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Hypothesis

The Link Between Caveolae, Metabolic Syndrome, and Cataractogenesis: A Mechanistic Hypothesis

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Abstract

Cataract, the leading cause of blindness worldwide, results from progressive lens opacification driven by oxidative stress, protein aggregation, and metabolic dysregulation. While aging remains the primary risk factor, systemic metabolic disorders, particularly metabolic syndrome (MetS), are increasingly recognized as major contributors to cataractogenesis. MetS, a constellation of central obesity, hypertension, hyperglycemia, and dyslipidemia, exacerbates oxidative stress, inflammation, and metabolic imbalance, thereby accelerating lens degeneration. A novel and largely unexplored mechanism underlying MetS-induced cataract involves dysfunction of caveolae, cholesterol-rich plasma membrane microdomains composed of caveolin proteins. Caveolae are highly expressed in lens epithelial cells and play essential roles in nutrient transport, insulin signaling, lipid trafficking, and oxidative stress regulation. Disruption of caveolae integrity in MetS impairs insulin receptor, PI3K/Akt signaling, reduces glucose uptake, and compromises lens cell survival. In parallel, loss of caveolae function diminishes antioxidant buffering capacity and alters lipid homeostasis, promoting lipid peroxidation, membrane instability, and crystallin aggregation. These processes collectively establish a pro-cataractogenic microenvironment, linking systemic metabolic dysfunction to lens pathology through a unique membrane-based pathway. Clinically, cataracts in patients with MetS often present with similar visual symptoms to age-related forms but demonstrate earlier onset and faster progression, especially under poorly controlled metabolic conditions. Recognition of caveolae-dependent pathways as mediators of this process not only provides a new perspective on cataract pathophysiology but also opens the possibility of integrated co-treatment strategies. Therapeutic strategies that restore caveolae function through molecular interventions, antioxidant therapy, and systemic metabolic control may offer a unified approach to slowing both MetS progression and cataract development. Elucidating this unexplored mechanism holds promise for the design of innovative, dual-targeted therapies for patients with coexisting metabolic and ocular disease.

Keywords: Caveolae; MetS; cataract; cataractogenesis; lens

1. Introduction

The human lens is a remarkable, transparent, biconvex structure situated within the eye, essential for focusing light onto the retina to produce sharp images, a process known as accommodation, despite the process of shape alteration remains unclear [1]. This dynamic structure can change shape to adjust focus for both near and distant vision [2,3]. The lens is avascular and highly organized, composed of three primary components: the capsule, the lens epithelium, and the lens fibers. The lens capsule, a thick, elastic basement membrane, surrounds the entire lens and supports the underlying anterior lens epithelial cells (LECs), a single layer of cuboidal cells responsible for active metabolism [4]. These cells maintain transparency by mediating protein synthesis, ion transport, ATP generation, and antioxidant production.

The bulk of the lens consists of tightly packed, elongated lens fibers filled with crystallin proteins, arranged in concentric layers in keeping transparent and correct refraction. As the lens ages, the central nucleus becomes increasingly compact and rigid, contributing to presbyopia, an age-

related loss of accommodative ability by changes in lens biomechanics [5]. Thus, the dual roles of the lens, refraction and accommodation, are critical for high-quality vision.

Cataracts, the leading cause of blindness worldwide [6], result from the opacification of the normally clear lens. This condition arises when the organization of lens fibers is disrupted or when crystallin proteins denature and aggregate. While age is the predominant risk factor for cataract formation, other contributors include ultraviolet radiation, smoking, diabetes, trauma, and long-term use of certain medications such as corticosteroids [7]. Cataractogenesis involves several overlapping mechanisms, including protein misfolding, oxidative stress, pigment deposition, and altered metabolism. Cataracts are typically categorized as age-related, traumatic, or secondary to systemic or ocular conditions, with diabetes being a particularly well-established risk factor [8] due to its metabolic impact on the lens. Cataractogenesis involves overlapping mechanisms.

Because of its avascularity, the lens has a unique metabolic pattern. Recent research has highlighted a strong association between metabolic disorders, particularly metabolic syndrome (MetS) [9], and cataract development. MetS is characterized by a cluster of interrelated conditions, including abdominal obesity, hypertension, elevated fasting glucose, hypertriglyceridemia, and low HDL cholesterol. This syndrome significantly increases the risk for cardiovascular disease, type 2 diabetes, and stroke. At the cellular level, many MetS-related molecules localize to caveolae—specialized, flask-shaped plasma membrane invaginations enriched in cholesterol, glycosphingolipids, and caveolin proteins [10,11]. Caveolae are abundant in multiple cell types, including LECs [12], and regulate signaling, endocytosis, mechanotransduction, lipid metabolism, and molecular trafficking [13].

Emerging study implies that caveolae may play a key role in metabolic disorder-induced cataracts [12]. Disrupted caveolar function may impair lens metabolism and transport, driving oxidative injury and opacification. Classic work by Zhang and Augusteyn [14–16] demonstrated concentric gradients of lens metabolism, with glucose levels correlating with activity. However, the precise mechanisms linking MetS and caveolae dysfunction to cataractogenesis remain unclear.

This commentary synthesizes current findings on the relationship between MetS and cataracts, with emphasis on the potential role of caveolae in LECs. Exploring this connection may provide new insights into the molecular basis of cataractogenesis and identify targets for preventive or interventional strategies.

2. The Distinct Patterns of MetS Components Associated with Cataract

MetS and metabolic dysfunction-associated fatty liver disease (MAFLD) [17] are systemic disorders linked to cataract development through shared metabolic and inflammatory pathways [9]. The cluster of MetS features, including abdominal adiposity, diabetes, and hypertension, has been strongly associated with increased cataract risk, particularly in men aged ≤ 65 years [18]. Cataract prevalence rises stepwise with the accumulation of MetS components [19]. The pathogenic mechanisms include insulin resistance, oxidative stress, chronic inflammation, and dyslipidemia, which together promote lens protein damage and opacification [20,21]. Biochemical alterations include advanced glycation end products (AGEs) that impair transparency [22]; lipid peroxidation and reduced glutathione that weaken antioxidant defense and structural stability [23]; elevated cytokines [24], and reactive oxygen species (ROS) [25] that disrupt lens homeostasis. These processes are amplified by overlapping risk factors such as obesity, diabetes, hypertension, and aging. Recognizing cataracts as an extrahepatic manifestation of systemic metabolic disorders [26] highlights the importance of integrated metabolic and ocular management. Notably, the individual components of MetS contribute differently to cataractogenesis, warranting closer analysis.

2.1. Hyperglycemia- and Diabetes-Induced Cataracts

Although age-related cataracts are most common, diabetes markedly accelerates cataract onset and progression. Diabetic patients have a 3–5-fold higher cataract risk compared with non-diabetic individuals [8], and over 25% of cataract surgery patients have diabetes [27]. Risk increases with both diabetes duration and hyperglycemia severity.

Pathogenesis is multifactorial, with chronic hyperglycemia as the central driver. Key mechanisms include:

a. Epithelial–Mesenchymal Transition (EMT) and Calcification

Hyperglycemia upregulates AKR1B1 and RAGE, inducing EMT in LECs [28]. Calcification of LECs, with hydroxyapatite deposition, reflects osteogenic differentiation via Runx2 and HIF-1 signaling [29].

b. Polyol Pathway Activation

Excess glucose enters the polyol pathway, where aldose reductase converts it to sorbitol [22]. Sorbitol accumulation induces osmotic stress and oxidative imbalance, causing lens swelling and protein aggregation [30].

c. Advanced Glycation End Products (AGEs)

Non-enzymatic glycation generates AGEs, which crosslink crystallins, impair function, and heighten oxidative damage [22].

d. Oxidative Stress and Antioxidant Deficiency

Excess glucose boosts ROS while suppressing antioxidant defenses, particularly glutathione, accelerating protein oxidation and lens opacification [31].

e. bFGF/TGF- β signaling pathways activation

Hyperglycemia can alter bFGF/TGF- β signaling pathways in LECs. Under high-glucose conditions, TGF- β promotes EMT in LECs, with c-Src acting as an upstream regulatory molecule in this process [32].

Risk factors include long diabetes duration, poor glycemic control, older age, female sex, and comorbid hypertension or chronic kidney disease [33,34]. Clinically, diabetic cataracts present with blurred vision, glare, halos, night vision difficulties, and frequent refractive changes.

Optimal management emphasizes tight glycemic control, early ophthalmic screening, and timely cataract surgery. Understanding these mechanisms underscores the importance of preventive strategies in high-risk patients.

2.2. Hypertension-Induced Cataract

Hypertension is an important systemic risk factor for cataract, particularly early-onset opacities. Chronic high blood pressure disturbs vascular and metabolic homeostasis, accelerating ocular degeneration through oxidative stress, vascular impairment, electrolyte dysregulation, systemic inflammation, and metabolic disturbance [35].

- Oxidative stress: Hypertension promotes ROS generation, which damages proteins, lipids, and membranes in the avascular lens [36].
- Microvascular impairment: Reduced oxygen and nutrient diffusion further compromises lens metabolism [37].
- Electrolyte imbalance: Altered calcium and sodium homeostasis disrupt hydration and protein stability [38].
- Inflammation: Circulating mediators distort protein conformation and accelerate degeneration [37].

Epidemiology links hypertension with posterior subcapsular cataracts [39], while Na⁺/K⁺-ATPase dysregulation may underlie cortical opacities [40]. Coexistence with diabetes, dyslipidemia, obesity, or kidney disease amplifies cataract risk [41].

Clinical manifestations mirror other cataract types—blurred vision, glare, poor night vision, and refractive changes [42]. Managing systemic risk factors (blood pressure, glucose, lipids, smoking, activity) and possibly antioxidants may delay cataract progression [43].

Thus, the hypertension-induced cataract should be considered not only as ocular pathology but also as a systemic marker of vascular and metabolic imbalance.

2.3. Hyperlipidemia- and Obesity-Induced Cataract

Hyperlipidemia and obesity are increasingly recognized as cataract risk factors through oxidative stress, lipid peroxidation, chronic low-grade inflammation, and metabolic dysregulation [43]. Hyperlipidemia: Lipid peroxidation compromises lens membrane integrity, while abnormal lipid–protein binding destabilizes crystallins [44]. Recent evidence shows oxidized crystallin aggregates scatter light and promote cataract [45]. Obesity: Adipose tissue releases pro-inflammatory cytokines (TNF- α , IL-6), disrupting homeostasis [46]. Obesity also promotes insulin resistance and hyperglycemia [47], further impairing metabolism. Risk factors include elevated LDL, triglycerides, central obesity, type 2 diabetes, hypertension, and sedentary lifestyle [48]. These factors synergize to intensify oxidative injury and structural damage.

Clinically, cataracts manifest as in other forms, but progression is often accelerated in patients with poor metabolic control [49]. Recognizing obesity and dyslipidemia as modifiable risks underscores the role of lifestyle and systemic metabolic care in vision preservation.

3. Caveolae Dysfunction: A Molecular Link Between MetS and Cataracts

Caveolae dysfunction has increasingly been recognized as a critical molecular mechanism linking MetS to cataract development. Emerging evidence indicates that MetS contributes significantly to ocular pathology, particularly the pathogenesis of cataracts [9]. Caveolae are highly abundant in LECs, and their dysfunction impairs essential cellular processes, creating a microenvironment that favors lens opacification [12].

Caveolae play a central role in regulating metabolic processes, and their dysfunction is implicated in the development of MetS. Many key molecules involved in MetS components, including insulin signaling, lipid transport, and nutrient uptake, are co-localized within caveolae. A reduction in plasma membrane caveolae impairs the uptake of glucose, lipids, and amino acids, thereby contributing to metabolic dysregulation and the onset of MetS [10]. In MetS, altered caveolin-1 expression disrupts insulin receptor signaling and downstream PI3K/Akt pathways [50], weakens antioxidant defenses through glutathione depletion [51], and impairs glucose uptake, thereby compromising lens cell survival.

Experimental evidence further demonstrates that oxidative stress can directly damage caveolae. Hydrogen peroxide (H₂O₂) stimulation redistributes caveolin, promotes caveolae disassembly, and

reduces caveolin expression in human LECs [52]. Such alterations promote apoptosis and accelerate cataract formation.

Beyond signaling, caveolae play a pivotal role in lipid homeostasis. In MetS, dyslipidemia combined with caveolae dysfunction enhances lipid accumulation and peroxidation within lens cells [53], destabilizing membrane integrity and transparency. Moreover, as caveolae normally buffer ROS [53], their dysfunction diminishes antioxidant capacity and exacerbates oxidative stress—a central driver of protein aggregation and lens opacification.

Clinically, patients with MetS and associated caveolae dysfunction are predisposed to earlier onset and faster progression of cataracts [9]. Thus, caveolae dysfunction represents a mechanistic bridge between MetS and cataractogenesis, converging impaired signaling, disrupted lipid trafficking, and elevated oxidative stress. Recognition of this link underscores the importance of integrated metabolic and ocular care and highlights caveolae as a promising therapeutic target for cataract prevention and management.

4. Conclusions and Future Perspectives

Lens transparency critically depends on the maintenance of redox balance and osmotic homeostasis. Disrupted metabolic processes in MetS, particularly those associated with caveolae dysfunction, compromise these protective mechanisms and thereby promote cataract formation. Loss of caveolae integrity not only impairs cellular signaling and nutrient transport but also triggers inflammatory cascades that further destabilize lens homeostasis. Caveolae-dependent metabolic pathways, therefore, represent a molecular bridge linking systemic metabolic dysfunction, such as that observed in MetS, with cataract development. Targeting these pathways holds promise for the development of innovative strategies to prevent or manage cataracts in vulnerable populations.

Despite the growing evidence, direct *in vivo* demonstration of caveolae or caveolin dysfunction in LECs during cataractogenesis remains scarce. Future research should employ high-resolution imaging techniques to characterize caveolae structure and dynamics in cataractous lenses. In addition, animal models with caveolin-1 knockout or overexpression under MetS conditions could yield critical mechanistic insights into the causal role of caveolae in lens pathology. From a therapeutic perspective, interventions designed to restore or enhance caveolae function [11], including targeted molecular therapies, antioxidant supplementation, and lifestyle modifications, may offer viable approaches to delay or prevent cataract development in at-risk populations.

Overall, the integration of mechanistic, imaging, and therapeutic approaches focused on caveolae in the lens has the potential to open new avenues for understanding and mitigating cataract formation in the context of MetS.

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