the HFD+STZ model (SIDD-like phenotype) precipitates acute cytotoxic edema and hydropic degeneration, driven by concurrent failure of osmotic (hyperglycemia) and oncotic (hypoproteinemia) regulation. This explains the paradoxical retinal thickening observed in insulin-deficient states as a hemodynamic failure rather than tissue preservation.

Our findings provide a mechanistic rationale for overcoming the "translational misalignment" in preclinical research by advocating for model selection based on specific clinical phenotypes rather than generic hyperglycemia. Furthermore, this work positions retinal morphometry not merely as a localized ocular assessment, but as a non-invasive biomarker of systemic metabolic toxicity. Clinically, this supports a shift toward precision medicine, where the detection of retinal atrophy signals a need for insulin-sensitizing and lipid-lowering interventions, while retinal edema necessitates aggressive management of glycemic variability and oncotic pressure to prevent irreversible vision loss.

CONFLICTS OF INTEREST

The authors declare there is no conflicts of interest.

DATA AVAILABILITY

Upon reasonable request.

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К. О. Усенко

Національний медичний університет імені О. О. Богомольця, Київ, Україна
https://orcid.org/0000-0001-9907-6109

Д. І. Євстифеєв

Національний медичний університет імені О. О. Богомольця, Київ, Україна
https://orcid.org/0009-0002-4166-6397

Г. В. Зайченко

Національний медичний університет імені О. О. Богомольця, Київ, Україна
https://orcid.org/0000-0002-3506-4800

В. М. Ганюк

Національний медичний університет імені О. О. Богомольця, Київ, Україна
https://orcid.org/0000-0001-6368-2916

Нейродегенерація сітківки при системних метаболічних фенотипах: різні цитоморфометрічні ознаки sird-подібної атрофії проти sidd-подібного набряку при експериментальному діабеті

Актуальність. Діабетична ретинопатія (ДР) все частіше визнається гетерогенним нейроваскулярним розладом, проте доклінічні моделі часто не розрізняють окремі патофізіологічні кластери діабету 2 типу. Нещодавні клінічні дані показують, що пацієнти з різними метаболічними фенотипами, зокрема з тяжким інсулінорезистентним діабетом (SIRD) та тяжким інсулінодефіцитним діабетом (SIDD), демонструють різні морфологічні патерни. Однак специфічні цитоморфометричні характеристики, які відрізняють ці фенотипи на клітинному рівні, залишаються погано вивченими.

Ціль: визначити, чи індукують специфічні системні метаболічні фенотипи, SIRD та SIDD, відмінні цитоморфометричні характеристики нейродегенерації сітківки в експериментальних моделях.

Матеріали та методи. Самців щурів Вістар було розділено на три метаболічні моделі: (1) Хронічна дієта з високим вмістом жирів (HFD, 180 днів), що імітує фенотип SIRD; (2) HFD у поєднанні з низькою дозою стрептозотоцину (HFD+STZ, через 30 днів після індукції), що імітує фенотип SIDD; та (3) HFD з додатковим навантаженням глюкозою. Системне фенотипування включало поздовжнє профілювання ліпідів, білків та функції печінки. Цитоархітектуру сітківки кількісно визначали за допомогою обчислювального патомічного конвеєра (QuPath/StarDist) із сегментацією >90 тис. ядер на основі глибокого навчання, проаналізованою за допомогою баєсівського ієрархічного моделювання.

Результати. Модель HFD демонструвала траєкторію «спочатку ліпотоксичність», де дисліпідемія та стеатоз печінки передували гіперглікемії. Цей фенотип, подібний до SIRD, характеризувався прогресуючою атрофією сітківки, зокрема зниженням щільності нейронів внутрішнього ядерного шару на 18-46 %, що супроводжувалося ядерною гіперхромазією, що свідчить про епігенетичну конденсацію. На противагу цьому, модель HFD+STZ, що характеризувалася гострою гіперглікемією та значною гіпопротеїнемією, демонструвала парадоксальне збільшення щільності та потовщення шару гангліозних клітин у 1,54 раза. Ця ознака, подібна до SIDD, відображає цитотоксичний набряк, спричинений осмотичною та онкотичною недостатністю, що морфологічно підтверджено тяжкою нерегулярною каріомегалією та глибоким розчиненням хроматину (гіпохромазією).

Висновки. Нейродегенерація сітківки не є монолітним процесом, а відображає специфічні системні метаболічні траєкторії. Хронічна інсулінорезистентність (SIRD) призводить до прогресуючої атрофії через ліпотоксичність, тоді як інсулінодефіцит (SIDD) провокує гострий набряк, спричинений гемодинамічною онкотичною недостатністю. Ці дані визначають морфометрію сітківки як чутливий біомаркер для системного метаболічного фенотипування, підтримуючи підхід прецизійної медицини до діабетичної ретинопатії.

Ключові слова: діабетична ретинопатія, комп'ютерна патологія, фенотипи SIRD/SIDD, нейродегенерація сітківки, цитотоксичний набряк, ліпотоксичність.