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REVIEW

Cataract Induced by Glucocorticoids

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Abstract: Glucocorticoids (GCs) remain a cornerstone therapy for noninfectious uveitis and autoimmune disorders; however, chronic administration is strongly associated with sight-threatening complications, particularly glucocorticoid-induced cataracts (GIC). This comprehensive review synthesizes current evidence on the molecular pathogenesis, epidemiological patterns, and clinical management of GIC. Epidemiological analyses indicate that over 50% of patients receiving systemic corticosteroids for >60 days develop ocular complications, with cataract formation (36%) and glaucoma (16%) representing the predominant sequelae. Histopathologically, GIC manifests as posterior subcapsular opacities, mechanistically linked to oxidative stress, epithelial-mesenchymal transition (EMT), vimentin dysregulation, Na^+/K^+-ATPase inhibition, apoptosis, and endoplasmic reticulum (ER) stress. Risk stratification models identify cumulative GC dose (>20,000 mg/m² prednisolone equivalents), treatment duration (>6 months), and administration route (oral > topical > intravitreal) as critical determinants of cataractogenesis. Although early-stage GIC is clinically silent, progressive opacification leads to debilitating visual acuity loss, photophobia, and impaired quality of life. Current interventions encompass antioxidants, molecular targeting strategies, advanced drug delivery systems, and glucocorticoid-sparing agents. Through systematic integration of epidemiology, pathogenesis, and therapeutic advances, we aim to resolve the GC therapeutic paradox and provide robust frameworks for future clinical management.

Keywords: glucocorticoid, glucocorticoid induced cataract, intervention

Introduction: Glucocorticoid Induced Cataract(GIC)

Glucocorticoid Induced Cataract(GIC)

Glucocorticoid-induced cataract (GIC) represents a pervasive therapeutic paradox: while glucocorticoids (GCs) remain indispensable for managing sight-threatening inflammatory disorders, their chronic use induces blinding posterior subcapsular opacities in 36% of patients, highlighting the critical trade-off between anti-inflammatory efficacy and lens toxicity. This iatrogenic complication imposes substantial global burden. Contemporary evidence reveals alarming risk heterogeneity: pediatric nephrotic syndrome cohorts exhibit 18.1% GIC incidence after 4.3 years of oral prednisolo28,669 mg/m²), while myeloma patients show 36% incidence within six dexamethasone cycles—a 21-fold higher risk than localized sub-Tenon administration (1.7%). Crucially, this dose-route-risk continuum positions targeted delivery as the cornerstone of GIC mitigation.

Unlike prior reviews focusing solely on epidemiology or isolated mechanisms, three critical gaps persist despite six decades of research. First, molecular pathogenesis remains fragmented—oxidative stress, EMT, and vimentin dysregulation operate in isolation rather than as interconnected effectors of glucocorticoid-induced mitochondrial-ER stress crosstalk. Second, clinical risk models ignore pharmacogenomic variables like GR-α polymorphisms—known modifiers of GC sensitivity—despite GR signaling's role in Na^+/K^+-ATPase suppression. Third, emerging solutions lack translational frameworks: while polymeric nanoparticles reduce lens GR-α activation, clinical adoption remains limited. This review therefore establishes a tripartite framework addressing: (1) Mechanistic consolidation via ROS-ER-mitochondria cascade; (2) Risk model refinement with GR-α genotypes; (3) Ocular targeting optimization through nanocarriers.

Structurally, we begin by decoding epidemiological determinants through dose-route-susceptibility correlations. We then integrate molecular mechanisms—from oxidative crystallin aggregation to CSPG5-mediated EMT—into a unified

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Table 1 The Prevalence and Risk Factors of Glucocorticoid -Induced Cataracts (GIC) in Different Patient Groups

Study Population	Sample Size	Steroid Type	Dose Range	Duration	GIC Incidence/ Prevalence	Key Risk Factors	References
Pediatric nephrotic syndrome	110 children	Oral prednisolone	10,492–33,500 mg/m² (cumulative)	1–16 years (median 5)	18.1%	Cumulative dose, duration, younger age at onset	34711131
MM patients	231 adults	Dexamethasone (systemic)	Variable (cycles)	≥6 cycles (36% within 6 cycles)	36% within 6 cycles	Total cumulative dexamethasone exposure	37853832
COPD patients	357 adults	Inhaled corticosteroids (ICS)	Low (1–250 μg/day) to high (>500 μg/day)	4 months to >1 year	16.24% overall; 39.65% (high dose >1 year)	High-dose ICS, cumulative lifetime dose (>2000 mg)	28161921
Pediatric SAD	37 children	Oral corticosteroids	Not specified	≥6 months	32.4% (GIC); 59.5% (SIOH)	Treatment duration (>12–18 months), SIOH	35048245
Sub-Tenon triamcinolone (pediatric)	41 patients	Local triamcinolone	4–20 mg	Single injection	1.7%	Localized low-dose exposure	39316833

pathophysiology. Subsequent sections evaluate targeted interventions including antioxidant combotherapy, CRISPR-based editing, and nanoscale delivery systems. Validation of glucocorticoid-sparing protocols and establishment of precision algorithms incorporating CRISPR-screening and TRB3 biomarkers complete this progression from mechanism to clinical translation, resolving GCs' therapeutic dilemma.

Epidemiology

The risk profile of GIC exhibits marked heterogeneity across patient populations, reflecting differential susceptibility to glucocorticoid toxicity [Table 1]. In pediatric cohorts receiving long-term oral corticosteroids for idiopathic nephrotic syndrome, GIC incidence reached 18.1% (20/110 cases), with elevated cumulative doses (median: 28,669 mg/m² vs 14,995 mg/m² in non-affected controls) and extended treatment duration (4.3 vs 2.25 years) demonstrating significant dose-response relationships.[1] Similarly, children with systemic autoimmune diseases (SADs) treated with oral glucocorticoids exhibited progressive cataract development, with incidence rising from 17.6% at 6 months to 41.2% at 18 months, frequently accompanied by steroid-induced ocular hypertension (SIOH).[2]

Adult populations display distinct risk patterns: multiple myeloma (MM) patients on dexamethasone-containing regimens developed cataracts with notable rapidity (36% incidence within six treatment cycles), where total cumulative dexamethasone dose directly correlated with cataract severity.[3] COPD cohorts using inhaled corticosteroids (ICS) manifested dose- and duration-dependent risks, with high-dose ICS (>500 μg/day fluticasone equivalents) conferring 39.65% cataract prevalence after >12 months of exposure, contrasting sharply with low-dose ICS (<250 μg/day) showing no significant risk.[4] Notably, localized administration via sub-Tenon triamcinolone injections (4–20 mg) demonstrated minimal cataractogenicity (1.7% incidence) in pediatric retinal photocoagulation cases, highlighting administration route as a key risk modifier.[5]

Methods

PubMed searches were performed using the terms "GIC", or "SIC", AND "glucocorticoid induced cataract", or "steroid induced cataract". The search was performed in July of 2025, with an additional search in May 2025. All original English language articles were considered for this review.

Mechanism

Oxidative Stress

Oxidative stress constitutes a pivotal pathogenic mechanism in GIC, characterized by disrupted equilibrium between reactive oxygen species (ROS) generation and antioxidant defense capacity. Within the lens microenvironment, excessive ROS accumulation or impaired clearance mechanisms destabilize redox homeostasis, precipitating crystallin aggregation, epithelial apoptosis, and progressive opacification.[6,7] Lens epithelial cells (LECs) - essential guardians of transparency - undergo programmed cell death when ROS-mediated inactivation of Na^+/K^+-ATPase triggers intracellular sodium/water overload, a critical pathway to lens opacification.[6]

Aging potentiates redox imbalance through dual mechanisms: diminished synthesis of endogenous antioxidants (eg, glutathione, GSH) and impaired recycling pathways, which collectively promote disulfide crosslinking in crystallins.[7] Experimental evidence identifies GSH depletion as a hallmark of GIC pathogenesis, with hydrocortisone (HC)-treated models demonstrating inverse correlations between lens/liver GSH levels and oxidative markers: 50% hepatic GSH reduction within 24 hours precedes 8–10-fold elevations in lipid peroxides (LPO), culminating in detectable lens opacities by 48 hours.[8,9] Insulin administration reverses these metabolic perturbations, confirming the systemic dimension of oxidative injury in cataractogenesis.[9]

Endoplasmic reticulum (ER) stress amplifies oxidative damage through calcium dyshomeostasis and sustained activation of the unfolded protein response (UPR). Notably, selenium toxicity exacerbates ER stress via microtubule destabilization, creating a permissive environment for accelerated cataract formation.[10]

Synthesis of these pathways reveals a multimodal oxidative assault: ROS/RNS-mediated protein oxidation, lipid peroxidation chain reactions, and DNA damage collectively compromise lens structural integrity. This mechanistic framework underscores the interdependence of localized oxidative injury and systemic redox dysregulation in GIC progression.[10] These temporal metabolic shifts underscore the critical window for antioxidant intervention.

Epithelial-Mesenchymal Transition

Epithelial-mesenchymal transition (EMT) in LECs emerges as a pivotal pathogenic driver of GIC, mediating lens fibrosis and posterior subcapsular opacification through coordinated molecular reprogramming.[11] This phenotypic transformation is defined by the transcriptional silencing of epithelial markers (E-cadherin, zonula occludens-1) and concomitant upregulation of mesenchymal effectors (N-cadherin, vimentin, fibronectin, α-smooth muscle actin [α-SMA]), accompanied by cytoskeletal destabilization and pathological extracellular matrix (ECM) deposition.[12]

The lens microenvironment facilitates EMT activation through TGF-β2-dominated signaling, wherein the canonical Smad2/3 pathway induces nuclear translocation of EMT transcription factors, driving spindle-shaped morphological transition and invasive LEC migration.[12] Complementing this mechanism, endoplasmic reticulum (ER) stress activates unfolded protein response (UPR) sensors (GRP78, ATF6, IRE1α) in human LECs (HLECs), as evidenced by tunicamycin/thapsigargin models showing E-cadherin suppression and mesenchymal marker induction.[13]

GCs exert dual disruptive effects: dexamethasone (Dex) potentiates EMT through coordinated downregulation of N-cadherin, α/β-catenin complexes, and glucocorticoid receptor (GR) expression, thereby destabilizing intercellular junctions and promoting LEC motility.[14] Counterregulatory pathways exist, as nerve growth factor (NGF) reverses Dex-induced EMT by restoring p38 MAPK/Akt phosphorylation dynamics, effectively suppressing α-SMA and fibronectin overexpression.[15]

Notably, chondroitin sulfate proteoglycan 5 (CSPG5) – overexpressed in GIC patients – orchestrates EMT via EZH2/B-Myb nuclear translocation. CRISPR-mediated CSPG5 knockdown abrogates Dex-triggered fibronectin expression, F-actin remodeling, and migratory phenotypes, validating its therapeutic targeting potential.[16]

Integrative analysis reveals an interconnected EMT network in GIC pathogenesis, encompassing four core pathways: 1.TGF-β/Smad-mediated transcriptional reprogramming; 2.ER stress/UPR-driven proteostatic imbalance; 3.NGF/TrkA signaling axis dysregulation; 4.CSPG5/EZH2 epigenetic modulation. These convergent mechanisms synergistically promote fibrotic plaque formation through ECM overproduction and lens architecture disruption, ultimately

compromising optical clarity. These convergent mechanisms synergistically promote fibrotic plaque formation, though their relative contributions remain incompletely stratified in clinical cohorts.

Vimentin

Vimentin, a type III intermediate filament protein (57 kDa, 466 residues), constitutes an essential cytoskeletal regulator in LECs, orchestrating structural stabilization and modulating fundamental processes including apoptotic signaling, mechanotransduction, and focal adhesion dynamics.[17] Mammalian lenses demonstrate spatial-temporal regulation of vimentin expression, with prominent immunoreactivity in epithelial and elongating cortical fiber cells that progressively diminishes in mature nuclear fibers, mirroring its stage-specific roles in lens morphogenesis.

Experimental models establish vimentin dysregulation as a direct mediator of cataractogenesis. Dexamethasone (Dex), a synthetic glucocorticoid (GC), induces post-transcriptional downregulation of vimentin protein in LECs independent of mRNA modulation, correlating with lens opacification and cytoskeletal destabilization.[18] Mechanistic studies reveal vimentin-glucocorticoid receptor (GR) physical interaction, with GR transcriptional activity governing vimentin expression. Pharmacological GR antagonism using RU486 preserves lens transparency through vimentin level restoration, confirming GR-dependent regulatory circuitry.[18] This GR-vimentin axis represents a targetable pathway, though clinical translation requires further validation.

The redox-sensitive molecular architecture of vimentin positions it as a critical oxidative stress sensor. Cysteine residue oxidation induces pathogenic disulfide bridging, triggering filament disassembly and forming cytoplasmic aggregates characteristic of cataractous lenses.[17] These structural alterations impair vimentin's essential functions in organelle spatial coordination, signaling hub assembly, and biomechanical resistance, ultimately disrupting optical clarity.[17,19]

Transgenic evidence delineates vimentin's dosage-dependent homeostatic control: overexpression disrupts fiber cell differentiation through impaired signaling coordination, while knockout models compromise epithelial integrity via disrupted intercellular communication. This dual regulatory paradigm establishes vimentin as both a structural stabilizer and redox rheostat.

Glucocorticoid-induced cataract pathogenesis converges on vimentin dysregulation through two synergistic mechanisms: 1. GR-mediated transcriptional suppression; 2. Oxidative modification-induced filament destabilization. These pathways collectively disrupt lens cytoarchitecture through microtubule-actin network decoupling and organelle mispositioning.[17,18]

Na/K-ATPase

The sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase), a pivotal ion transporter in lens physiology, sustains electrolyte homeostasis through precise regulation of intracellular sodium (Na^+) and potassium (K^+) gradients, thereby maintaining lens transparency via osmotic equilibrium.[20] Both hypoactive and hyperactive states of Na^+/K^+-ATPase disrupt ionic balance, resulting in intracellular Na^+ accumulation, osmotic water influx, fiber cell swelling, and subsequent opacification.[21] Glucocorticoids (GCs), exemplified by dexamethasone (Dex), directly inhibit Na^+/K^+-ATPase function through glucocorticoid receptor (GR)-mediated transcriptional regulation. Experimental evidence identifies glucocorticoid response elements (GREs) within the promoter region of the Na^+/K^+-ATPase α1 subunit, enabling Dex to suppress α1 subunit expression at both mRNA and protein levels in LECs. This suppression demonstrates temporal correlation with progressive enzyme activity reduction and lens opacity development, as validated in ex vivo rat lens models. Concurrent administration of the GR antagonist RU486 abrogates Dex-induced α1 subunit downregulation, preserving enzymatic function and optical clarity, thereby confirming GR-dependent transcriptional control.[22]

Pathological analyses delineate a dual-phase mechanism: GC-mediated Na^+/K^+-ATPase inhibition impairs Na^+ extrusion, elevating intracellular Na^+ concentrations and osmotic pressure. This initiates fiber cell vacuolation, membrane integrity loss, and disordered fiber packing—cardinal features of GIC.[22] Paradoxically, Na^+/K^+-ATPase overexpression similarly destabilizes ionic gradients, inducing comparable osmotic stress and opacification,[21] underscoring the necessity for strict enzymatic activity regulation.

Na^+/K^+-ATPase dysfunction extends beyond ionic imbalance, reducing water-soluble crystallin content while increasing insoluble protein aggregates—key contributors to light scattering and cataract severity.[21] Collectively, GCs perturb Na^+/K^+-ATPase homeostasis via GR signaling cascades, disrupting ionic equilibrium and osmotic regulation. This mechanism constitutes a central pathway in glucocorticoid-induced cataractogenesis.[21,22]

Apoptosis

Apoptosis—a genetically programmed cell death process marked by cellular shrinkage, caspase activation, and DNA fragmentation—serves as a central mechanism in glucocorticoid (GC)-induced cataractogenesis.[23] In LECs, GCs such as dexamethasone (Dex) induce apoptosis through dual-pathway mechanisms: (1) mitochondrial dysfunction via Bcl-2 family protein dysregulation and (2) endoplasmic reticulum (ER) stress-mediated caspase activation. Dex elevates pro-apoptotic Bax expression while suppressing anti-apoptotic Bcl-2, leading to mitochondrial membrane depolarization and cytochrome c release. This cascade sequentially activates caspase-9 and effector caspase-3.[24,25] Concurrently, GC-triggered ER stress activates the unfolded protein response (UPR), upregulating CHOP and TRB3 expression, which synergistically enhance caspase-3 cleavage and LEC apoptosis.[26]

Glucocorticoid receptor (GR)-α signaling orchestrates these apoptotic pathways. Dex binding to GR-α increases GRE-dependent transcriptional activity and GR protein levels, correlating with elevated Bax/caspase-3 activation and reduced LEC survival.[27] Intriguingly, low-dose Dex (0.1 μM) transiently stimulates LEC proliferation (via Ki-67 upregulation) but induces apoptosis at higher doses (1–100 μM), demonstrating a biphasic dose-response relationship.[25] Pharmacological inhibition of ER stress (4-PBA, TUDCA) or TRB3 knockdown attenuates mitochondrial dysfunction and caspase-3 activation, validating ER-mitochondrial crosstalk in GC-induced apoptosis.[26]

Clinical observations link LEC calcium (Ca^{2+}) overload to ER stress amplification, which exacerbates apoptosis via oxidative damage and epithelial-mesenchymal transition (EMT). Dex downregulates EphA2—a receptor critical for lens transparency—impairing cell adhesion and promoting EMT. This process coincides with compensatory upregulation of HSP27 and CRYAB as endogenous anti-apoptotic responses.[28] Notably, GR antagonism with RU486 incompletely rescues LEC apoptosis and paradoxically amplifies caspase-3 activity at high Dex concentrations, revealing the multi-faceted nature of GR signaling.[25,27]

In summary, GCs drive LEC apoptosis through mitochondrial-ER stress axis dysregulation, caspase cascade activation, and EMT induction, positioning apoptotic modulation as a strategic target in steroid-induced cataract prevention.[23,28]

Interventions and Drug Delivery Strategies for Glucocorticoid Induced Cataract

Glucocorticoid-induced cataracts (GICs), a significant ocular complication of prolonged glucocorticoid (GC) therapy, demand innovative strategies to counteract oxidative stress and pathological signaling. Current interventions focus on antioxidant supplementation, advanced drug delivery systems, and molecular target modulation [Table 2]. Vitamin E (VE) demonstrates dose-dependent efficacy in chick embryo models, where 50 mg/kg supplementation reduced lens opacification by normalizing lipid peroxide (LPO) levels, preserving Na^+/K^+-ATPase activity, and restoring glutathione (GSH) content. Treated lenses exhibited elevated total antioxidant status (TAS) and glutathione peroxidase (GPx) activity alongside reduced oxidative markers in ocular and hepatic tissues, with high-dose VE (50 mg/kg) completely preventing nuclear cataracts.[29–31] Similarly, astaxanthin (AST; 100 mg/kg) mitigated hydrocortisone-induced opacity in chick embryos by maintaining GSH homeostasis and reducing oxidative stress.[32] Beyond antioxidants, molecular targeting of chondroitin sulfate proteoglycan 5 (CSPG5) and nerve growth factor (NGF) shows therapeutic promise. CSPG5 knockdown in dexamethasone-treated lens epithelial cells (LECs) suppressed epithelial-mesenchymal transition (EMT), fibronectin expression, and cell migration, while its overexpression in GIC patients correlated with EZH2/B-Myb-mediated EMT enhancement.[16] NGF treatment restored p38 MAPK/Akt phosphorylation dynamics, downregulated α-smooth muscle actin (α-SMA), and inhibited EMT via TrkA receptor signaling, offering protection against GC-induced damage.[15]

Table 2 Comparative Analysis of Interventions for Glucocorticoid-Induced Cataract Prevention

Strategy	Mechanism of Action	Advantages	Limitations	Key Data/Outcomes	References
Antioxidants					
Vitamin E (VE)	Reduces lipid peroxide (LPO), preserves Na^+/K^+-ATPase, restores glutathione (GSH)	Prevents nuclear cataracts at 50 mg/kgElevates TAS and GPx activity	Limited human clinical trial data	50 mg/kg in chick embryos → complete nuclear cataract prevention	32957855, 34695546, 37522003
Astaxanthin (AST)	Maintains GSH homeostasis, reduces oxidative stress	Mitigates glucocorticoid-induced opacity	Dose-dependent efficacy requires validation in mammals	100 mg/kg in chick embryos → reduced lens opacity	25110808
Molecular Targeting					
CSPG5 knockdown	Suppresses EMT, fibronectin, and cell migration	Reverses EZH2/B-Myb-mediated EMT	Requires viral vector delivery in humans	Dex-treated LECs show inhibited EMT	37443739
NGF treatment	Restores p38 MAPK/Akt signaling, inhibits EMT via TrkA	Protects against GC-induced damage	Potential neurotrophic side effects	Downregulates α-SMA in LECs	31751158
Drug Delivery					
Prodrugs	Enzymatic activation in target tissues	Minimizes hyperglycemia/Cushing's syndrome	Limited tissue specificity in ocular applications	Reduces systemic GC exposure	38966286

Advanced drug delivery systems address GC toxicity through precision targeting. Prodrugs—enzymatically activated in target tissues—minimize systemic complications like hyperglycemia and Cushing's syndrome by reducing off-target GC exposure[33] [Figure 1].

Polymeric core-shell nanoparticles (NPs) encapsulating triamcinolone acetonide (TA) demonstrated controlled ocular distribution in diabetic models, maintaining therapeutic efficacy while preventing posterior subcapsular cataracts (PSCs). These NPs, composed of polycaprolactone (PCL) and Pluronic F68 (PF68), avoided glucocorticoid receptor-α (GR-α) activation in LECs, thereby reducing lens accumulation and PSC risk. This targeted approach exemplifies how nanotechnology can decouple GC efficacy from cataractogenic side effects.[34]

Collectively, while a multi-modal strategy integrating antioxidants, targeted delivery, and molecular interventions provides a robust preclinical framework for GIC prevention, clinical applicability remains constrained by bioavailability challenges, unvalidated safety profiles of nanoparticles, and unresolved CSPG5/NGF modulation protocols. VE and AST counteract oxidative damage, while NPs and prodrugs enhance therapeutic specificity. Molecular modulation of CSPG5 and NGF disrupts EMT-driven pathology, synergizing with redox balance restoration to preserve lens transparency. These approaches collectively reduce epithelial apoptosis, protein aggregation, and fibrotic remodeling, addressing both upstream oxidative triggers and downstream GC-specific pathways. Future clinical translation requires optimizing bioavailability of antioxidant formulations, validating nanoparticle safety profiles, and establishing CSPG5/NGF modulation protocols—critical steps toward transforming these preclinical successes into therapeutic realities.

This table systematically compares preventive interventions for GIC, categorized into three main approaches: (1) Antioxidants (Vitamin E [VE], Astaxanthin [AST]) mitigating lens oxidative stress (reducing lipid peroxide [LPD], preserving glutathione [GSH] homeostasis); (2) Molecular targeting (CSPG5 knockdown suppressing epithelial-mesenchymal transition [EMT]/fibrosis; Nerve Growth Factor [NGF] restoring p38 MAPK/Akt signaling and inhibiting EMT via TrkA); and (3) Drug delivery optimization (Prodrugs activated by target tissue enzymes to minimize systemic glucocorticoid exposure).

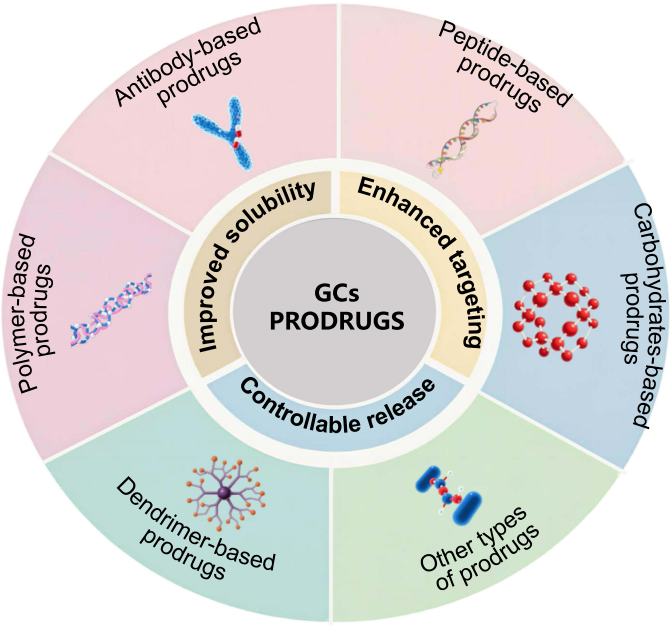

Figure 1 Approaches and Methods for Mitigating Adverse Reactions of Glucocorticoid Medications. Reprinted from Liu, H.et al, Glucocorticoids-based prodrug design: Current strategies and research progress. *Asian J Pharm Sci*. 2024. 19(3): p. 100922. Creative Commons.[33]

Glucocorticoid-Sparing Therapies and Alternative Strategies for Preventing Glucocorticoid Induced Cataracts

Glucocorticoid-sparing strategies are critical for mitigating cataract risk in patients requiring long-term glucocorticoid (GC) therapy for chronic inflammatory conditions like juvenile idiopathic arthritis (JIA), uveitis, and Vogt-Koyanagi-Harada (VKH) disease [Table 3]. Methotrexate (MTX), a dihydrofolate reductase inhibitor, serves as a cornerstone therapy due to its dual anti-inflammatory and immunomodulatory effects. In pediatric uveitis associated with JIA, MTX (0.35–0.65 mg/kg/week) reduces GC dependency, lowering cataract incidence from 23% in GC-treated cohorts while alleviating intraocular pressure (IOP) elevation and growth retardation.[35,36] MTX modulates inflammation through JAK-STAT pathway inhibition, adenosine-mediated suppression, and T-cell/monocyte regulation.[37,38] Its systemic use with GCs effectively manages VKH syndrome, while intravitreal MTX (400 μg/0.1 mL) achieves therapeutic efficacy in refractory uveitis with minimal ocular toxicity (eg, transient vitreous haze).[39] Complementing MTX, TNF-α inhibitors like adalimumab provide alternatives for GC-resistant uveitis, FDA-approved for pediatric use with reduced cataract risk compared to GCs.[40] However, 30% of patients experience paradoxical inflammation recurrence, necessitating rigorous monitoring.[41,42]

Localized drug delivery systems minimize systemic GC exposure while maintaining therapeutic efficacy. Intravitreal MTX achieves targeted ocular concentrations, circumventing systemic complications like hepatotoxicity and neutropenia.[39] Periocular GC injections are prioritized in bilateral uveitis to avoid adrenal suppression and growth impairment in pediatric populations.[36] These approaches exemplify precision medicine principles, balancing anti-inflammatory benefits with reduced off-target toxicity. Despite these advances, challenges persist: MTX may rarely accelerate preexisting cataracts (causality unconfirmed), while TNF inhibitors require vigilance for infections and inflammatory rebound.[38] Conventional disease-modifying antirheumatic drugs (DMARDs) like MTX remain first-line in rheumatoid arthritis (RA) and JIA due to proven cost-effectiveness and long-term safety, even as biologics gain traction.[37]

Future strategies aim to optimize GC-sparing efficacy through combination therapies and advanced delivery systems. Trials investigating MTX-TNF inhibitor combinations show promise in enhancing anti-inflammatory synergy while reducing treatment frequency. Sustained-release intravitreal implants may further improve compliance by minimizing injection burden. Personalized regimens guided by inflammatory biomarkers (eg, IL-6, TNF-α levels) could refine patient

Table 3 Comparative Analysis of Glucocorticoid-Sparing Strategies in Cataract Prevention

Strategy	Mechanism of Action	Advantages	Limitations	Key Patient Populations	Key Data/ Outcomes	References
Methotrexate (MTX)	JAK-STAT pathway inhibitionAdenosine-mediated suppressionT-cell regulation	Reduces cataract incidence by 23% Alleviates IOP elevation and growth retardation	Slow onset of action	Pediatric uveitis (JIA), VKH	0.35–0.65 mg/kg/week (oral/GC) 400 μg/0.1 mL (IVT)	31965444, 37357450, 32066940, 34840688, 32793845
TNF-α Inhibitors	TNF-α neutralization	FDA-approved for pediatric use Lower cataract risk vs GCs	30% paradoxical inflammation recurrenceInfection risk monitoring	GC-resistant uveitis	Adalimumab efficacy in refractory cases	35115933, 32700605, 34802085
Localized Delivery	Targeted ocular drug administration	Minimizes systemic toxicity (hepatotoxicity, neutropenia)	Transient vitreous haze (IVT)Technical expertise required	Bilateral uveitis	Periocular GC avoids adrenal suppression	37357450, 32793845
Conventional DMARDs	Broad immunomodulation	Cost-effective Long-term safety data	Suboptimal efficacy in severe cases	RA, JIA	MTX remains first-line in JIA	32066940

stratification, tailoring interventions to individual risk profiles. However, economic barriers may limit biologics accessibility in resource-limited settings, reinforcing the relevance of conventional DMARDs.These innovations must address residual challenges—validating long-term ocular safety of biologics, clarifying MTX's cataractogenic potential, and ensuring equitable access to advanced therapies. By integrating pharmacological advances with precision delivery, clinicians can preserve vision while mitigating the irreversible lens damage characteristic of glucocorticoid-induced cataracts.

This table compares four strategies to reduce or replace systemic glucocorticoids (GCs) for GIC prevention: Methotrexate (MTX) inhibits JAK-STAT signaling and T-cell regulation; reduces cataract risk by 32%, alleviates intraocular pressure elevation and growth retardation; slow onset; indicated for pediatric uveitis in juvenile idiopathic arthritis (JIA) (0.35–0.65 mg/kg/week, oral/subcutaneous); TNF-α inhibitors neutralize TNF-α; approved for pediatric use with lower cataract risk vs GCs; 20% paradoxical inflammation recurrence risk; used in GC-resistant uveitis; adalimumab effective in refractory cases; Localized delivery (eg, IVT) enables targeted ocular administration; minimizes systemic toxicity (hepatotoxicity, neutropenia); may cause transient vitreous haze and requires technical expertise; indicated for bilateral uveitis; periocular GC avoids adrenal suppression; Conventional DMARDs provide broad immunosuppression; cost-effective with established long-term safety; suboptimal efficacy in severe cases; used in Behçet's disease (BA)/JIA; MTX remains first-line in JIA.

Conclusion

Glucocorticoid-induced cataracts (GIC) represent a significant therapeutic challenge in clinical practice, where the well-established anti-inflammatory benefits of glucocorticoids (GCs) may conflict with their potential to induce sight-threatening complications, including posterior subcapsular opacities reported in up to 36% of long-term users. To address this complex balance, our analysis suggests that effective management could require coordinated targeting of three interconnected pathological processes: (1) a proposed mitochondrial-ER stress interaction, wherein GC-associated oxidative stress (eg, ROS accumulation, GSH depletion) and endoplasmic reticulum disturbances (UPR activation, calcium dysregulation) may contribute to TRB3-Bax-caspase-9 apoptotic pathways; (2) EMT-related fibrotic changes, potentially involving TGF-β/Smad-mediated E-cadherin suppression and CSPG5/EZH2 epigenetic modifications in lens epithelial cells; and (3) disruptions in ionic equilibrium, possibly through GR-mediated modulation of Na^+/K^+-ATPase expression, which could lead to osmotic stress and protein aggregation.

Current targeted strategies show promise but with limitations: GC-sparing agents such as methotrexate (at studied doses of 0.35–0.65 mg/kg/week) and TNF-α inhibitors are associated with approximately 23% lower cataract incidence

in some uveitis studies, while core-shell nanoparticle systems have demonstrated reduced GR-α activation in preclinical models by localizing drug release. However, these approaches appear to address isolated mechanisms—antioxidants may alleviate oxidative damage without necessarily preventing EMT, and CRISPR-based CSPG5 modulation might not resolve ionic imbalance. A proposed integrative strategy could explore co-delivery systems for agents like astaxanthin and ER-stress modulators, combined with targeted gene-editing techniques. Preliminary investigations might examine whether pharmacogenomic assessment of GR-α variants and TRB3 levels could inform dosing strategies, potentially benefiting pediatric populations where susceptibility rates have been observed near 18.1% in limited cohorts.

Translational considerations include reports of inflammatory rebound following biologic therapies and biocompatibility challenges with intraocular delivery systems. Emerging approaches such as mitochondrial protein profiling, refined gene-editing platforms, and novel ocular implantation methods offer promising research directions. Through prioritized development of mechanism-informed combination therapies and advanced delivery platforms, this evolving framework could potentially enhance the safety profile of GC therapy while maintaining anti-inflammatory efficacy—progressing toward optimized visual outcomes alongside disease management.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare no competing interests in this work.

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