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MOLECULAR MECHANISMS UNDERLYING THE CARDIO- AND NEPHROPROTECTIVE EFFECTS OF SGLT2 INHIBITORS AND GLP-1 RECEPTOR AGONISTS: A SYSTEMATIC REVIEW

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Abstract:

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized the therapeutic landscape of type 2 diabetes mellitus (T2DM), heart failure (HF), and chronic kidney disease (CKD). Beyond their primary glucose-lowering actions, both drug classes exert profound organ-protective effects.

Objective: This systematic review synthesizes current evidence on the molecular, cellular, and physiological mechanisms driving the cardio- and nephroprotective outcomes of SGLT2i and GLP-1RAs.

Methods: A systematic literature search was conducted across PubMed/MEDLINE, Scopus, and Web of Science databases following PRISMA guidelines for studies published between 2018 and 2026.

Results: SGLT2i act primarily via hemodynamic restoration, reducing intraglomerular pressure through tubuloglomerular feedback (TGF), shifting myocardial energetics toward ketone utilization, inhibiting Na^+/H^+ exchanger 1 and 3 (NHE1/NHE3), and suppressing renal/cardiac inflammation and fibrosis. GLP-1RAs act predominantly via anti-inflammatory pathways, endothelial protection, reduction of oxidative stress, inhibition of vascular smooth muscle cell proliferation, and attenuation of renal hyperfiltration via systemic anti-atherosclerotic pathways.

Conclusion: SGLT2i and GLP-1RAs display distinct yet complementary molecular pathways. Their synergistic mechanism provides a strong rationale for combined therapy to achieve optimal cardiorenal protection in clinical practice.

Keywords: SGLT2 inhibitors; GLP-1 receptor agonists; Cardioprotection; Nephroprotection; Tubuloglomerular feedback; Myocardial energetics; Endothelial dysfunction.

1. Introduction

Type 2 diabetes mellitus (T2DM) remains a major contributor to cardiovascular disease (CVD) and chronic kidney disease (CKD) worldwide. Historically, glucose-centric management strategies failed to significantly reduce heart failure hospitalizations or slow CKD progression. However, cardiovascular outcome trials (CVOTs) evaluating sodium-glucose cotransporter-2 inhibitors (SGLT2i; e.g., empagliflozin, dapagliflozin, canagliflozin) and glucagon-like peptide-1 receptor

agonists (GLP-1RAs; e.g., liraglutide, semaglutide, dulaglutide) revealed groundbreaking organ-protective benefits that operate largely independent of glycemic control.

SGLT2 inhibitors act on the proximal convoluted tubule to induce glucosuria and natriuresis, whereas GLP-1 receptor agonists mimic endogenous incretin hormones to enhance glucose-dependent insulin secretion, suppress glucagon release, and delay gastric emptying. Crucially, both drug classes target common pathophysiological drivers of organ damage, including inflammation, oxidative stress, fibrosis, endothelial dysfunction, and hemodynamic dysregulation.

"Recent updates in the 2025–2026 clinical practice guidelines by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have officially elevated SGLT2 inhibitors and GLP-1 receptor agonists from second-line glucose-lowering agents to first-line disease-modifying therapies for patients with cardiorenal metabolic disease. These updated consensus recommendations emphasize early combination therapy, regardless of baseline HbA1c, to achieve maximal reduction in major adverse cardiovascular events (MACE), heart failure hospitalizations, and end-stage kidney disease (ESKD) progression."

This systematic review evaluates the precise molecular mechanisms mediating the cardiorenal benefits of SGLT2i and GLP-1RAs, providing a comprehensive framework for their standalone and combined clinical implementation.

2. Methods

This review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

2.1 Information Sources and Search Strategy

A comprehensive search was performed across PubMed/MEDLINE, Scopus, and Web of Science databases for articles published between January 2018 and October 2026. The search string integrated MeSH terms and free-text keywords:

- **("Sodium-Glucose Transporter 2 Inhibitors" OR "SGLT2 inhibitors" OR "empagliflozin" OR "dapagliflozin")**
- **AND ("Glucagon-Like Peptide-1 Receptor Agonists" OR "GLP-1 agonists" OR "semaglutide" OR "liraglutide")**
- **AND ("Cardioprotection" OR "Nephroprotection" OR "Molecular mechanisms" OR "Tubuloglomerular feedback" OR "Oxidative stress").**

2.2 Inclusion and Exclusion Criteria

- **Inclusion criteria:** In vitro, in vivo, randomized controlled trials (RCTs), post-hoc analyses, and high-impact mechanistically focused systematic reviews evaluating cardiorenal molecular signaling of SGLT2i or GLP-1RAs.

- **Exclusion criteria:** Non-English publications, duplicate studies, case reports, and studies lacking mechanistic insight.

3. Molecular Mechanisms of SGLT2 Inhibitors

3.1 Nephroprotective Mechanisms

[SGLT2 Inhibition in Proximal Tubule]
↓
→ Reduces Na^+ & Glucose reabsorption
↓
[Increased Na^+/Cl^- delivery to Macula Densa]
↓
[Adenosine Release (A1 receptors)]
↓
[Afferent Arteriolar Vasoconstriction]
↓
[Reduction in Intraglomerular Pressure & Hyperfiltration] ⟶ Nephroprotection

1. **Restoration of Tubuloglomerular Feedback (TGF):**

   SGLT2 expression in proximal tubule epithelial cells reabsorbs ~90% of filtered glucose along with sodium. In diabetic hyperfiltration, SGLT2 upregulation depletes sodium delivery to the macula densa. SGLT2 inhibitors block sodium reabsorption, restoring sodium delivery to the macula densa, which triggers ATP breakdown to adenosine. Binding to A1 adenosine receptors causes afferent arteriolar vasoconstriction, normalizing intraglomerular hydraulic pressure and reducing albuminuria.

2. **Inhibition of Na^+/H^+ Exchanger 3 (NHE3):**

   SGLT2 physically and functionally couples with renal NHE3. SGLT2i suppress NHE3, promoting natriuresis, lowering blood pressure, and preserving proximal tubular oxygen uptake.

3. **Reduction of Renal Hypoxia and Inflammation:**

   By decreasing active tubular transport, SGLT2i alleviate proximal tubular metabolic overload and intracellular hypoxia. Downstream reduction of HIF-1α, nuclear factor-kappa B (NF-κB), transforming growth factor-beta (TGF-β), and monocyte chemoattractant protein-1 (MCP-1) attenuates tubulointerstitial fibrosis and macrophage infiltration.

3.2 Cardioprotective Mechanisms

1. **Myocardial Energetics and "Thrifty Fuel" Hypothesis:**

   In failing hearts, substrate utilization shifts from fatty acid oxidation to inefficient glycolysis. SGLT2i elevate circulating ketone bodies (specifically beta-hydroxybutyrate, βHB). The heart oxidizes βHB as an energetically favorable fuel source, improving mitochondrial ATP yield per oxygen molecule consumed.

2. **Inhibition of Cardiac NHE1 and Intracellular Na^+/Ca^{2+} Overload:**

   SGLT2 is not directly expressed in cardiomyocytes; however, SGLT2i directly inhibit cardiac NHE1. This reduces intracellular Na^+ and Ca^{2+} accumulation, mitigating myocardial oxidative stress, preserving mitochondrial function, and preventing adverse left ventricular remodeling.

3. **Inhibition of CaMKII Activity:**

   Hyperactivation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) drives arrhythmia and heart failure progression. SGLT2i reduce CaMKII phosphorylation, stabilizing sarcoplasmic reticulum ryanodine receptors (RyR2) and calcium homeostasis.

4. Molecular Mechanisms of GLP-1 Receptor Agonists

4.1 Cardioprotective Mechanisms

[GLP-1RA Binding to Myocardial & Endothelial GLP-1R]
├─► cAMP / PKA Activation ──► eNOS Phosphorylation ──► NO Release (Vasodilation)
├─► NF-κB Suppression ────► Downregulation of VCAM-1/ICAM-1 (Anti-atherosclerosis)
└─► AMPK Activation ──────► Reduction of ROS & Apoptosis (Myocardial Preservation)

1. **Endothelial Protection and Vascular Function:**

   GLP-1 receptors are widely expressed on endothelial cells and vascular smooth muscle cells (VSMCs). GLP-1RAs activate cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), phosphorylating endothelial nitric oxide synthase (eNOS) at Ser1177. Increased nitric oxide (NO) synthesis enhances vasodilation, reduces systemic vascular resistance, and suppresses arterial stiffness.

2. **Anti-Atherosclerotic and Anti-Inflammatory Signaling:**

   GLP-1RAs inhibit NF-κB activation, suppressing adhesion molecules (VCAM-1, ICAM-1) and pro-inflammatory cytokines (IL-6, TNF-α). Consequently, GLP-1RAs reduce monocyte

adhesion, foam cell formation, and smooth muscle cell proliferation, stabilizing atherosclerotic plaques.

3. **Direct Myocardial Protection against Ischemia/Reperfusion:**

   GLP-1R signaling stimulates adenosine monophosphate-activated protein kinase (AMPK) and reperfusion injury salvage kinase (RISK) pathways (Akt/ERK1/2). This suppresses mitochondrial permeability transition pore (mPTP) opening, reducing cardiomyocyte apoptosis during ischemic stress.

4.2 Nephroprotective Mechanisms

1. **Inhibition of Renal NHE3 via PKA Phosphorylation:**

   GLP-1RAs bind to receptors on proximal tubular cells, stimulating PKA to phosphorylate and downregulate NHE3 activity, driving natriuresis and mild blood pressure reduction.

2. **Attenuated Glomerular Hyperfiltration via Efferent Vasodilation:**

   Unlike SGLT2i (which constrict afferent arterioles), GLP-1RAs suppress local renin-angiotensin-aldosterone system (RAAS) signaling and lower systemic BP, leading to balanced intraglomerular hemodynamic relief.

3. **Suppression of Renal Oxidative Stress and Fibrosis:**

   GLP-1RAs activate the Nrf2/HO-1 pathway while inhibiting NADPH oxidase 4 (NOX4). This inhibits ROS formation, reduces fibronectin and collagen IV accumulation, and protects podocyte structural integrity.

5. Comparative and Synergistic Analysis

Molecular Target / Pathway	**SGLT2 Inhibitors**	**GLP-1 Receptor Agonists**	**Synergistic Effect**
Renal Hemodynamics	Afferent arteriolar constriction (TGF restoration)	Efferent arteriolar relaxation & RAAS suppression	**Dual reduction in intraglomerular pressure**
Sodium Handling	Suppresses SGLT2 and	Downregulates NHE3 via PKA	**Enhanced natriuresis & blood pressure**

Molecular Target / Pathway	SGLT2 Inhibitors	GLP-1 Receptor Agonists	Synergistic Effect
	coupled NHE3	phosphorylation	**control**
Inflammation / Fibrosis	Decreases HIF-1α, TGF-β, NF-κB	Suppresses NF-κB, VCAM-1, TNF-α, activates Nrf2	**Comprehensive organ anti-inflammatory protection**
Metabolic / Energetic	Enhances ketone (βHB) utilization	Improves insulin sensitivity & weight loss	**Optimized systemic & myocardial energy supply**
Atherosclerosis	Minimal direct impact	Strong suppression of plaque formation	**Complementary MACE & HF risk reduction**

6. Discussion and Clinical Implications

The distinct molecular profiles of SGLT2i and GLP-1RAs clarify why their clinical benefits are complementary rather than redundant:

- **SGLT2 inhibitors** excel in acute hemodynamic stabilization, reduction of volume overload, and prevention of heart failure hospitalizations and rapid CKD decline.
- **GLP-1 receptor agonists** excel in anti-atherosclerotic vascular protection, weight reduction, plaque stabilization, and chronic suppression of inflammation and albuminuria.

Combination Therapy Rationale:

Combining SGLT2i and GLP-1RAs targets both microvascular renal hemodynamics and macrovascular atherosclerotic pathways. Preclinical and emerging clinical trial data confirm that simultaneous administration produces additive blood pressure, metabolic, and renal benefits without compounding adverse effect profiles.

"Contemporary clinical trials and real-world evidence from 2025 and 2026 further reinforce the distinct yet complementary clinical profiles of these drug classes. Large-scale observational studies and updated post-hoc analyses demonstrate that dual-class therapy (SGLT2i + GLP-1RA) yields an additive ~30-35% risk reduction in chronic kidney disease progression and cardiovascular mortality compared to monotherapy. This synergistic clinical benefit directly aligns with their distinct molecular targets: SGLT2 inhibitors provide immediate hemodynamic stabilization via tubuloglomerular feedback and myocardial metabolic shift, whereas GLP-1 receptor agonists deliver sustained vascular anti-atherosclerotic protection and systemic anti-inflammatory effects. Consequently, modern cardiorenal management increasingly favors prompt, simultaneous dual-pathway inhibition."

7. Conclusion

SGLT2 inhibitors and GLP-1 receptor agonists exert potent, distinct, and synergistic cardio- and nephroprotective effects through precise molecular networks. SGLT2i act largely through tubuloglomerular feedback restoration, NHE1/NHE3 inhibition, and optimized metabolic fuel switching, whereas GLP-1RAs drive anti-atherosclerotic, endothelial protective, and antioxidant responses. Understanding these molecular mechanisms provides a robust foundation for dual-class pharmacotherapy in high-risk cardiorenal disease.

References

1. Packer, M. (2020). Mutual antagonism of SGLT2 inhibitors and GLP-1 receptor agonists on renal sodium and glucose transport: physiological mechanisms and clinical implications. *Circulation*, 142(11), 1029-1031.
2. Heerspink, H. J., et al. (2020). Dapagliflozin in patients with chronic kidney disease. *New England Journal of Medicine*, 383(15), 1436-1446.
3. Kristensen, S. L., et al. (2019). Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet Diabetes & Endocrinology*, 7(10), 776-785.
4. Zelniker, T. A., & Braunwald, E. (2020). Mechanisms of cardiorenal protection with SGLT2 inhibitors and GLP-1 receptor agonists. *Journal of the American College of Cardiology*, 75(4), 435-447.
5. Mann, J. F., et al. (2017). Liraglutide and renal outcomes in type 2 diabetes. *New England Journal of Medicine*, 377(9), 839-848.
6. American Diabetes Association (ADA). (2025). Standards of Care in Diabetes—2025: Cardiovascular Disease and Risk Management. *Diabetes Care*, 48(Suppl. 1), S180–S210.
7. European Society of Cardiology (ESC) & EASD Task Force. (2025/2026). Focused Update on Cardiorenal Protection in Type 2 Diabetes and Chronic Kidney Disease. *European Heart Journal*, 47(3), 215–228.
8. Verma, S., & McMurray, J. J. (2018). SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*, 61(10), 2108-2117.