RESEARCH PAPER

Interplay Between Calcium Dysregulation and Nrf2 Signalling Cascade in Diabetic Retinopathy

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ABSTRACT
Diabetic retinopathy (DR) remains a major cause of preventable blindness worldwide, particularly as the global prevalence of diabetes continues to rise. Early DR is characterised by oxidative stress (OS), endothelial dysfunction, vascular leakage, and subtle cellular changes that often progress unnoticed until irreversible damage occurs. Despite these early pathological alterations, current treatments primarily target advanced DR, highlighting a critical unmet need for early-stage interventions. OS plays a pivotal role in early DR pathogenesis through excessive production of reactive oxygen species (ROS), which impair mitochondrial function, disrupt the blood-retina barrier, and promote inflammation. Calcium dysregulation further amplifies retinal injury by triggering mitochondrial dysfunction, activating calpains and apoptotic pathways, and exacerbating ROS production. The Nrf2/HO-1 pathway, a key endogenous antioxidant defence system, has emerged as a promising therapeutic target. Emerging therapies demonstrates therapeutic potential by reducing OS, stabilising calcium homeostasis, and enhancing Nrf2/HO-1 signalling. Preclinical evidence suggests that certain agents may attenuate mitochondrial dysfunction, endothelial damage, and inflammation associated with early DR. This review aims to explore the mechanistic insight in modulating OS, calcium dysregulation, and Nrf2/HO-1 activation in offering promising prospects for early therapeutic intervention of DR.

Keywords: *Calcium dysregulation, Nrf2 signalling, diabetic retinopathy, oxidative stress, neurodegeneration*
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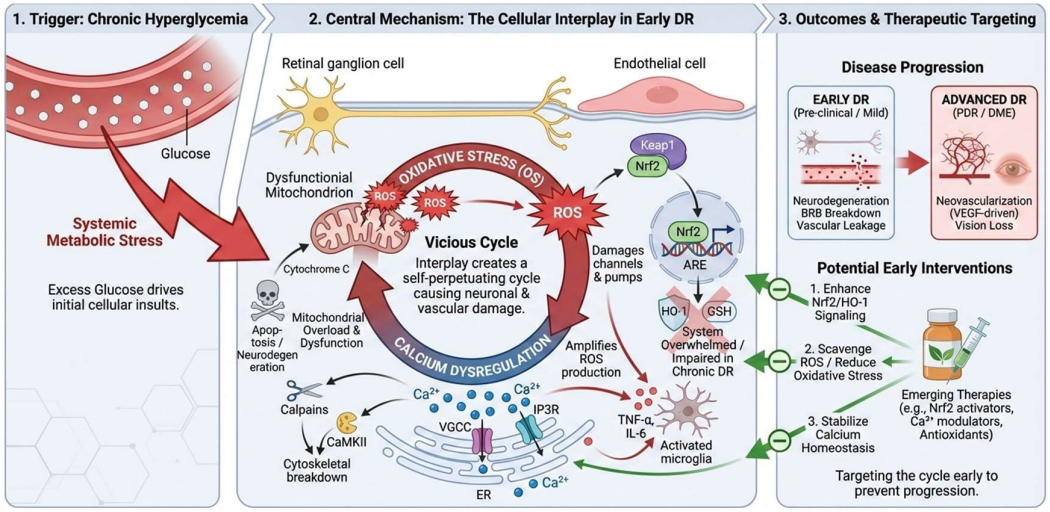

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Graphical Abstract: The Vicious Cycle of OS and Calcium Dysregulation in Early Diabetic Retinopathy and Nrf2 as a Therapeutic Target. Chronic hyperglycemia triggers a self-perpetuating cycle where ROS impairs calcium homeostasis, which further amplifies ROS, overwhelming the Nrf2 antioxidant defense. This interplay drives inflammation, apoptosis, and endothelial dysfunction, leading to DR progression. Emerging therapies aim to break this cycle early.

1. INTRODUCTION

Diabetic retinopathy (DR) is a leading cause of blindness, particularly affecting individuals with diabetes. Diabetes has become a global health crisis, with the World Health Organization (WHO) reporting that over 460 million people worldwide will surpass 700 million by 2045. In Malaysia, the prevalence of diabetes is similarly alarming, with recent estimates indicating that over 3.6 million (18%) Malaysian adults are living with diabetes which has been accompanied by a significant increase in DR [1]. This disease starts off with early DR which is characterised by retinal vascular leakage, endothelial dysfunction, and the early onset of oxidative stress (OS). These early changes often go unnoticed, making early detection and intervention crucial to prevent the progression to advanced stages of the disease which are associated with severe vision loss.

Despite the significant issues in early DR, current therapies mainly focus on the later stages of the disease, leaving a critical gap in the management of early DR [2]. OS plays a central role in the pathogenesis of DR, with the accumulation of reactive oxygen species (ROS) causing damage to retinal cells and vasculatures. However, evidence suggested that calcium dysregulation further exacerbates OS and contributes to disease progression. Intracellular calcium overload disrupts cellular functions and triggers a cascade of events leading to cell death and increased vascular permeability. The Nrf2/HO-1 signaling pathway, a key regulator of the cellular antioxidant defence system, has gained attention as a potential therapeutic target. Activation of Nrf2 leads to the upregulation of antioxidant enzymes, including heme oxygenase-1 (HO-1), which can counteract OS and inflammation. Emerging therapies have shown promise with both antioxidative and calcium-modulating effects. However, despite its potential, the specific mechanisms by which the therapies modulate OS, Nrf2/HO-1 signalling, and calcium homeostasis in early DR remain poorly understood. This review aims to explore the effects of multiple therapies on OS, Nrf2/HO-1 pathway activation, and calcium dysregulation in early DR. The interconnections among these pathways will also be discussed. This is important as it offers hope for improved interventions and better outcomes for diabetic populations globally. This review not only aligns with the global pursuit of safer and more accessible treatments but also holds particular significance for growing diabetic population worldwide.

2. LITERATURE SEARCH

A comprehensive literature search was conducted to identify relevant studies examining calcium dysregulation, Nrf2 signalling (including Nrf2/HO-1), oxidative stress, neurodegeneration, and their roles in diabetic retinopathy (DR), as well as reports on potential therapeutic modulators (e.g., magnesium, taurine, and related derivatives). The search was performed across major scientific databases PubMed, Scopus, Web of Science, and Google Scholar. Keywords and MeSH terms were combined with Boolean operators to refine results; primary search terms included: “diabetic retinopathy,” “early diabetic retinopathy,” “oxidative stress,” “reactive oxygen species,” “calcium dysregulation,” “intracellular Ca^{2+},” “Nrf2,” “Nrf2/HO-1,” “neurodegeneration,” “retinal neurodegeneration,” “mitochondrial dysfunction,” “retinal ganglion cells,” “retinal endothelial cells,” “magnesium,” “taurine,” and “acetyltaurate.” Additional sources were retrieved through hand-searching reference lists, consulting key review articles, and screening relevant grey literature to capture emerging or unpublished findings.

Inclusion criteria were: (1) articles published in English, (2) experimental, clinical, or review studies addressing DR pathophysiology or interventions relevant to OS, calcium signalling/dysregulation, Nrf2/HO-1-mediated antioxidant responses, or retinal neurodegeneration, and (3) publications within the last 15 years (with seminal older studies included as needed). Exclusion criteria comprised non-peer-reviewed material, studies not related to retinal pathology or mechanistic pathways of interest, and reports lacking sufficient methodological detail. Retrieved records were screened for relevance and quality, and data from eligible studies were extracted and synthesized narratively.

2. DR

DR is a major complication of diabetes mellitus and a leading cause of blindness worldwide [3]. As the global prevalence of diabetes rises, the incidence of DR also increases. Individuals with long-standing diabetes are at the highest risk of developing DR, with the likelihood increasing significantly after 5-10 years of disease duration. Poor glycaemic control remains the strongest modifiable risk factor, as chronic hyperglycaemia accelerates microvascular damage within the retina [4]. Patients with type 1 diabetes often develop DR earlier due to longer lifetime exposure, while those with type 2 diabetes may already have DR at diagnosis because hyperglycaemia may have been present for years before detection. Hypertension, dyslipidaemia, and obesity further exacerbate retinal microvascular injury by promoting endothelial dysfunction and OS. Pregnant women with pre-existing diabetes are also at elevated risk due to rapid metabolic changes. Additional non-modifiable factors include advancing age, male sex, longer diabetes duration, and genetic susceptibility. Furthermore, individuals with nephropathy or other microvascular complications are more likely to develop or progress to sight-threatening DR, as these conditions share common

underlying pathophysiological mechanisms [4]. Figure 1 indicates the major risk factors of DR.

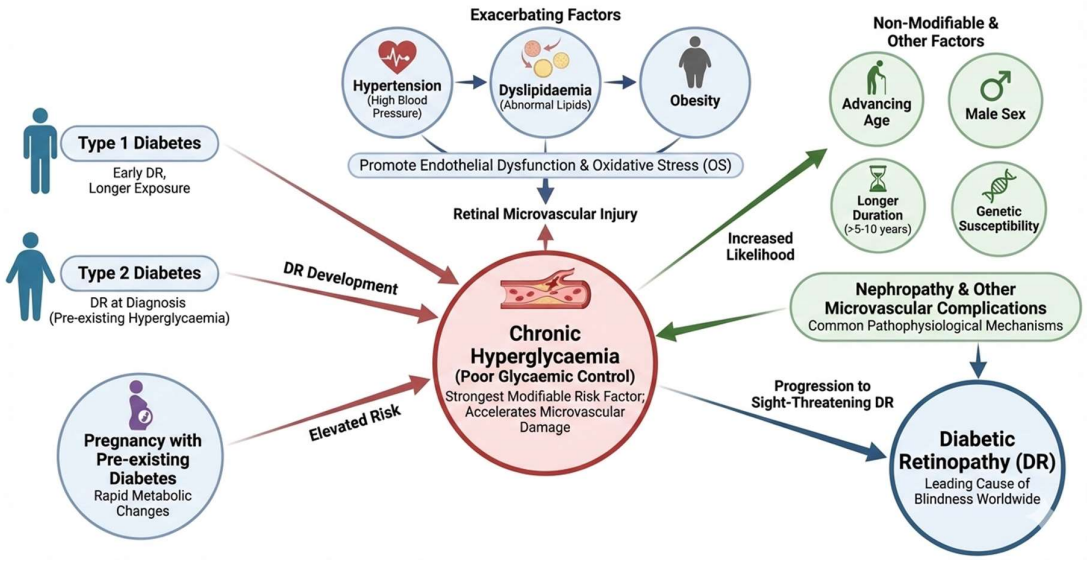

Figure 1: Major risk factors of DR. This diagram illustrates the risk factors and pathological mechanisms involved in the development and progression of DR. It highlights the central role of chronic hyperglycemia, exacerbating factors like hypertension and obesity, and non-modifiable factors leading to retinal microvascular injury and sight-threatening DR.

The World Health Organization (WHO) reported over 460 million people have diabetes, which expected to exceed 700 million by 2045 [5]. In Malaysia, approximately 18% (3.6 million) of adults are diagnosed with diabetes, which likely to develop DR over time. This phenomenon has led to a significant rise in diabetic complications including DR, creating a huge burden on healthcare systems. DR pathophysiology is complex, involving hyperglycaemia-induced OS, inflammation, and vascular changes [6]. DR typically begins as non-proliferative (NPDR) with vascular leakage, endothelial dysfunction, and accumulation of reactive oxygen species (ROS). If left untreated, NPDR can progress to more severe stages called as proliferative (PDR) and diabetic macular oedema (DME), which lead to irreversible vision loss [7] (Table 1). DR has long been studied not only in clinical but also various experimental models for therapeutic discoveries [8].

Table 1: Clinical features in different DR stages [9]

Feature	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	Proliferative DR (PDR)
Primary Pathology	Normal retinal vasculature	Microaneurysms only	Increased microvascular damage	Marked retinal ischemia	Neovascularization
Key Clinical Signs	No abnormalities	Microaneurysms	Microaneurysms, dot/blot haemorrhages hard exudates, cotton-wool spots	4-2-1 Rule: • ≥4 quadrants hemorrhages/microaneurysms • ≥2 quadrants venous beading • ≥1 quadrant intraretinal microvascular abnormalities (IRMA)	Neovascularization or preretinal/vitreous hemorrhage
Macular Involvement	None	May have early changes	More common; risk of DME increases	High risk of DME	Often associated with DME
Ischemia	None	Minimal	Moderate	Significant, widespread	Severe with retinal hypoxia driving

					neovascularizatio n
Vascular Abnormaliti es	None	Microaneurys ms	Microaneurysms, venous dilation, IRMA (mild)	Pronounced IRMA and venous beading	Fragile neovascular vessels
Risk of Vision Loss	Very low	Low	Moderate	High	Very high
Risk of Progression	None	Slow	Moderate	Rapid progression to PDR	Rapid deterioration without treatment
Diagnostic Clues	Normal fundus	Isolated microaneurys ms	Presence of hemorrhages/exudat es but < severe criteria	Meets ≥1 criteria of 4-2-1 rule	Neovascularizatio n ± fibrous proliferation
Recommen ded Follow-Up	12 months	6-12 months	3-6 months	1-3 months	Immediate treatment and close follow-up (weeks)

3. PATHOPHYSIOLOGY OF DR

OS is a key pathological mechanism in DR resulting from an imbalance between ROS production and antioxidant defences. In diabetes, chronic hyperglycaemia promotes excessive ROS generation through several biochemical pathways, including the polyol, protein kinase C (PKC), and the advanced glycation end-products (AGEs), which further exacerbate OS by triggering inflammatory responses via RAGE receptors. Elevated ROS levels in retinal cells significantly contribute to early DR [10]. Also, ROS induce lipid peroxidation, disrupt cellular membranes, damage DNA, and impair mitochondrial function, creating a vicious cycle of cellular damage as shown previously in preclinical model [11, 12]. In retinal endothelial cells, OS weakens the blood-retina barrier (BRB), leading to vascular leakage, microaneurysms, and retinal oedema, as hallmarks of early-stage DR [13]. Additionally, ROS activate pro-inflammatory signalling pathways, which further increasing retinal inflammation, vascular permeability, and endothelial dysfunction. Elevated levels of proinflammatory cytokines such as IL-6, TNF-α, and IL-1β leading to oxidative damage and recruiting immune cells [14, 15].

Retinal inflammation plays a central role in DR pathophysiology and closely interacts with OS. Hyperglycaemia and ROS activate microglia, the resident immune cells of the retina, transforming them into a pro-inflammatory phenotype [16]. Activated microglia release cytokines, chemokines, and matrix metalloproteinases (MMPs), contributing to chronic low-grade inflammation. This inflammatory markers disrupts tight junction proteins in endothelial cells, worsening BRB breakdown. Leukocyte adhesion (leukostasis), driven by increased expression of ICAM-1 and VCAM-1, further contributes to vascular occlusion, capillary dropout, and tissue hypoxia. Chronic inflammation also promotes Müller cell activation (gliosis), which alters retinal homeostasis and exacerbates neuronal and vascular dysfunction [17].

As retinal hypoxia worsens due to capillary non-perfusion, angiogenesis becomes a major contributor to DR progression [18]. Hypoxia-inducible factor-1α (HIF-1α) accumulates under low-oxygen conditions and promotes transcription of angiogenic mediators, most notably vascular endothelial growth factor (VEGF). Elevated VEGF levels increase vascular permeability, leading to DME, and stimulate the formation of fragile, abnormal new blood vessels characteristic of PDR [19]. These new vessels are prone to leakage and haemorrhage, increasing the risk of vitreous bleeding and tractional retinal detachment [20]. Angiogenesis is further aggravated by the combined effects of OS, inflammatory cytokines, and endothelial dysfunction [15, 21].

DR is increasingly recognised not only as a microvascular disease but also as a neurodegenerative disorder [22]. Long before vascular lesions appear, retinal neurons undergo apoptosis driven by OS, glutamate excitotoxicity, and chronic inflammation [23, 24]. Loss of ganglion cells, amacrine cells, and photoreceptors leads to thinning of the retinal nerve fibre layer (RNFL) and impaired visual processing [25]. Müller glial dysfunction further exacerbates neurodegeneration by reducing neurotrophic support and failing to maintain extracellular glutamate homeostasis. Mitochondrial dysfunction, calcium overload, and impaired autophagy contribute to early neuronal loss, which may explain why it exhibits visual deficits even before clinical signs of DR become detectable [25, 26]. Figure 2 represents the pathophysiological mechanism of DR.

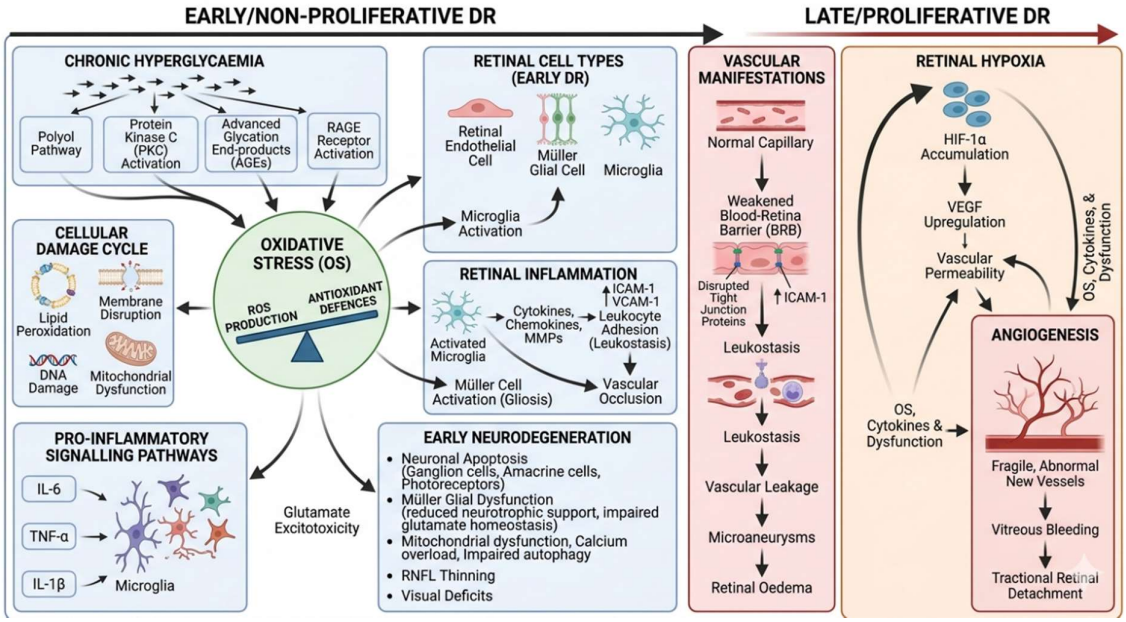

Figure 2: Pathophysiology in DR. This diagram provides a comprehensive overview of the pathophysiology of Diabetic Retinopathy (DR), tracing the disease from early metabolic changes to late-stage vision-threatening complications.

4. NRF2/HO-1 PATHWAY AS A TARGET FOR OS

The Nrf2/HO-1 pathway is crucial for cellular defence against OS, making it a potential therapeutic target for DR. Nrf2, a transcription factor, activates antioxidant enzymes like HO-1 and NQO1 in response to OS [27]. These enzymes help to neutralize ROS and protect cells from damage. HO-1, in particular, has antioxidant and anti-inflammatory properties. Activation of the Nrf2/HO-1 pathway has shown protective effects in animal models, reducing ROS levels and improving BRB function [28]. However, in early DR, Nrf2 activation may not fully counteract the OS from prolonged hyperglycaemia [29]. Enhancing Nrf2 activity through pharmacological agents could strengthen cellular defences and protect against OS [30]. The Nrf2/HO-1 axis represents one of the most compelling endogenous defence systems against oxidative injury in the diabetic retina; however, increasing evidence suggests that its role is far more complex than previously recognized. Under physiological conditions, Nrf2 is tightly regulated by Keap1-mediated ubiquitination, ensuring a rapid response to acute oxidative insults [31]. In DR, however, chronic and sustained hyperglycaemia generates persistent OS that appears to overwhelm this adaptive system. Although transient ROS elevations can activate Nrf2, prolonged redox imbalance paradoxically leads to blunted Nrf2 responsiveness, partly due to hyperglycaemia-induced Keap1 upregulation, dysfunction of the Keap1–Cul3 E3 ligase system, and impaired Nrf2 nuclear translocation [32]. This suggests that the retinal antioxidant defence machinery may become progressively exhausted, contributing to the shift from early compensatory responses toward irreversible retinal damage.

HO-1 is classically viewed as a cytoprotective effector of Nrf2 signalling [33], yet its role in DR may not be universally beneficial. While the biliverdin/bilirubin pathway provides potent antioxidant effects, the induction of free iron during heme degradation may potentiate Fenton chemistry, generating more ROS if iron sequestration systems including ferritin are compromised. This dual behaviour raises important mechanistic questions whether chronic HO-1 induction in diabetes inadvertently exacerbate oxidative injury [34]. Emerging studies suggest this may occur in tissues where iron-handling is dysregulated, an area that remains underexplored in the retina. Thus, the HO-1 pathway may operate within a narrow therapeutic window, beyond which its net effect could shift from protective to harmful [35].

Another unresolved issue is the cell-type-pecific regulation of Nrf2 signalling. Müller glia, retinal pigment epithelial (RPE) cells, endothelial cells, and neurons exhibit markedly different oxidative thresholds and Nrf2 activation kinetics [36]. Yet most current studies rely on whole-retina homogenates or single-cell in vitro models that fail to capture this heterogeneity. A more granular understanding is needed because impaired Nrf2 signalling in one retinal cell population could propagate dysfunction to others via paracrine inflammatory mediators or metabolic coupling pathways [37]. This may be particularly relevant in neurodegenerative aspects of early DR, where early neuronal vulnerability may precede microvascular lesions, a paradigm shift not fully reconciled with traditional vascular-centric models.

Although exogenous Nrf2 activators, including plant-derived polyphenols and synthetic electrophiles, show promising antioxidative and anti-inflammatory effects,

their translational value remains uncertain [38]. Many compounds lack retinal bioavailability, have short half-lives, or demonstrate off-target effects [39]. Moreover, chronic systemic Nrf2 activation may interfere with normal cellular homeostasis or promote oncogenic signalling in susceptible tissues, a concern well-documented in oncology but rarely addressed in ophthalmic research [40].

Finally, although Nrf2 activation clearly attenuates NF-κB, a transcription factor that mediate inflammation [41], it is still unknown whether this crosstalk is strong enough to modulate the broader inflammatory networks involved in DR, such as microglial activation, leukostasis, or complement dysregulation. A major limitation in current studies is the reliance on acute or short-term models that do not fully replicate the chronic, metabolic, and low-grade inflammatory environment of human diabetes [42]. The following Table 2 summarizes key Nrf2/HO-1 pathway-related markers in DR.

Table 2: The key Nrf2/HO-1 pathway-related markers in DR.

Marker	Role in redox	Mechanism in DR
Nrf2	Master transcription factor regulating antioxidant response	Nrf2 is protective in DR: in a mouse model, Nrf2 deficiency worsened OS, increased superoxide, lowered glutathione (GSH), increased inflammatory cytokines, TNF-α, and caused earlier blood–retina barrier breakdown and neuronal dysfunction [43].
Keap1	Cytoplasmic inhibitor of Nrf2 (sequesters Nrf2 preventing nuclear translocation)	In DR, impairment in Nrf2-Keap1-ARE signaling observed: despite increased Nrf2 levels, DNA-binding activity of Nrf2 and binding to target gene promoters GCLC is reduced, leading to decreased downstream antioxidant gene expression [44, 45].
HO-1 (Heme oxygenase-1)	Key Nrf2 target	Induction of HO-1 in diabetic rats protected retinal ganglion cells: reduced apoptosis, decreased pro-apoptotic and pro-angiogenic markers VEGF, p53, increased SOD1, Bcl-2 supporting a cytoprotective, anti-oxidative-stress role in DR [46, 47].
NQO1 (NAD(P)H-quinone oxidoreductase 1)	Nrf2 downstream antioxidant enzyme	NQO1 upregulation is part of Nrf2 activation in DR models treated with Nrf2 activators-associated with decreased oxidative damage and improved retinal protection [48].
GCLC (Glutamate-cysteine ligase catalytic subunit)	Rate-limiting enzyme for GSH synthesis	In diabetic retina and endothelial cells exposed to high glucose, Nrf2-GCLC binding and DNA-binding activity is reduced, contributing to lower GSH generation and impaired antioxidant defense [45, 49].
GSH	Central intracellular antioxidant	Nrf2 pathway impairment → decreased GCLC → reduced GSH → increased vulnerability of retinal cells to oxidative damage in DR [50].
ROS markers including superoxide, lipid peroxidation products	Readout of oxidative damage	In DR models, ROS is increased, especially when Nrf2 is deficient; Nrf2 activation reduces ROS, oxidative damage, and downstream inflammatory and angiogenic signalling [51].
VEGF, TNF-α and IL-6	Mediators influenced by OS / redox balance	In a diabetic rat model, pharmacologic Nrf2 activation (with dh404) prevented increases in VEGF, Ang-2, TNF-α, IL-6, and reduced vascular leakage and gliosis, suggesting Nrf2/HO-1 modulation dampens pro-inflammatory/angiogenic responses in DR [52].

5. CALCIUM DYSREGULATION IN DR

Calcium ions are essential for maintaining cellular function like signal transduction, gene expression, and apoptosis [53]. In DR, calcium dysregulation contributes significantly to retinal injury. The retina, a metabolically active tissue, is particularly vulnerable to calcium imbalance secondary to hyperglycaemia. Elevated blood glucose in early DR increases OS, disrupting calcium homeostasis within retinal cells [54].

Under normal conditions, intracellular calcium levels are tightly regulated, but in early DR, calcium influx becomes dysregulated, leading to cellular dysfunction [55]. Elevated intracellular calcium triggers the activation of calpains and phospholipases, which degrade cellular structures [56]. Additionally, calcium overload in mitochondria induces mitochondrial dysfunction, generating more ROS, accelerating retinal cell death and impairing vascular function. Calcium-induced mitochondrial dysfunction also activates apoptotic pathways by opening mitochondrial permeability

transition pores (mPTP), releasing cytochrome C into the cytosol. Calcium dysregulation also disrupts processes in retinal endothelial cells, leading to endothelial dysfunction, a hallmark of early DR [57].

Key calcium-regulating proteins, such as calmodulin and CaMKII play significant roles in calcium overload that was previously studied in streptozotocin-induced diabetic rats [58]. Calmodulin modulates calcium-dependent signalling in retinal cells, with changes in its expression altering endothelial behaviour, contributing to vascular permeability [59]. Whereas CaMKII regulates apoptosis, inflammation, and endothelial cell function, and its dysregulation has been linked to retinal damage in DME [60]. The other critical markers that may contribute in the regulation of calcium include L-type voltage-gated calcium channels (VGCCs), transient receptor potential channels (TRPV1, TRPC6), SERCA (sarco/endoplasmic reticulum Ca^{2+}-ATPase), PMCA (plasma membrane Ca^{2+}-ATPase), IP3 receptors (IP3R), ryanodine receptors (RyR), calpain (Ca^{2+}-dependent protease), calcineurin (Ca^{2+}/calmodulin-dependent phosphatase), mitochondrial calcium uniporter (MCU), N-methyl-D-aspartate receptors (NMDAR), VEGF (indirect calcium modulator) are summarized in Table 3.

Table 3: Key Calcium Dysregulation Markers in DR

Marker	Role in Calcium Regulation	Pathophysiological Impact	Significance
CaM [61, 62]	Primary Ca^{2+} sensor that activates Ca^{2+}-dependent enzymes (e.g., CaMKII, calcineurin); regulates ion channels and signal transduction	Dysregulated CaM signalling → impaired neuronal survival pathways, increased vascular permeability, and altered cytoskeletal stability	Dysfunctional CaM signalling contributes to BRB breakdown, endothelial dysfunction, and early neurodegeneration
CaMKII [63, 64]	Key Ca^{2+}-activated kinase that regulates gene expression, synaptic activity, and cell survival	Promotes inflammation (NF-κB signalling), apoptosis, and excitotoxic neuronal injury; enhances VEGF expression	Overactive CaMKII is linked to retinal ganglion cell (RGC) degeneration and contributes to microvascular injury in DR
VGCCs [65, 66]	Mediate Ca^{2+} influx in retinal neurons and vascular cells	Excess Ca^{2+} entry → neuronal excitotoxicity, vascular dysfunction	Contributes to early neurodegeneration and retinal capillary damage
TRPV1 and TRPC6 [67, 68]	Non-selective Ca^{2+} entry channels involved in sensory signalling	Promotes inflammation, glial activation, vascular leakage	Linked to increased retinal permeability and VEGF upregulation
SERCA [69, 70]	Pumps Ca^{2+} into ER to maintain cytosolic homeostasis	Ca^{2+} accumulation in cytosol → ER stress → apoptosis	Implicated in endothelial dysfunction
PMCA [71]	Extrudes Ca^{2+} from the cytoplasm to maintain resting levels	Sustained intracellular Ca^{2+} overload → cell death	Major contributor to calcium toxicity in retinal neurons
IP3R [72]	Release Ca^{2+} from ER stores during signalling	Excessive Ca^{2+} release → mitochondrial dysfunction & apoptosis	Linked to pericyte loss and vasoregression
RyR [73]	Mediate ER Ca^{2+} release during excitation	Creates Ca^{2+} leak → mitochondrial Ca^{2+} overload	Promotes inflammatory and apoptotic pathways
Calpain [74]	Activated by elevated intracellular Ca^{2+}	Cleaves cytoskeletal proteins → neuronal degeneration	Strongly associated with RGC death
Calcineurin [75, 76]	Integrates Ca^{2+} signals into transcriptional responses	Drives apoptosis, inflammation, and barrier breakdown	Contributes to blood–retinal barrier (BRB) dysfunction
MCU [77]	Uptake of Ca^{2+} into mitochondria	Mitochondrial Ca^{2+} overload → ROS → cytochrome-c release	Key mediator of mitochondrial-mediated apoptosis
NMDAR [78]	Ca^{2+}-permeable glutamate	Excitotoxic Ca^{2+} influx →	Major contributor to early retinal neurodegeneration

	receptors on retinal neurons	neuronal injury	
VEGF (indirect calcium modulator) [79]	Activates Ca^{2+} signalling pathways	Stimulates endothelial Ca^{2+} influx → neovascularisation	Calcium-dependent VEGF signalling drives PDR progression

Despite growing evidence linking these calcium-regulating proteins to early retinal pathology, major uncertainties remain regarding the sequence and specificity of calcium-driven events in DR. One critical limitation in current research is the tendency to view calcium dysregulation as a uniform process across retinal cell types, whereas emerging data suggest highly divergent calcium-signalling vulnerabilities among neurons, glia, endothelial cells, and pericytes. For example, Müller glia exhibits extensive calcium oscillations that coordinate neurovascular coupling [80], yet diabetes induces aberrant calcium waves that impair gliotransmission [81], promote glial activation, and disrupt metabolic support to neurons. This glial dysfunction may precede overt vascular lesions [82], but its contribution remains under-investigated in human tissue, creating an important translational gap.

Similarly, calcium disturbances in pericytes cells essential for microvascular stability [83] which have received limited mechanistic attention. Loss of pericyte calcium homeostasis may underlie early capillary nonperfusion and the breakdown of retinal autoregulation [84], yet most experimental models insufficiently differentiate between endothelial- and pericyte-driven defects. This lack of cell-specific resolution limits the field's ability to identify true upstream drivers of early microvascular damage.

Another critical issue is that calcium dysregulation does not occur in isolation but intersects with parallel pathological pathways, including OS, mitochondrial failure, inflammation, and metabolic inflexibility [85]. However, existing studies often treat these pathways independently, making it difficult to determine whether calcium overload is an initiating insult or a secondary amplifier. For instance, persistent OS can impair Ca^{2+} pumps and channels, while calcium overload itself increases mitochondrial ROS production creating a bidirectional pathogenic loop that is poorly characterized temporally in vivo [86, 87].

Therapeutically, attempts to modulate calcium pathways have lagged behind other DR targets. While inhibitors of CaMKII, calpain blockers, and stabilizers of mitochondrial calcium uptake have shown neuroprotective effects in preclinical models, their clinical translation faces major barriers. Systemic calcium-channel blockade lacks retinal specificity and may alter physiological neurotransmission or vascular tone, while targeted inhibitors often fail to cross the inner BRB in therapeutically relevant concentrations. Novel drug-delivery strategies, such as nanoparticle-mediated targeting of calcium regulators or cell-specific gene silencing of CaMKII isoforms, are needed to overcome these limitations.

6. CURRENT AND EMERGING THERAPIES IN DR

Current DR management is depending solely on anti-VEGF, laser photocoagulation and vitrectomy [88]. Most of these therapies are given at the late stage of the disease progression thus the needs of targeting the early DR stages are crucial [89]. Several pharmacological strategies are under investigation to prevent or delay the onset of DR include antioxidants like lutein, zeaxanthin, curcumin, and alpha-lipoic acid are being studied for their ability to reduce retinal OS [2]. Calcium channel blockers such as nifedipine and diltiazem have been explored to modulate calcium influx in retinal degeneration [90]. ACE inhibitors and ARBs (including enalapril, losartan) have shown potential in slowing DR progression by reducing vascular damage [91]. Fenofibrate originally used for dyslipidaemia, fenofibrate has demonstrated DR-protective effects in patients with type 2 diabetes, possibly through anti-inflammatory and endothelial-stabilizing mechanisms [92]. Corticosteroids and NSAIDs have also been evaluated to control low-grade inflammation contributing to early retinal damage [93]. Other than that, emerging therapies are being explored in preclinical studies [94] (Table 4). Figure 3 summarizes the therapeutic options in DR.

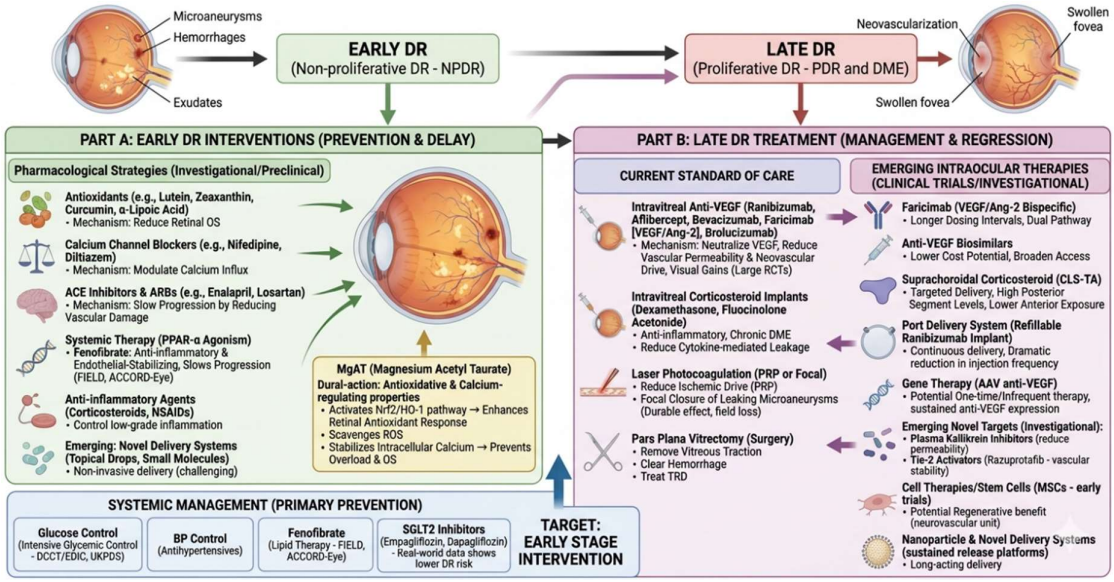

Figure 3: Therapeutic options for DR. This illustrates the progression of DR from Early (Non-proliferative) to Late (Proliferative/DME) stages, characterized by microaneurysms, hemorrhages, and neovascularization.

Table 4: Current and emerging therapies in DR.

Therapy	Mechanism	Typical clinical indication(s)	Key evidence or pivotal trials	Advantages	Limitations
Intravitreal anti-VEGF such as ranibizumab, aflibercept, bevacizumab	Neutralize VEGF → reduce vascular permeability & neovascular drive	First-line for centre-involving DME; widely used in PDR	Multiple large RCTs and guideline statements [95].	Proven visual gains, established protocols	Frequent injections; treatment burden; some non-responders; cost variations [96].
Anti-VEGF biosimilars such as ranibizumab biosimilars	Same target as reference biologics; biosimilar manufacturing	Same indications as reference biologics once approved	Regulatory approvals and comparative studies for several biosimilars; growing availability may reduce cost [97].	Lower cost potential; broadening access	Regulatory and interchangeability nuances; real-world long-term data accumulating [98].
Faricimab (bispecific anti-VEGF/anti-Ang-2)	Blocks VEGF and Ang-2 → vascular stabilization	DME (centre-involving); PDR under study	YOSEMITE & RHINE phase-3: non-inferior vision vs aflibercept; improved durability (many patients extended to 12–16 weeks) [99]	Longer dosing intervals for many patients; dual pathway targeting	Not all patients extend to long intervals; long-term real-world data pending.
Brolucizumab	Small antibody fragment anti-VEGF with high tissue penetration	Studied in DME; used in neovascular age-related macular degeneration	Phase 3 DME programs show efficacy; safety signals (intraocular inflammation/retinal vasculitis) in broader use [100].	Good anatomical response; potential for extended intervals	Rare but serious IOI/vasculitis events → vigilance required.
Intravitreal corticosteroid	Anti-inflammatory;	Chronic or anti-VEGF refractory	RCTs and long-term series show	Reduces injection	Cataract progression,

implants such as dexamethasone (Ozurdex®), fluocinolone acetonide (Iluvien®).	reduce cytokine-mediated leakage	DME; pseudophakic or steroid-tolerant patients	efficacy in chronic DME; fluocinolone provides multi-year effect [101].	frequency; effective in inflammatory phenotype	raised IOP; careful patient selection.
Suprachoroidal corticosteroid (CLS-TA / suprachoroidal triamcinolone acetonide)	Targeted suprachoroidal delivery of steroid → high posterior segment levels, lower anterior exposure	DME investigational and clinical use increasing	Growing clinical evidence and trials reporting improved CMT and VA with favourable anterior-segment safety profile vs intravitreal steroids [102].	Potentially less IOP, cataract risk vs intravitreal steroids; targeted delivery	Technique dependent.
Port delivery system with refillable ranibizumab implant	Refillable intraocular reservoir delivering continuous ranibizumab	Intent to reduce injection frequency for chronic retinal disease (DME/DR under study)	Clinical programs and regulatory updates demonstrate durability and reduced visit frequency; device surgical risks described [103].	Dramatic reduction in injection frequency for suitable patients	Surgical implantation; device-related complications (endophthalmitis, hypotony); candidate selection critical [104].
Gene therapy (AAV mediated anti-VEGF expression)	AAV vector drives intraocular production of anti-VEGF antibody fragments → sustained expression	Clinical trials in nAMD & DME/DR aim to reduce injection burden	Early phase I, II and interim phase II data show reductions in treatment burden and maintained anatomy/vision in many subjects [105].	Potential one-time or infrequent therapy → dramatic reduction in clinic visits	Long-term durability & safety, immune responses, surgical delivery risks under study.
Plasma kallikrein inhibitors (intravitreal or other)	Inhibit kallikrein-kinin system → reduce vascular permeability, inflammation	Investigational for DME, especially anti-VEGF suboptimal responders	Phase 1 showed early efficacy for THR-149; later phase programs had mixed results and some high-profile failures [106].	Targets non-VEGF pathway, potential in anti-VEGF nonresponders	Several programs failed primary endpoints; clinical development status variable.
Tie-2 pathway activators-razuprotafib	Activates Tie-2 → vascular stability and reduced permeability	Investigational for NPDR / DME (systemic or topical/subcutaneous)	Phase II TIME-2 trials showed biological activity; larger trials had mixed outcomes and development refocusing [107].	Non-VEGF, vascular stabilizing mechanism; potential additive benefit	Mixed trial phase results; development paused/redirected in parts of industry.
Topical drop agents (non-invasive delivery) investigational topical anti-VEGF,	Local non-invasive drug delivery to retina via drops or small molecules	Very early clinical testing for DME and DR	Few agents reached human testing; research active but clinical efficacy for posterior disease remains	Non-invasive administration attractive for adherence	Drug penetration to posterior segment is a major barrier; limited human efficacy data.

integrin inhibitors			challenging [108].		
Pars plana vitrectomy (surgery)	Remove vitreous traction, clear hemorrhage, treat TRD	Non-clearing vitreous hemorrhage, tractional retinal detachment in PDR	Surgical series and contemporary outcomes show good anatomical results in appropriate indications [109].	Restores anatomy, addresses tractional complications	Surgical risks; cataract progression common; requires vitreoretinal expertise.
Laser photocoagulation (PRP or focal/grid)	Reduce ischemic drive for neovascularization (PRP); focal closure of leaking microaneurysms	PRP for PDR; historically for DME (now less used for centre-involving DME)	Landmark RCTs and guidelines support PRP for PDR; laser remains important when injection therapy not feasible [110].	Durable effect in reducing PDR vision loss	Peripheral field loss and night vision impairment with PRP; less effective for centre-involving DME.
Systemic lipid therapy — Fenofibrate	PPAR-α agonism; pleiotropic vascular protective effects	Systemic therapy to slow DR progression in T2DM (adjunct to systemic care)	FIELD and ACCORD-Eye secondary analyses and subsequent meta-analyses show reduced progression of retinopathy and reduced need for laser in some cohorts [111].	Systemic, non-ocular route; cost-effective for eligible patients	Not a direct ocular therapy; visual-acuity benefits less clear; therapy chosen as part of systemic care.
Systemic glucose/BP control (intensive glycemic control, antihypertensives)	Modify systemic risk factors that drive microvascular injury	Primary prevention and slow progression of DR	Landmark trials (DCCT/EDIC in T1DM; UKPDS in T2DM; ACCORD) show that intensive glycemic and BP control reduce DR incidence and progression [112].	Proven prevention strategy at population level	Requires systemic management and monitoring; hypoglycemia risk with intensive glycemic regimens.
SGLT2 inhibitors (systemic antidiabetics) empagliflozin, dapagliflozin	Improve glycemic control/metabolic and hemodynamic effects; possible direct retinal neurovascular benefits	Systemic therapy with potential to reduce DR progression (adjunct)	Emerging real-world meta-analyses and observational studies suggest lower DR incidence and progression with SGLT2 inhibitors; RCT evidence still evolving [113].	Potential systemic cardiometabolic and renal benefits plus DR protection	Evidence still evolving for direct retinal outcomes; confounding in observational studies [114].
Cell therapies or stem cell approaches, MSCs (early trials)	Support retinal cells; modulate inflammation	Early stage experimental and phase 1 safety trials	Mostly preclinical and early-phase clinical work; some small human safety studies but efficacy signal not yet robust [115].	Potential for regenerative benefit in advanced disease	Early phase; substantial translational hurdles; efficacy uncertain.
Nanoparticle & novel delivery systems	Various nanoparticles, microparticles, hydrogels for	Platform technology for chronic retinal disease	Preclinical and early clinical programs exploring sustained	Reduced dosing frequency; controlled	Platform and regulatory complexity; limited long-

(sustained release)	long-acting intraocular delivery		release of anti-VEGF, steroids, small molecules [95].	release	term human data.
Other small molecules or novel targets e.g. integrin inhibitors, anti-inflammatory small molecules (early-clinical)	Various non-VEGF mechanisms (integrin blockade, anti-inflammatory)	Investigational	Early phase trials and preclinical data for several small molecules; limited human efficacy data in DR presently [116].	Diverse mechanisms may complement anti-VEGF	Mostly early stage; requires confirmatory trials.

Magnesium supports over 300 enzymatic reactions, including those related to energy production and DNA repair [117]. It acts as a cofactor for SOD, neutralizing superoxide radicals and enhancing antioxidant defences [118, 119]. Additionally, magnesium modulates mitochondrial function, which may help prevent OS in rats with high fat diet [120]. Magnesium also maintains calcium homeostasis, regulating the activity of calcium-dependent enzymes and signalling pathways [121]. In diabetes, magnesium's ability to stabilize intracellular calcium levels prevents calcium overload, thereby maintaining normal cellular function and preventing apoptosis and mitochondrial dysfunction [122]. Whereas taurine contributes further protective effects against OS and calcium dysregulation. It stabilizes cell membranes, modulates calcium signalling, and scavenges ROS. Taurine also possesses anti- inflammatory properties, which are beneficial in managing DR-associated chronic inflammation [123].

MgAT combines magnesium, an essential cofactor for various cellular processes, with taurine, an amino acid known for its calcium-regulating and antioxidative properties [124]. This formulation shows promise as a therapeutic agent in early DR by targeting OS and calcium dysregulation as critical elements in DR pathogenesis. Together, magnesium and taurine in MgAT provide a dual-action approach to early DR by addressing OS and calcium dysregulation. MgAT is not yet widely approved for clinical use but has shown therapeutic potential in preclinical and early clinical research, particularly in the management of neurodegenerative diseases and ocular disorders [125]. It has been studied for its neuroprotective effects in glaucoma, retinal ischemia, and diabetic neuropathy due to its ability to reduce OS, stabilize calcium homeostasis, and preserve mitochondrial function [125, 126]. While not yet indicated for DR in clinical practice, its pharmacological properties suggest relevance in diseases characterized by oxidative and excitotoxic damage. MgAT could modulate the Nrf2/HO-1 pathway, enhancing the retinal antioxidant response and reducing ROS production, while regulating intracellular calcium levels to prevent OS and endothelial dysfunction. These findings bridge preclinical research and potential clinical relevance, supporting further investigation into therapeutic candidates for early DR and advancing its translational journey from bench to bedside.

LIMITATIONS

Despite the growing understanding of OS and calcium dysregulation in the early pathogenesis of DR, several knowledge gaps remain. First, most available evidence is derived from preclinical models, with limited translation into human studies, making it difficult to generalise mechanistic findings to clinical populations. Second, although the Nrf2/HO-1 pathway is recognised as a critical antioxidant target, the extent to which its activation can prevent or reverse early DR remains unclear due to inconsistent experimental outcomes and variations in model systems. Third, while emerging therapies shows promising antioxidative and calcium-modulating effects, its mechanisms of action in retinal cells have not been fully elucidated, particularly concerning its interplay with mitochondrial dynamics and endothelial barrier integrity. Additionally, no long-term safety or pharmacokinetic studies of emerging therapies in ocular disease have been conducted. The lack of standardised dosing, limited data from human retinal tissues, and absence of clinical trials pose significant limitations to the current understanding of therapeutic candidates.

HIGHLIGHTS OF THE CURRENT REVIEW

This review synthesises current evidence on OS, calcium dysregulation, and Nrf2/HO-1 signalling as interconnected mechanisms driving early DR progression. It highlights how excessive ROS production, mitochondrial impairment, and intracellular calcium overload initiate endothelial dysfunction and retinal damage before the onset of advanced clinical features. The review also emphasises MgAT as an emerging dual-action compound with antioxidant and calcium-stabilising properties, positioning it as a promising candidate for early intervention. Through findings from molecular, cellular, and animal studies, this review brings together three critical mechanistic pathways OS, calcium homeostasis, and Nrf2/HO-1 activation and provides a conceptual framework for targeting early pathology in DR rather than late-stage complications.

FUTURE DIRECTIONS

Future research should employ mechanistic studies in human retinal endothelial cells, retinal organoids, and advanced in vivo imaging platforms to clarify how emerging therapeutic agents influence mitochondrial function, calcium homeostasis, OS, and Nrf2/HO-1 signalling in DR. Longitudinal and dose-response investigations are required to establish pharmacokinetics, safety, and optimal delivery strategies for novel interventions within ocular tissues. Early-phase clinical trials in individuals with early DR or those at high risk of progression are essential to determine translational relevance. Emerging evidences suggested the use of targeted therapy [127], nanoparticles [128, 129] and liposomes [130] for management of ocular neurodegenerative diseases. Combination-therapy strategies, including agents that activate Nrf2, stabilise mitochondrial function, modulate intracellular calcium, or attenuate inflammatory signalling, warrant systematic evaluation for potential synergistic effects. Multi-omics approaches such as proteomics, metabolomics, transcriptomics, and epigenomics should be integrated to identify additional molecular targets and to delineate the broader neurovascular effects of emerging therapies. The development of validated biomarkers for early DR progression will further support effective clinical implementation.

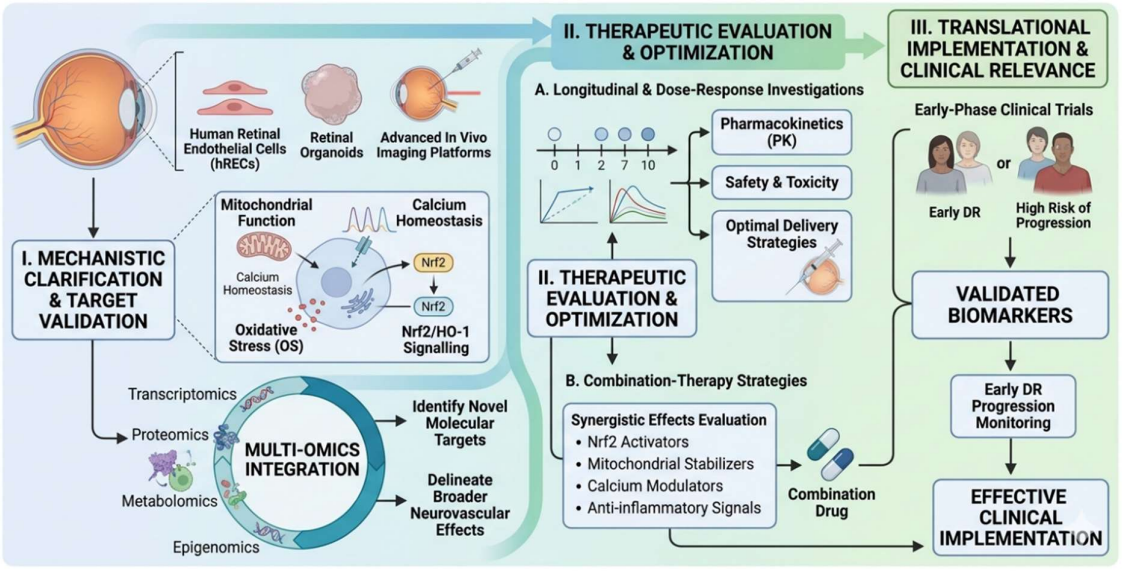

Figure 4: Future directions in DR therapeutics. This schematic outlines the three-stage development process for novel treatments: 1) Mechanistic Clarification: Identifying targets using multi-omics (transcriptomics, proteomics) and advanced retinal models (organoids). 2) Evaluation & Optimization: Refining dosing, safety, and synergistic combination therapies (e.g., Nrf2 activators and mitochondrial stabilizers). 3) Clinical Implementation: Validating biomarkers and conducting early-phase trials to monitor and treat high-risk DR progression.

CONCLUSION

Early DR is characterised by interrelated disturbances in OS, calcium regulation, mitochondrial dynamics, inflammation, and neurodegeneration. Although substantial progress has been made in defining these mechanisms, available therapies predominantly target late-stage disease, underscoring the need for interventions directed at earlier pathogenic events. Emerging therapeutic strategies that modulate OS responses, restore calcium equilibrium, enhance Nrf2/HO-1 activity, and preserve neurovascular integrity show considerable potential for modifying disease trajectory. Nonetheless, further mechanistic studies and rigorous clinical evaluation are required before these approaches can be translated into clinical practice. Continued advancement in this field is essential to develop effective, accessible, and timely interventions for individuals at risk of diabetes-related visual impairment.

ABBREVIATIONS

DR (diabetic retinopathy), WHO (World Health Organization), OS (oxidative stress), ROS (reactive oxygen species), MgAT (magnesium acetyltaurate), Nrf2 (nuclear factor erythroid 2–related factor 2), HO-1 (heme oxygenase-1), NPDR (non-proliferative diabetic retinopathy), PDR (proliferative diabetic retinopathy), DME (diabetic macular oedema), PKC (protein kinase C), AGE (advanced glycation end-products), RAGE (receptor for advanced glycation end-products), BRB (blood–retina barrier), IL-6 (interleukin-6), TNF-α (tumour necrosis factor-alpha), IL-1β (interleukin-1 beta), CaMKII (calcium/calmodulin-dependent protein kinase II), mPTP (mitochondrial permeability transition pore), NQO1 (NAD(P)H quinone dehydrogenase 1), ACE (angiotensin-converting enzyme), ARB (angiotensin receptor blocker), RAS (renin–angiotensin system), BDNF (brain-derived neurotrophic factor), and SOD (superoxide dismutase).

Author Contributions
M.Z.S.: Conceptualization, literature research, investigation, formal analysis, original draft preparation, figure development. H.A.H. and R.R.J.: Literature research, validation, writing-review and editing. F.A.J.: Literature research, methodology input, writing-review and editing.

Ethical Statement
This study does not involve any human or animal trials and no ethical approval required.

Data Availability
All data underlying this review are available within the cited literature.

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Conflicts of Interest
Authors declare none.

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