ORIGINAL ARTICLE

CONTENTS

Retinal glial activation in diabetic retinopathy: therapeutic impact of multikinase inhibition with sorafenib

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ABSTRACT

Aim: This study aimed to evaluate the effects of sorafenib on macroglial and microglial activation in the retina under diabetic conditions, using a streptozotocin-induced model of diabetic retinopathy. Special emphasis was placed on examining early and chronic phases of gliosis, assessing molecular markers of glial activation, and determining whether sorafenib can attenuate glial remodelling and neuroinflammation in the diabetic retina.

Materials and Methods: Sixty male Wistar rats were divided into three groups: untreated diabetic controls, insulin-treated, and insulin + sorafenib-treated. Diabetic retinopathy was induced via intraperitoneal injection of streptozotocin (50 mg/kg). Retinal samples were collected at 7, 14, 28 days, and 3 months post-induction. Histological analysis (H&E staining), immunohistochemistry (GFAP, S100), and Western blotting (GFAP, Iba-1) were used to assess glial activation. Statistical analysis was conducted using ANOVA with significance set at $p < 0.05$.

Results: Untreated diabetic rats exhibited severe retinal oedema, neurodegeneration, and increased GFAP, S100, and Iba-1 expression, indicating pronounced macroglial and microglial activation. Sorafenib co-treatment significantly reduced the expression of glial markers and preserved retinal structure, with near-complete suppression of gliosis and no evidence of glial-mesenchymal transition. These effects were more pronounced than those of insulin monotherapy.

Conclusions: Sorafenib attenuates retinal glial activation and neuroinflammatory changes in experimental diabetic retinopathy, suggesting its potential as a neuroprotective and antifibrotic agent. Targeted kinase inhibition may represent a promising adjunct strategy in early-stage disease management.

KEY WORDS: Diabetic retinopathy, sorafenib, gliosis, macroglia, microglia, neuroinflammation, kinase inhibitors, retina

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INTRODUCTION

According to the International Diabetes Federation, diabetic retinopathy (DR) is the fifth most common cause of moderate to severe vision impairments and blindness globally and the only one whose incidence has increased between 1990 and 2020 [1]. It is estimated that 1 in 5 people with diabetes have some degree of DR, which accounts for nearly 103 million adults, with 47 million of them having vision-threatening retinopathy and requiring prompt treatment [2]. Given the rising prevalence of diabetes, these numbers are expected to increase significantly by 2045, positioning DR as a critical medical and social challenge [3].

DR is a multifactorial disease arising from chronic hyperglycaemia, oxidative stress and inflammation, which culminates in neurovascular dysfunction [4]. Traditionally, its pathogenesis has been primarily attributed to microvascular abnormalities, such as pericyte loss, capillary basement membrane thickening, increased vascular permeability, and neovascularisation. However, recent studies highlight the critical role of neuronal and glial cells in DR progression, redefining the condition as a complex neurovascular pathology rather than a purely vascular microangiopathy [5].

Among the earliest changes observed in the diabetic retina is the reactive transformation of astrocytes and Müller glial cells — a process known as gliosis, which includes the upregulation of glial fibrillary acidic protein (GFAP) expression, release of inflammatory mediators, and structural alterations [6]. Reactive Müller cells can profoundly affect the retinal microenvironment, impairing neurotransmitter recycling, contributing to blood-retinal barrier breakdown, and promoting cytokine release [7]. Concurrently, activation of resident microglia adds a layer of proinflammatory stress, exacerbating neuronal injury and capillary degeneration [8, 9].

A growing body of research has linked chronic gliosis in DR to a transition toward a more mesenchymal,

fibrotic phenotype — the so-called glial-mesenchymal transition (GMT) [10]. This pathological process, driven by sustained stress and growth factor signalling (e.g., via VEGFR, PDGFR, and TGF-β), may underlie irreversible remodelling and neurovascular decoupling. Thus, pharmacological strategies that disrupt key signalling pathways in glial activation could represent promising therapeutic approaches beyond traditional glycemic control and anti-VEGF therapy.

Sorafenib, a well-characterised multikinase inhibitor approved for oncologic indications, inhibits a spectrum of receptor and intracellular kinases, including RAF, VEGFR-1/2, PDGFR, and c-KIT — many of which are implicated in retinal inflammation, glial activation, and fibrotic signalling [11]. Although extensively studied in cancer models, its potential for modulating neuroinflammation and gliosis in diabetic retinal disease has not been adequately explored.

AIM

This study aimed to evaluate the effects of sorafenib on macroglial and microglial activation in the retina under diabetic conditions, using a streptozotocin-induced model of diabetic retinopathy. Special emphasis was placed on examining early and chronic phases of gliosis, assessing molecular markers of glial activation, and determining whether sorafenib can attenuate glial remodelling and neuroinflammation in the diabetic retina.

MATERIALS AND METHODS

The study was conducted in compliance with the norms and principles of EU Directive 2010/63 on the protection of animals, the Helsinki Declaration (2008), and the requirements of the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 1759-VI dated 15.12.2009). The animals were housed under standard conditions in the vivarium of Bogomolets National Medical University (Kyiv, Ukraine) and were provided with a standard diet.

A total of 60 three-month-old male Wistar rats weighing 140–160 g were included in the study. On the first day of the experiment, rats were injected with either streptozotocin (STZ, 50 mg/kg; Sigma-Aldrich, Co., China) or 0.1 M citrate buffer of an equal volume by a single intraperitoneal injection. Blood glucose levels were measured every 3 days after the first STZ or citrate buffer injection in blood samples collected from the tail vein after fasting. Diabetes was defined as a blood glucose level of > 15 mM/l, which was measured using a glucometer and glucose test

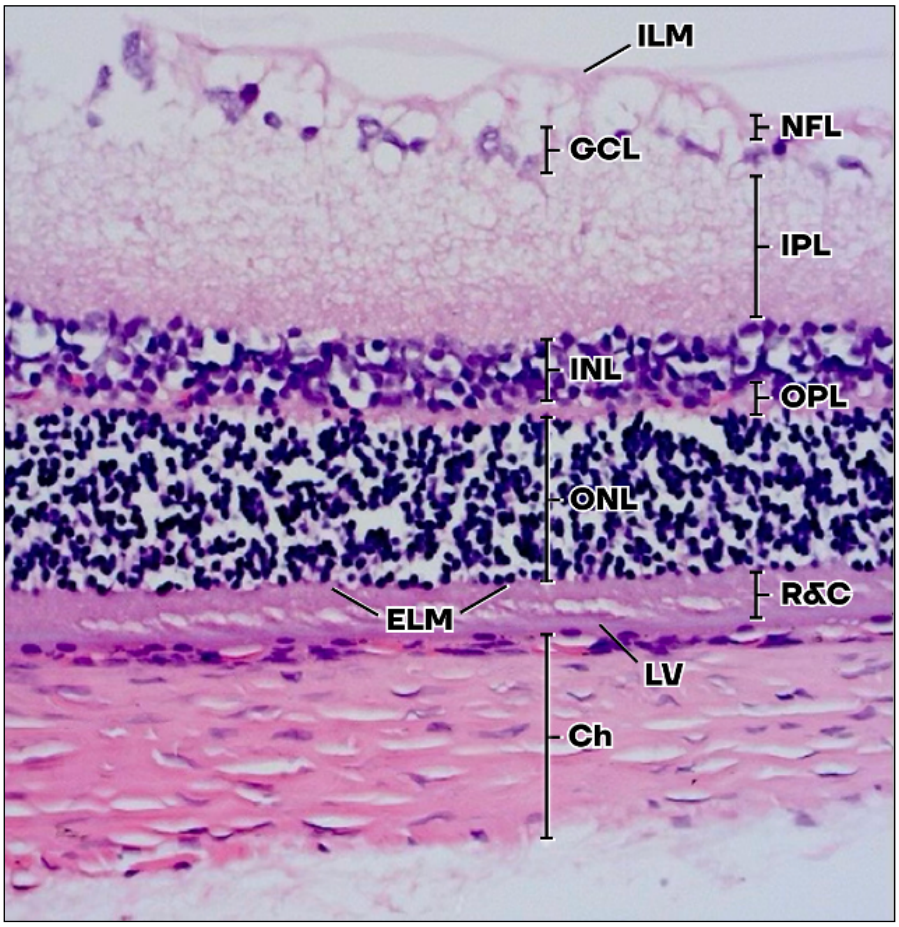

Fig. 1. Retinal tissue from control rats on day 7 post-diabetes induction. Photomicrograph showing oedema across all retinal layers and ischemic changes in the inner plexiform layer. H&E staining; magnification ×200
ILM – internal limiting membrane; NFL – nerve fibre layer; GCL – ganglion cell layer; IPL – inner plexiform layer; INL – inner nuclear layer; OPL – outer plexiform layer; ONL – outer nuclear layer; ELM – external limiting membrane; R&C – rods and cones layer; LV – lamina vitrea; Ch – choroid

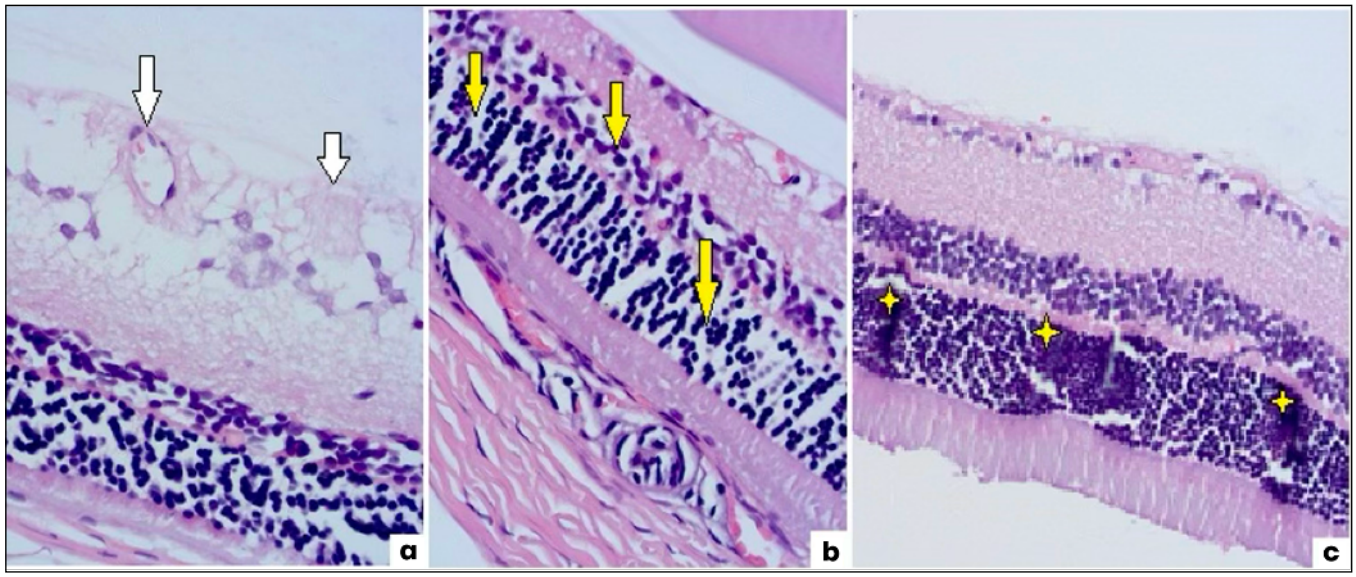

Fig. 2. Retinal morphology in control rats at different time points post-diabetes induction. (a) 14 days: formation of microaneurysms (white arrows), widespread oedema, blood stasis and venule ectasia. (b) 3 months: neuronal rarefaction (yellow arrows), degeneration, loosening of nerve fibres. (c) 3 months: dense clusters of proliferating cells (yellow asterisks) in the outer nuclear layer. H&E staining; magnification ×200

strips (ACCU-Chek Instant, Roche, Mannheim, Germany). Throughout the experiment, the animals exhibited pronounced polydipsia, polyuria, ketonuria, glucosuria, and significant weight loss, confirming the adequacy of the induced type 1 diabetes model with ketosis. The animals were observed for three months. Five additional intact animals were used to establish baseline data.

Seven days post-injection, rats with confirmed hyperglycaemia were randomly divided into three groups, with a sample size of n = 20 per group. The first group received no treatment, the second group was treated with intraperitoneal injections of short-acting insulin (30 IU, Actrapid HM Penfill, Novo Nordisk A/S, Bagsvaerd, Denmark), while the third group received combined treatment with short-acting insulin (30 IU) and sorafenib (50 mg/kg, per os, Cipla, India).

Animals were euthanised at 7, 14, and 28 days, as well as at three months (five animals per time point), using a lethal dose of thiopental (75 mg/kg), followed by decapitation. After euthanasia, bilateral enucleation was performed. For morphological analysis, the eyes were fixed in a 10% neutral formalin solution and embedded in paraffin. Serial histological sections (2–3 μm thick) were prepared from paraffin blocks using a rotary microtome (HM 325, Thermo Shandon, UK). The sections were stained with hematoxylin and eosin (H&E, BIOGNOST Ltd, Zagreb, Croatia) for light microscopy. Microscopic examination and photodocumentation were carried out using ZEISS light microscopes (Germany) equipped with the Axio Imager.A2 image analysis system.

Immunohistochemical analysis was performed using monoclonal mouse anti-GFAP and anti-S100 antibodies (ThermoFisher Scientific, USA), with additional hematoxylin staining. Staining intensity was assessed based on the visual-analogue scale proposed by D. Dabbs (2014), with 0 points corresponding to no staining, 1 point - weak staining, 2 points - moderate staining and 3 points - strong staining.

GFAP and Iba-1 levels in retinal tissue lysates were determined using Western blot analysis. Tissue samples were snap-frozen in liquid nitrogen, homogenised in 50 mM Tris-HCl buffer (pH 7.4) supplemented with protease and phosphatase inhibitors (Pierce Protease and Phosphatase Inhibitor, ThermoScientific, USA, #A32961). Protein separation was performed by SDS-PAGE in 8% polyacrylamide gels using a vertical electrophoresis system (BioRad, USA). Proteins were then transferred onto a nitrocellulose membrane via electroblotting. The membranes were incubated with monoclonal anti-GFAP or anti-Iba1 antibodies (Santa Cruz Biotechnology, USA). β-actin (β-actin (loading control), no. MA5-15739, mouse, 1:3,000, Invitrogen, USA) was used as a loading control. After primary antibody incubation, membranes were washed and treated with secondary anti-species antibodies conjugated with horseradish peroxidase (goat anti-rabbit or anti-mouse IgG, Invitrogen, USA, cat. nos. G-21234 and 31430, respectively, diluted 1:8,000). Densitometric analysis was performed using TotalLab software (TL120, Nonlinear Inc., USA). Western blot results were expressed as relative optical density values of the respective polypeptide bands, normalised to β-actin levels in each sample.

For statistical analysis, Statistica 10 software (StatSoft, Inc., USA) was used. Descriptive statistics included the calculation of means and standard errors. Group means

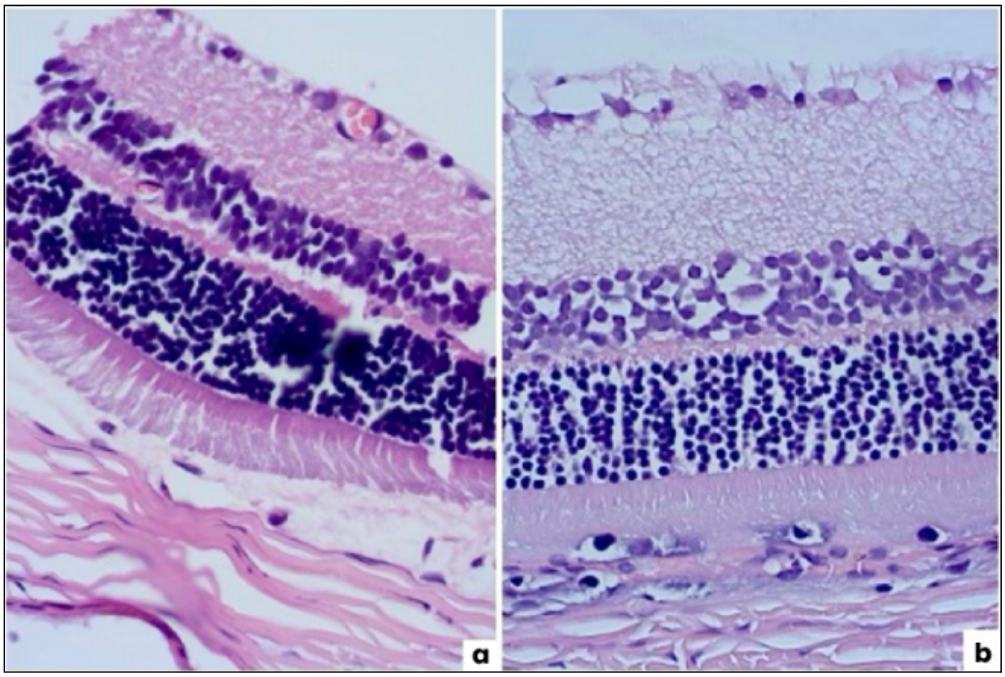

Fig. 3. Retinal structure in experimental groups 3 months post-diabetes induction. (a) Insulin-treated group: rarefaction of nuclear layers and neuronal degeneration. (b) Combined treatment (insulin + sorafenib): structural preservation and absence of proliferative foci. H&E staining; magnification ×400

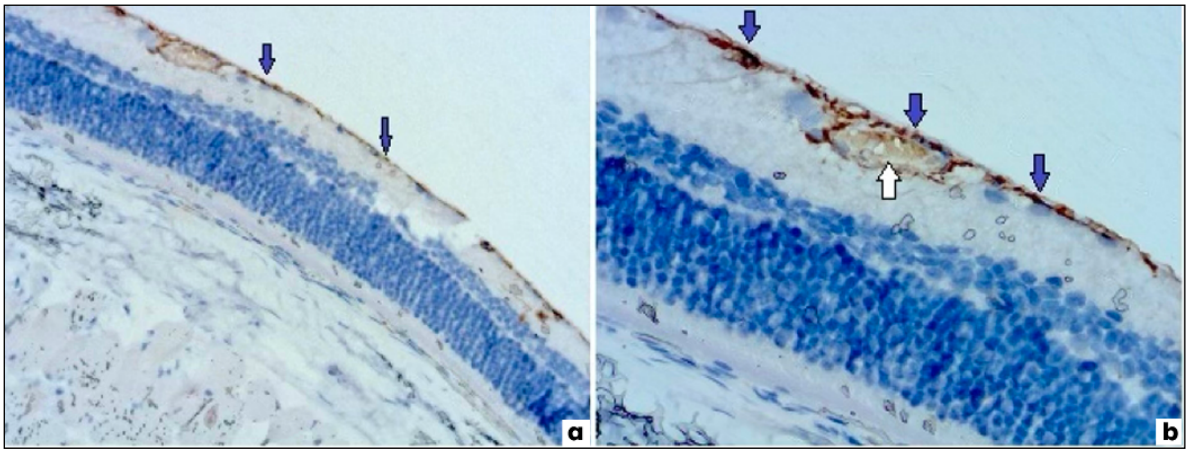

Fig. 4. Immunohistochemical detection of GFAP in intact rat retina. (a) GFAP-positive astrocyte fibres (blue arrows) localized in the nerve fibre layer. (b) Higher magnification showing perivascular glial fibres (white arrow). GFAP immunostaining with hematoxylin counterstain; magnifications ×200 and ×400

were compared using analysis of variance, with statistical significance set at $p < 0.05$.

RESULTS

DR MORPHOGENESIS

Histological analysis of retinal tissue samples from the control group of rats in our study confirmed the presence of neurovascular dysfunction. A reduction in cell density within the nuclear layers, tissue oedema across all retinal layers (most pronounced in the inner plexiform layer), ischemic areas with cytoplasmic vacuolisation of neural cells, as well as dilation of choroidal and inner retinal blood vessels were observed 7 days post-diabetes induction (Fig. 1).

Numerous vascular anomalies were identified in the nerve fibre and ganglion cell layers, including microaneurysms (Fig. 1). The density of ganglion cells decreased, showing signs of degeneration, cellular oedema, and nuclear pyknosis. These pathological changes progressed from day 7 to three months of observation (Fig. 2). At the final stage, cellular proliferative foci in the outer nuclear layer of the retina were detected, appearing as dense clusters of basophilic cells with a tendency for radial growth beyond the layer's boundaries (Fig. 2c).

Our experimental results demonstrated that insulin treatment (Fig. 3a) and combined therapy with insulin and sorafenib (Fig. 3b) were associated with less pronounced early manifestations of DR.

The insulin-treated group's nuclear layer cell density remained stable, with minimal oedema and ischemic

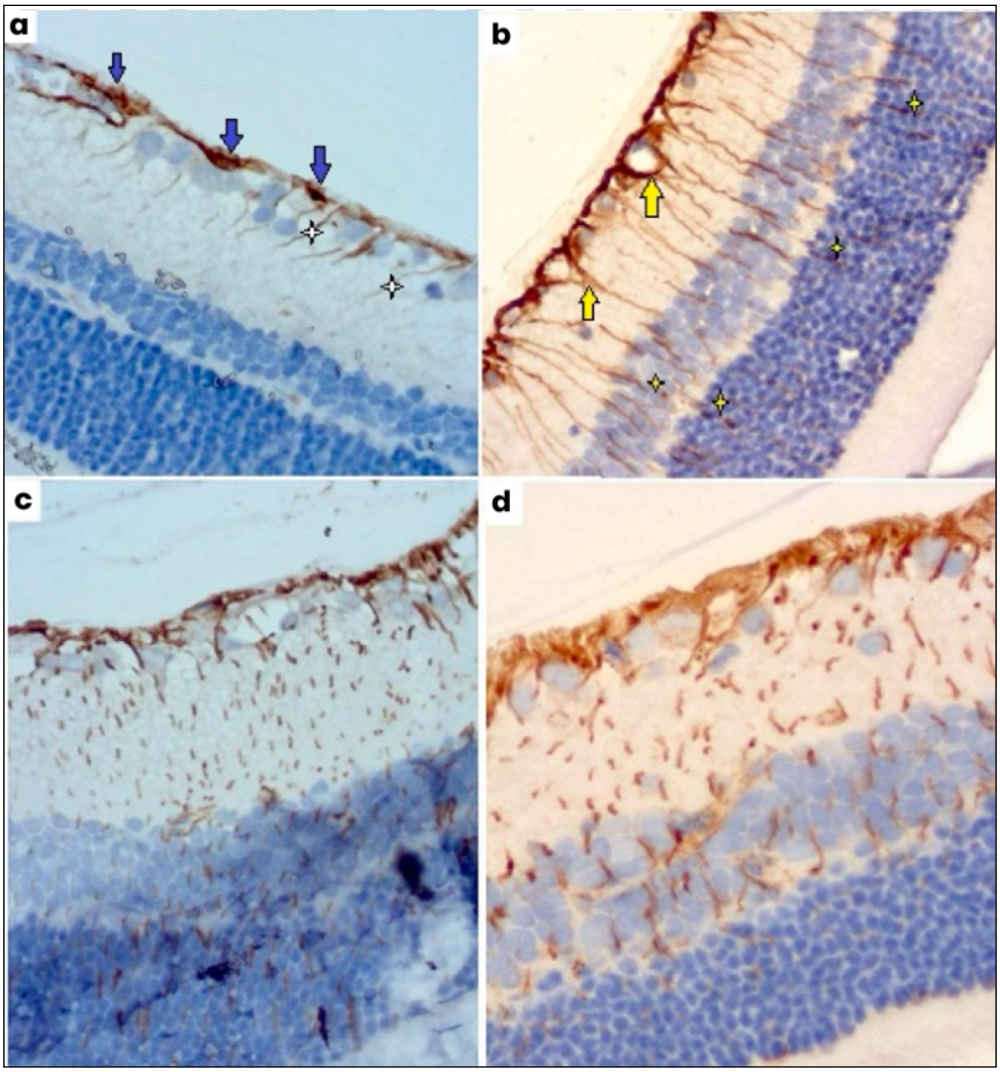

Fig. 5. Immunohistochemical detection of GFAP in control and experimental rat retinas. (a) 7 days, control group: intense radial staining (blue arrows, white asterisks) indicating gliosis. (b) 3 months, control group: maximum immunoreactivity with vessel-associated fibres (yellow arrows) and nuclear layer staining (yellow asterisks). (c) 3 months, insulin-treated group: reduced expression. (d) 3 months, combined treatment group: minimal GFAP expression. GFAP immunostaining with hematoxylin counterstain; magnification ×400

areas. However, a reduction in ganglion cell numbers and increased nuclear layer cell density was observed. In the combined treatment group, the retinal structure remained intact, and DR-related pathological changes characteristic of the control group were absent. No angiogenic or cellular proliferative foci were detected.

MACROGLIA

A characteristic response of both astrocytes and Müller cells to neural tissue damage is reactive gliosis, which might be considered a process of partial dedifferentiation, during which terminally differentiated macroglial cells regain the ability to divide and exhibit a certain level of plasticity, accompanied by excessive cytoplasmic expression of GFAP (which is either absent or minimally expressed under normal conditions in Müller cells and moderately expressed in astrocytes) and S100 family of Ca^{2+}-binding proteins. Macroglial activation is a complex, multifactorial process that involves both mechanisms associated with elevated glucose levels and intercellular interactions [31].

Immunohistochemical analysis of the retina in intact animals revealed GFAP expression exclusively in astrocytes and their fibres (Fig. 4, blue arrows). No specific staining was observed in other retinal layers. The positively stained astrocytes and their fibres surrounded capillaries on the inner retinal surface. The staining intensity, assessed using the D. Dabbs scale, was rated at 1–2 points.

Increased GFAP expression was detected as early as seven days after the induction of hyperglycaemia (Fig. 5a, blue arrows). Staining intensity, assessed using the D. Dabbs scale, ranged from 2 to 3 points. Numerous GFAP-positive fibres were observed in the nerve fibre layer, radiating across the retina (Fig. 5a, white asterisks).

Throughout the experiment, GFAP staining intensity progressively increased, reaching a maximum at three months (Fig. 5b). At this stage, numerous long radial fibres were present, encircling blood vessels in the nerve fibre layer (Fig. 5b, yellow arrows). Additionally, individual GFAP-positive Müller cells were detected in the nuclear layers of the retina (Fig. 5b, yellow asterisks), reflecting a pattern of reactive gliosis characteristic of DR.

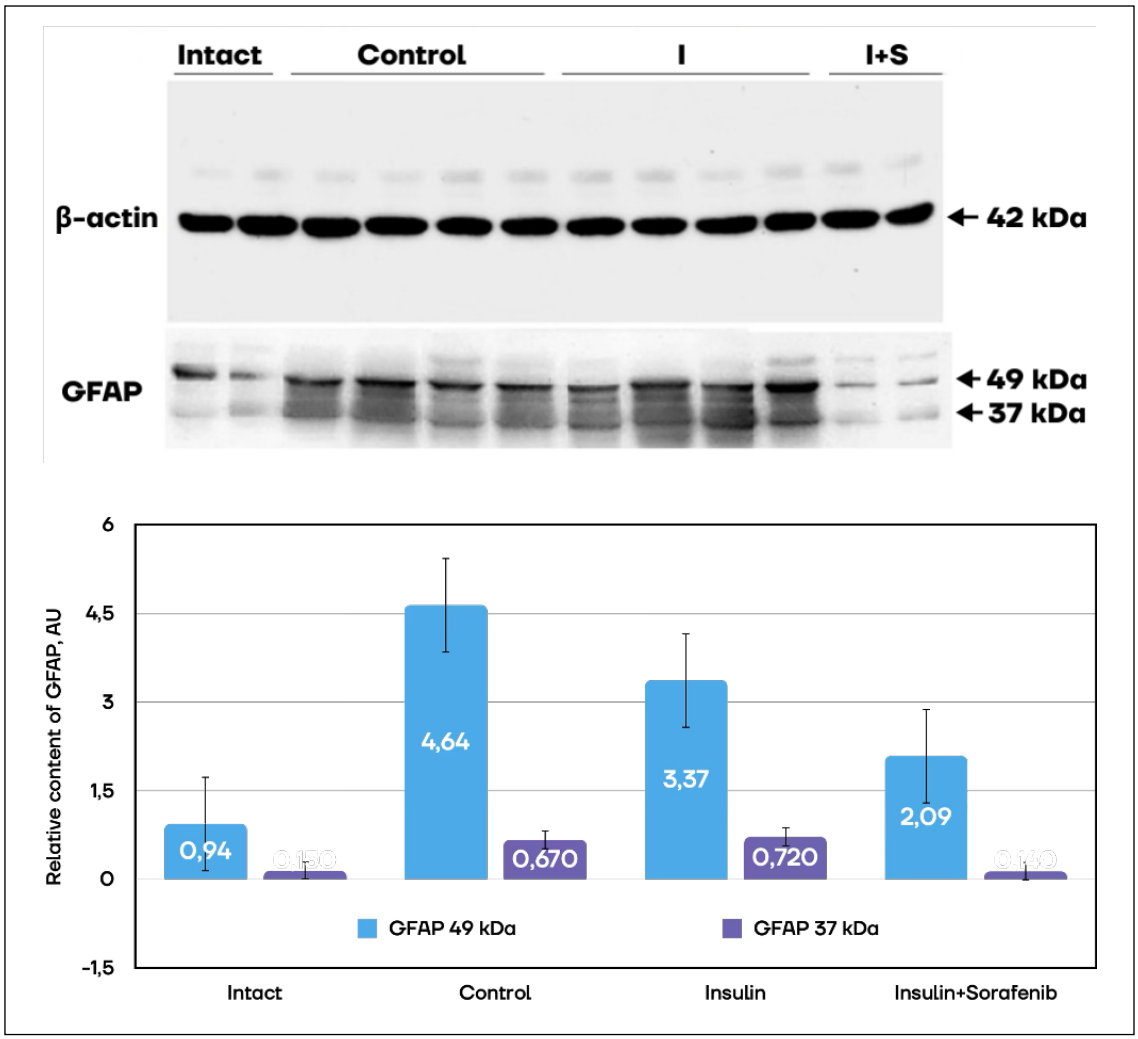

Fig. 6. GFAP protein levels in retinal tissue 3 months post-diabetes induction. (a) Representative Western blot showing GFAP and β-actin bands. (b) Densitometric analysis of GFAP expression normalized to β-actin. $p < 0.05$ compared to intact rats

Treatment with insulin reduced GFAP staining intensity (Fig. 5c), while the combined administration of insulin and sorafenib almost entirely prevented GFAP overexpression (Fig. 5d). This finding indicates that combination therapy effectively suppresses reactive gliosis in the retina.

Western blot analysis confirmed a 4.9-fold increase in GFAP levels in retinal tissue from the control group after three months compared to intact animals (Fig. 6). Treatment with insulin and the insulin-sorafenib combination significantly reduced GFAP expression (Fig. 6b). Immunoblots revealed both the primary GFAP band at 49 kDa and lower molecular weight fragments (37 kDa), suggesting intermediate filament proteolysis during reactive gliosis.

Significant changes in S100 expression were also observed by the 7th day after hyperglycaemia induction (Fig. 7). Intense S100-positive staining was observed as a continuous border in the nerve fibre layer (Fig. 7a, white asterisks). Reactive Müller cells with intense staining (3 points on the D. Dabbs scale) were identified in the inner nuclear layer (Fig. 7a, white arrows). Their processes extended into the outer nuclear layer with a radial orientation (Fig. 7b, yellow arrow). Additionally, positive staining was detected in the boundary zone between the outer nuclear layer and the inner segment of photoreceptors (Fig. 7b, black arrows).

Over the course of the experiment, an increase in the intensity of S100-positive staining (3–4 points on the D. Dabbs scale) was observed in the control group. By the 28th day, sporadic round immunopositive cells were detected in the outer nuclear layer (Fig. 8a, white asterisks), possibly indicating the early stages of Müller cell migration.

In the insulin-treated group, a reduction in the density of S100-positive Müller cells in the inner nuclear layer was observed (Fig. 8b). On the contrary, combined administration of insulin and sorafenib resulted in a significant decrease in both the number and intensity of stained Müller cells and their fibres (2–3 points on the D. Dabbs scale; Fig. 8c).

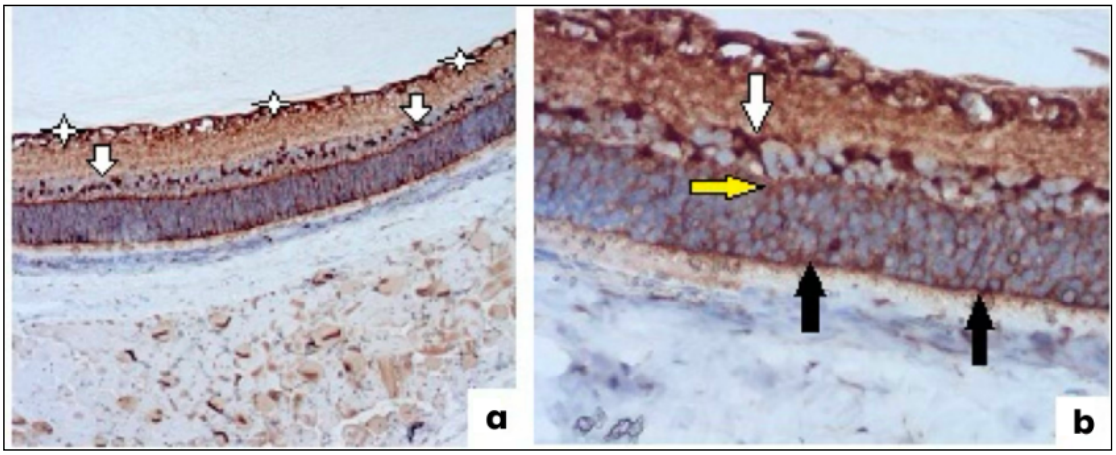

Fig. 7. Immunohistochemical detection of S100 in control and experimental rat retinas on day 7 post-diabetes induction. (a) Strong immunoreactivity in the nerve fibre (white asterisks) and inner nuclear (white arrows) layers. (b) Radial extension into outer layers (yellow arrow) and staining in the photoreceptor boundary zone (black arrows). S100 immunostaining with hematoxylin; magnifications ×200 and ×400

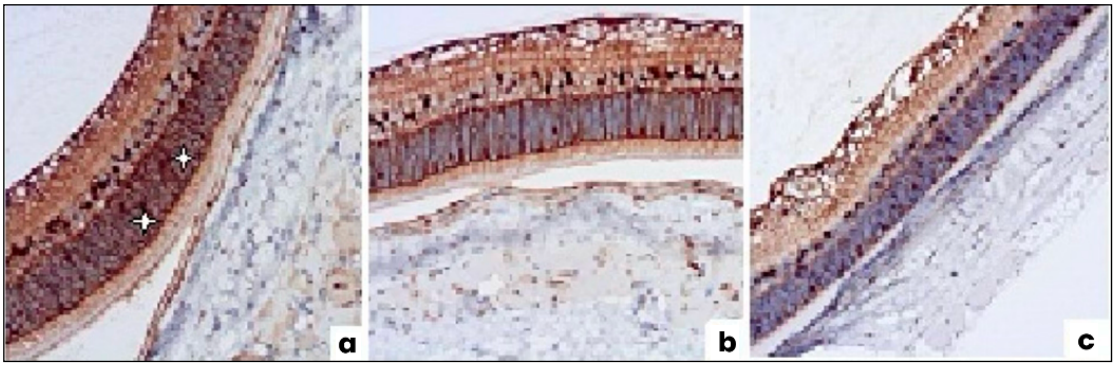

Fig. 8. S100 expression in the retina on day 28 post-diabetes induction. (a) Control group: immunopositive round cells in the outer nuclear layer (white asterisks). (b) Insulin group: reduced S100-positive Müller cells. (c) Insulin + sorafenib group: further reduction in staining intensity and number of reactive cells. S100 immunostaining with hematoxylin counterstain; magnification ×200

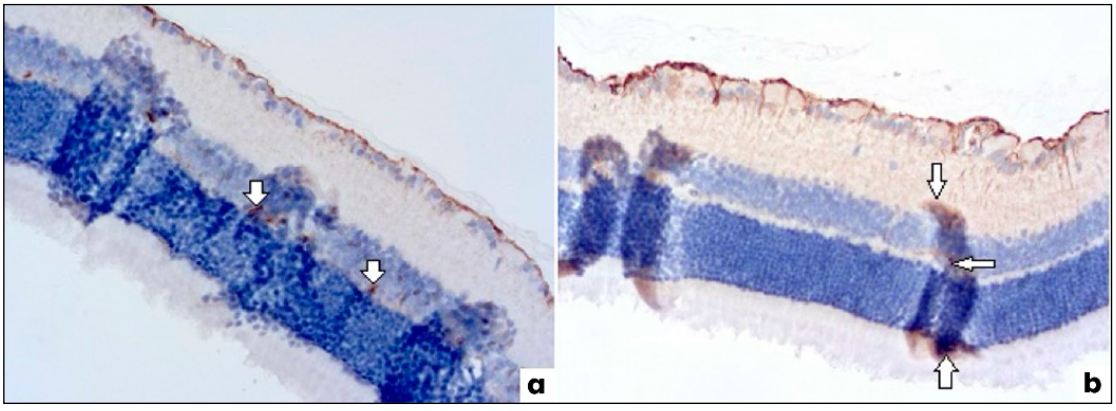

Fig. 9. Immunohistochemical signs of glial-mesenchymal transition. (a) S100-positive cells involved in proliferative foci. (b) GFAP-positive elements within retinal proliferations. S100/GFAP immunostaining with hematoxylin counterstain; magnification ×400

One of the most critical aspects of DR pathogenesis, arising as a consequence of reactive gliosis in the later stages of the disease, is the glial-mesenchymal transition of Müller cells. GMT is a process in which Müller cells completely lose their glial characteristics and acquire mesenchymal properties, such as the ability to migrate, proliferate, and secrete extracellular matrix components. This transition contributes to the formation of cellular proliferative foci and epiretinal membranes, fibrosis, and neovascularisation—key components of DR progression.

GMT is triggered by various pathological factors, including hyperglycaemia, oxidative stress, inflammation, and hypoxia. Transforming growth factor-beta (TGF-β),

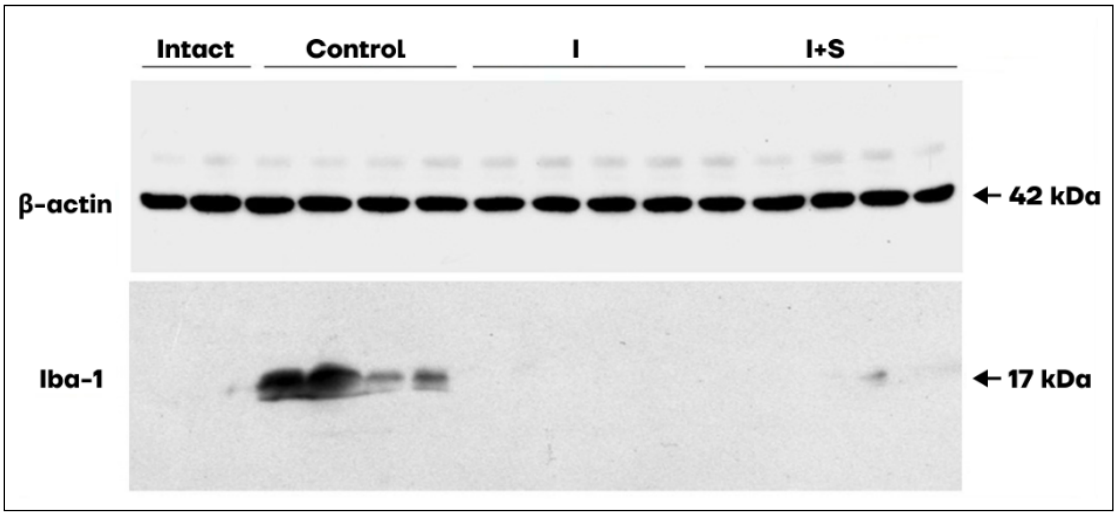

Fig. 10. Iba-1 protein expression in retinal tissue 3 months post-diabetes induction. (a) Western blot bands for Iba-1 and β-actin. (b) Densitometric analysis of Iba-1 expression normalized to β-actin. $p < 0.05$ compared to intact rats

the Wnt/β-catenin signalling pathway and other molecular mechanisms play essential roles in regulating the expression of mesenchymal markers such as α-smooth muscle actin (α-SMA) and fibronectin [34].

In our study, after three months, signs of GMT were observed in the control group, including the formation of cellular proliferative foci in the outer nuclear layer of the retina (Fig. 9). Both S100-positive (Fig. 9a) and GFAP-positive elements (Fig. 9b, white arrows) were involved in proliferations, confirming the active participation of macroglia in GMT mechanisms. On the contrary, no signs of GMT were detected in the insulin or insulin + sorafenib-treated group.

MICROGLIA

A well-established marker of activated microglia is Iba-1. Immunoblotting analysis confirmed an increase in Iba-1 expression in the retina in DR (Fig. 10). While Iba-1 was not detected in the retinas of healthy control rats, its expression was significantly elevated in DR (Fig. 10b). Treatment with insulin led to a substantial reduction in Iba-1 levels, whereas the combination of insulin with sorafenib resulted in only trace amounts of the marker in retinal tissues. These findings highlight the potential for suppressing diabetes-induced microglial activation through the inhibition of cellular protein kinases using sorafenib.

DISCUSSION

Diabetic retinopathy is now understood not only as a vascular complication but also as a neuroinflammatory disorder, with glial dysfunction at its core. Our study reinforces this concept, demonstrating that both macroglial (Müller cells, astrocytes) and microglial activation precede and accompany retinal neurodegeneration and vascular dysfunction in the STZ-induced model. The upregulation of GFAP and S100, along with increased Iba-1 positivity, illustrates progressive gliosis and inflammatory infiltration during DR development.

The observed increase in GFAP levels aligns with classical indicators of Müller cell reactivity in hyperglycaemic environments. Elevated GFAP, particularly in the intermediate and peripheral retinal zones, reflects a breakdown in Müller homeostatic functions, supporting evidence from previous studies where GFAP overexpression was associated with impaired glutamate clearance and oxidative stress in DR [12]. S100 overexpression further underlines Müller cell dysregulation, suggesting calcium buffering and pro-inflammatory signalling deficits. Importantly, the prolonged presence of reactive Müller cells indicates a chronic stress response, even when neuronal death is not yet advanced.

Iba-1 staining revealed that microglial activation is not transient but sustained in STZ-induced DR, echoing the findings that chronic hyperglycemia promotes a switch to pro-inflammatory (M1) phenotypes [13]. These microglia are likely contributing to cytokine release, phagocytic dysfunction, and vascular injury through TNF-α, IL-1β, and VEGF signalling [14].

Our data provide evidence that sorafenib, a multi-kinase inhibitor known for targeting RAF, VEGFR, and PDGFR, can modulate these gliotic responses. The reduction in GFAP and Iba-1 expression after sorafenib treatment suggests it may suppress both macroglial and microglial reactivity. This is consistent with prior non-retinal studies indicating sorafenib's ability to downregulate ERK/NF-κB pathways, key mediators of

inflammatory cascades [15]. Inhibition of these kinases may halt the progression of gliosis by interfering with glial mesenchymal transition, a process implicated in retinal fibrosis and chronic neuroinflammation.

Notably, the neuroprotective effects observed in the peripheral retina after sorafenib treatment, including better preservation of retinal architecture and decreased glial clustering, highlight its potential in early intervention settings. This effect appears superior to commonly used anti-VEGF treatments, which primarily target vascular changes but neglect neuroinflammatory components [16].

Although sorafenib is primarily approved for oncology, its pleiotropic kinase inhibition profile provides rationale for repositioning in neurodegenerative and retinal diseases. However, systemic toxicity and off-target inhibition remain limitations that require formulation refinement (e.g., localised delivery via intravitreal nanoparticles) [17].

Future directions should include delineating the exact downstream effectors inhibited in retinal glial cells, exploring combination regimens with antioxidants or microglia modulators, and long-term safety evaluation in preclinical models. The ability to reverse or prevent glial mesenchymal transition may be a crucial mechanism in DR therapy beyond glycemic control.

CONCLUSIONS

Our findings highlight the crucial role of glial dysfunction in the pathogenesis of diabetic retinopathy and demonstrate that sorafenib, a multi-kinase inhibitor, exerts a protective effect against retinal gliosis and microglial activation in a STZ-induced diabetes model. Sorafenib treatment significantly reduced GFAP, S100, and Iba-1 expression, preserved retinal architecture, and attenuated both macroglial and microglial inflammatory responses.

These results suggest that sorafenib can modulate key signaling pathways involved in glial activation and neuroinflammation, offering a promising avenue for early intervention in diabetic retinal disease. Given its ability to target kinases implicated in vascular and glial pathology, sorafenib represents a candidate for drug repurposing aimed at the neurodegenerative and inflammatory aspects of DR.

Further studies are needed to elucidate the specific molecular targets of sorafenib in retinal glial cells, to assess long-term safety and efficacy, and to explore optimised delivery strategies for localised retinal therapy. Nonetheless, this study lays the groundwork for a novel approach to DR management focused on glial modulation and inflammatory control.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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