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New Targets For Vascular Remodeling: Evaluating The Role Of Sulfated Glycosaminoglycans In The Prevention Of In-Stent Restenosis (Literature Review)

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Abstract

Percutaneous coronary intervention (PCI) with stenting is the cornerstone of revascularization in ischemic heart disease. However, in-stent restenosis (ISR), a pathobiological response to vascular injury, remains a significant limitation, affecting a substantial subset of patients and necessitating repeat interventions. This review aims to critically analyze the multifactorial pathogenesis of ISR, focusing on the pivotal roles of inflammation, smooth muscle cell (SMC) phenotype switching, and extracellular matrix (ECM) dysregulation. Moving beyond conventional anti-proliferative strategies, we explore a novel pathogenetic approach centered on the pleiotropic properties of specific sulfated glycosaminoglycans (GAGs)—chondroitin sulfate (CS) and glucosamine sulfate (GS). Traditionally used in osteoarthritis management, these molecules exhibit potent anti-inflammatory, anti-thrombotic, and ECM-modulating effects relevant to vascular pathophysiology. We synthesize evidence from molecular, experimental, and early clinical studies suggesting that CS/GS can inhibit key drivers of ISR, such as versican-CD44-mediated signaling and NF-κB activation. The review also discusses the importance of pharmaceutical-grade purity for clinical translation and positions this approach within the evolving landscape of adjunctive pharmacotherapy for PCI, highlighting its potential to improve long-term vascular patency and patient outcomes.

Keywords: In-stent restenosis, neointimal hyperplasia, vascular remodeling, chondroitin sulfate, glucosamine sulfate, glycosaminoglycans, versican, CD44, percutaneous coronary intervention, personalized cardiology.

1. Introduction: The Persistent Challenge Of In-Stent Restenosis

Ischemic heart disease (IHD) maintains its status as a leading cause of global morbidity and mortality, driving continuous innovation in treatment strategies [1]. The evolution from medical management to surgical bypass and, most prominently, to percutaneous coronary intervention (PCI) has revolutionized coronary revascularization. Modern PCI, primarily employing stent implantation, offers a minimally invasive, highly effective solution for relieving coronary stenosis and alleviating angina symptoms, accounting for the majority of revascularization procedures worldwide [9].

The introduction of drug-eluting stents (DES), coated with anti-proliferative agents like sirolimus or paclitaxel, dramatically reduced the incidence of restenosis compared to bare-metal stents (BMS) by targeting neointimal hyperplasia [11]. Despite this progress, in-stent restenosis (ISR) persists as a clinically relevant complication, with reported rates varying from 3-5% in simple lesions with modern DES to over 30% in complex scenarios (e.g., long lesions, small vessels, diabetes) [10]. ISR typically manifests 6-9 months post-PCI, often requiring repeat revascularization, which increases healthcare costs, procedural risks, and patient anxiety.

The pathophysiology of ISR is complex and multifactorial, representing an exaggerated healing response to the controlled injury induced by balloon inflation and stent struts. It involves a cascade of events: platelet activation and thrombus formation, acute and chronic inflammation, phenotypic modulation and migration of vascular smooth muscle cells (VSMCs), excessive proliferation of these cells, and pathological deposition of extracellular matrix (ECM) components, culminating in neointimal hyperplasia and lumen loss [2, 11]. Current first-line pharmacotherapy—dual antiplatelet therapy (DAPT)—is essential for preventing stent thrombosis but has minimal impact on the biological processes driving late ISR.

While DES effectively suppress VSMC proliferation, they can also impair endothelial healing, potentially leading to late stent thrombosis and require prolonged DAPT. Furthermore, "edge restenosis" and heterogeneous drug distribution remain challenges [11].

Therefore, there is an unmet need for complementary pathogenetic therapies that can safely modulate the vascular healing process, promoting endothelial recovery while simultaneously inhibiting pathological remodeling. This review posits that naturally occurring sulfated glycosaminoglycans, specifically chondroitin sulfate (CS) and its precursor glucosamine sulfate (GS), represent promising candidates for such a role due to their multifaceted bioactivity.

2. Materials And Methods

A systematic narrative review of the literature was conducted to identify relevant studies on the pathogenesis of ISR and the biological effects of CS/GS in cardiovascular contexts. Electronic databases PubMed/MEDLINE, CyberLeninka, eLibrary, and Google Scholar were searched for articles published between 2018 and 2024, with seminal older publications also included. The search strategy employed a combination of keywords and MeSH terms: ("in-stent restenosis" OR "neointimal hyperplasia") AND ("chondroitin sulfate" OR "glucosamine sulfate" OR "glycosaminoglycans") AND ("inflammation" OR "vascular smooth muscle cell" OR "extracellular matrix"). Additional searches included "versican," "CD44," and "NF-kappa B." Inclusion criteria were: open-access full-text articles, studies in English or Russian, experimental (in vitro, in vivo) and clinical research, and relevant review articles. Excluded were non-peer-reviewed sources and articles not directly related to vascular biology or the specified compounds. Identified publications were screened by title and abstract, and selected full texts were analyzed to extract data on molecular mechanisms, experimental models, and clinical correlations.

3. The Pathophysiological Cascade Of In-Stent Restenosis: A Multi-Stage Process

Understanding ISR requires a timeline-based perspective of the vascular response to injury.

3.1. Phase I: Thrombosis and Early Inflammation (Minutes to Days). Immediate endothelial denudation and medial injury expose the subendothelial matrix, triggering platelet adhesion, activation, and aggregation, forming a provisional fibrin-rich thrombus. This acts as a scaffold and a reservoir of cytokines and growth factors (e.g., PDGF, TGF-β). Concomitantly, damaged cells release damage-associated molecular patterns (DAMPs), initiating a robust inflammatory response. Neutrophils and monocytes infiltrate the vessel wall, with monocytes differentiating into macrophages [2, 5].

3.2. Phase II: Cellular Proliferation and Migration (Days to Weeks). This is the critical phase for

therapeutic intervention. Activated macrophages and resident cells release mitogens and chemoattractants. VSMCs in the media undergo a phenotypic switch from a "contractile" to a "synthetic" state, characterized by reduced expression of contractile proteins (α-SMA) and increased proliferation, migration into the intima, and secretion of ECM components. This migratory/proliferative wave is the primary source of neointimal cells [5, 11].

3.3. Phase III: ECM Remodeling and Maturation (Weeks to Months). The migrated VSMCs and myofibroblasts synthesize vast amounts of ECM, predominantly collagens (types I and III) and proteoglycans. This ECM expansion, not just cellular hyperplasia, contributes significantly to final lumen loss. The neointima gradually matures and stabilizes, but excessive and disorganized ECM deposition leads to a fibrotic, stenotic lesion [6, 11].

A key proteoglycan in this process is **versican,** a large chondroitin sulfate proteoglycan. Its expression surges in the provisional ECM following injury. Versican interacts with cell-surface receptors like CD44 and promotes VSMC migration, proliferation, and leukocyte retention, acting as a central orchestrator of the restenotic process [6, 7].

4. Chondroitin Sulfate And Glucosamine Sulfate: From Joints To Arteries

CS and GS are natural amino-sugars, essential components of proteoglycans in connective tissues like cartilage. Their oral supplements are widely used for osteoarthritis symptom management. Beyond their chondroprotective effects, extensive research reveals systemic anti-inflammatory and vascular-modulating properties [3, 4].

4.1. Molecular Pharmacology. GS is a precursor for the biosynthesis of GAGs, including CS. CS chains, when sulfated, carry a high negative charge, enabling interactions with a wide array of proteins, growth factors, and receptors. Their biological activity is highly dependent on their sulfation pattern and degree of polymerization.

4.2. Mechanisms Relevant to ISR Pathogenesis. The proposed protective mechanisms of high-purity CS/GS against ISR are multi-targeted:

* **Inhibition of Pro-inflammatory Signaling:** CS can bind to and modulate the activity of the cell-surface receptor CD44. This interaction competitively inhibits the binding of pro-inflammatory ligands like versican or hyaluronan fragments to CD44. Downstream, this stabilizes IκBα, the endogenous inhibitor of the master transcription factor NF-κB. Suppressed NF-κB nuclear translocation leads to decreased transcription of genes encoding potent inflammatory cytokines (IL-1β, IL-6, TNF-α) and adhesion molecules (VCAM-1, ICAM-1) [3, 10, 11].

* **Modulation of VSMC Phenotype and Migration:** By interfering with the versican-CD44 axis and reducing the inflammatory milieu, CS/GS can attenuate the phenotypic switching of VSMCs from contractile to synthetic, thereby limiting their proliferative and migratory potential observed in experimental models [7, 11].

* **Promotion of Endothelial Integrity:** Some sulfated GAGs, including chondroitin-4-sulfate, have been shown to enhance endothelial cell adhesion, reduce apoptosis, and promote endothelial progenitor cell function. Faster and more complete re-endothelialization ("endothelial healing") after stent deployment is a key factor in reducing both thrombotic risk and the stimulus for underlying SMC proliferation [11].

* **Mild Antithrombotic and Anticoagulant Effects:** CS exhibits heparin-like properties, potentiating the action of antithrombin III and exhibiting anti-factor Xa activity. This could provide complementary local antithrombotic protection at the stent site, potentially allowing for optimization of systemic anticoagulant regimens [18].

4.3. The Critical Importance of Purity. The biological effects of CS/GS are highly sensitive to product quality. Impurities, especially residual proteins from animal cartilage sources, can act as immunogens, triggering pro-inflammatory responses that could paradoxically exacerbate vascular inflammation and neointimal growth. Therefore, any clinical application for cardiovascular indications would mandate the use of highly purified, pharmaceutical-grade, and well-characterized preparations [12].

5. Clinical And Experimental Evidence: Translating Concept To Practice

While direct large-scale RCTs on CS/GS for ISR prevention are lacking, converging evidence from related fields supports the biological plausibility of this approach.

* **Experimental Models:** Studies in animal models of arterial injury (balloon angioplasty in rodents or rabbits) have demonstrated that systemic or local administration of CS reduces neointimal area, macrophage infiltration, and collagen deposition. These effects are correlated with reduced expression of versican, TNF-α, and MMP-9 in the vessel wall [7, 11].

* **Biomarker Studies in Humans:** Epidemiological and small interventional studies in osteoarthritis patients have shown that chronic supplementation with CS/GS is associated with a significant reduction in systemic inflammatory biomarkers, such as high-sensitivity C-reactive protein (hs-CRP), IL-6, and COMP (cartilage oligomeric matrix protein), which is also involved in vascular calcification [4]. Lowering this systemic

inflammatory burden could be beneficial in the context of PCI.

* **Synergistic Potential:** Research by Gromova et al. [8] suggests synergistic interactions between GS and non-steroidal anti-inflammatory drugs (NSAIDs), indicating a potential for combination therapy with lower doses of NSAIDs, thereby reducing their gastrointestinal and renal toxicity while maintaining anti-inflammatory efficacy in the post-PCI period.

6. Discussion: Positioning Gag-Based Therapy In Modern Interventional Cardiology

The proposed use of CS/GS represents a paradigm shift from purely cytotoxic/anti-proliferative strategies (as with DES) towards a **pathogenetic modulation** of the healing response. The ideal post-PCI adjuvant would simultaneously calm inflammation, discourage pathological VSMC activity, and encourage endothelial recovery. CS/GS, through their pleiotropic mechanisms, appear to target this exact triad.

This approach could be particularly relevant in several clinical scenarios:

1. **As an adjunct to DES:** To mitigate the delayed endothelialization associated with potent anti-proliferative drugs, potentially allowing for shorter durations of DAPT.

2. **In high-risk ISR patients:** Such as those with diabetes, chronic kidney disease, or complex anatomy, where baseline inflammation and remodeling are exaggerated.

3. **With bioresorbable vascular scaffolds (BVS):** Where modulating the inflammatory response to the degrading polymer could be crucial.

Challenges and future directions are clear. First, rigorous **pharmacokinetic and dosing studies** are needed to determine optimal regimens (oral vs. potentially local delivery via coated stents) and treatment duration (likely covering the critical 1-3 month remodeling window). Second, well-designed **randomized controlled trials (RCTs)** with clinical endpoints (e.g., target lesion revascularization, late lumen loss on angiography or intravascular imaging) are essential to prove efficacy and safety in the cardiac population. Finally, research should focus on identifying **biomarkers** (e.g., specific CS epitopes, versican fragments) that could help personalize this therapy.

7. Conclusion

In-stent restenosis remains a dynamic field of research, reflecting the complexity of the vascular response to injury. While drug-eluting stents have addressed the issue of cellular proliferation, a comprehensive solution requires a more nuanced approach to managing inflammation and matrix remodeling. Chondroitin sulfate and glucosamine sulfate, with their documented anti-inflammatory, pro-endothelial, and ECM-stabilizing properties, emerge as novel and promising candidates for pathogenetic therapy. Their mechanism of action, targeting fundamental pathways like CD44/versican and NF-κB, offers a complementary strategy to existing technologies.

The translation of this concept from bench to bedside necessitates a concerted effort: the production of high-purity pharmaceutical agents, robust preclinical validation, and ultimately, definitive clinical trials. If successful, this "vascular chondroprotection" strategy could mark a significant advance, not only in reducing restenosis rates but also in improving the overall safety and long-term success of percutaneous coronary interventions, paving the way for more personalized and biology-driven adjunctive therapies in interventional cardiology.

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