RESEARCH PAPER

The Role of the Renin-Angiotensin-Aldosterone System and Endothelin-1 in the Progression of the Cardiorenal-Metabolic Triad

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ABSTRACT
The synergistic "triple burden" of type 2 diabetes, hypertension, and chronic kidney disease (CKD) represents a premier global health challenge, accounting for over 70% of end-stage renal disease (ESRD) cases worldwide. This review, conducted in accordance with PRISMA 2020 guidelines, synthesizes literature from 2000 to 2026 to evaluate the pathophysiological interplay and evolving therapeutic landscape of this triad.
Epidemiological data reveal a staggering rise in prevalence, with CKD-related mortality increasing by 98% between 1990 and 2016, disproportionately affecting low- and middle-income regions. Pathophysiologically, the progression of organ damage is driven by a "vicious cycle" of metabolic toxicity and hemodynamic stress. Chronic hyperglycemia triggers oxidative stress and the formation of advanced glycation end-products (AGEs), while hypertension inflicts mechanical shear stress, mediated significantly by Endothelin-1 (ET-1). These forces converge to induce glomerular hyperfiltration, podocyte loss, and eventual tubulointerstitial fibrosis. Central to this progression is the Renin-Angiotensin-Aldosterone System (RAAS), which, when overactivated, promotes both systemic hypertension and localized renal scarring.
Traditionally, management focused on "glucocentric" targets and RAAS blockade via ACE inhibitors or ARBs. However, recent clinical breakthroughs have shifted the paradigm toward integrated cardiorenal risk reduction. Emerging "pillars of therapy" now include SGLT2 inhibitors, which restore tubuloglomerular feedback, and GLP-1 receptor agonists, which offer potent anti-inflammatory benefits. Furthermore, the introduction of non-steroidal mineralocorticoid receptor antagonists (MRAs), such as finerenone, addresses "aldosterone breakthrough" with a superior safety profile compared to traditional steroidal agents.
In conclusion, addressing the triple burden requires a transition from monotherapy to comprehensive, pathophysiology-based combination strategies. This review underscores the paradigm shift towards integrated, cardiorenal-protective strategies—moving from monotherapy to comprehensive, pathophysiology-based combinations—and highlights key avenues for future research to mitigate the global rise in cardiorenal mortality..

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INTRODUCTION

The Triple Burden of Diabetes, Hypertension and CKD (chronic kidney disease)
Type 2 Diabetes mellitus as well as hypertension are the principal contributors of the global chronic kidney disease (CKD) epidemic and collectively responsible for the majority of end-stage kidney disease (ESKD) worldwide. Recent studies show that diabetes affects about 589 million adults globally, while CKD effects nearly 850 million individuals, with hypertension hampering more than one billion people and acting as a key accelerator of cardiovascular and renal injury [1-3]. Diabetic kidney disease plays the leading cause of CKD, contributing to almost half of ESKD cases and substantially increasing mortality risk caused due cardiovascular disorders [2], [4]. The combination of hyperglycaemia and elevated blood pressure impacts a synergistic cascade of metabolic toxicity, intraglomerular hypertension, tubulointerstitial fibrosis, and endothelial dysfunction, resulting in decrease in glomerular filtration rate and early proteinuria [5].
This epidemiological overlap is mechanistically intertwined. Chronic hyperglycaemia enhances advanced glycation end-product accumulation, mitochondrial damage, and activation of pro-inflammatory biomarkers by various pathways, while hypertension creates

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hemodynamic shear stress and RAAS-mediated vasoconstriction, together driving podocyte injury, mesangial growth, and enhancement in nephrosclerosis [6,7]. This bidirectional interplay has led to the conceptualization of a combined cardiovascular–kidney–metabolic (CKM) syndrome, which emphasizes shared pathobiology and the need for unified management approaches rather than organ-specific methods [8].

In the last decade, the therapeutic landscape has shifted from a largely glucocentric model to a mechanism- based cardiorenal-protective context. Extensive randomized trials have established that sodium–glucose cotransporter-2 (SGLT2) inhibitors substantially slow CKD advancement, reduce hospitalization for heart failure, and lower the risk of kidney failure regardless of glycaemic control [9–11]. Similarly, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) deliver cardiovascular and renal benefits through anti-oxidative, anti-inflammatory, and weight-reducing effects, with current trials showing meaningful reductions in composite kidney effects [12]. Whereas non-steroidal mineralocorticoid receptor antagonists such as finerenone have risen as a key pillar of therapy by targeting aldosterone-mediated fibrosis and inflammation on top of optimized RAAS blockade [13].

These advances have reshaped international guidelines (KDIGO, ADA) toward early initiation of multi-drug cardiorenal-protective therapy, yet real-world uptake remains suboptimal, particularly in resource-limited settings [14]. Moreover, traditional biomarkers such as serum creatinine and albuminuria detect kidney injury relatively too late, highlighting the need for novel molecular markers and precision-based risk assessment [15].

Despite key progress in dissecting the separate contributions of diabetes, hypertension, and chronic kidney disease (CKD), clinical management often stays siloed and centered on risk factors rather than mechanisms and integration. Much of the current literature examines these disorders separately or spotlights individual drug classes, offering scant integration of their overlapping biology across the cardiovascular–kidney–metabolic (CKM) spectrum [16]. While recent trials highlight strong cardiorenal gains from SGLT2 inhibitors, GLP-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists, major challenges linger in their everyday application, ideal ordering, and combined use—especially for those with severe CKD, multiple conditions, or limited resources. In addition, diagnostic methods depend too much on delayed signals like serum creatinine and albuminuria, missing early cellular damage and highlighting gaps in reliable biomarkers and targeted risk tools. Thus, a thorough, mechanism-led review linking pathophysiology, novel multi-target therapies, and rollout strategies is essential to guide unified, equitable plans for lasting cardiorenal safeguard [17].

Methodology

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure a comprehensive and unbiased synthesis of the literature [20]. A systematic search was performed across major electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, covering publications from January 2000 to January 2026.

The search strategy utilized a combination of Medical Subject Headings (MeSH) and keywords such as "Diabetes Mellitus," "Hypertension," "Chronic Kidney Disease," "Diabetic Nephropathy," "Renin-Angiotensin-Aldosterone System," "SGLT2 Inhibitors," "GLP-1 Receptor Agonists," and "Cardiorenal Syndrome." Boolean operators (AND, OR) were employed to refine the search results. Inclusion criteria were defined as: (1) Peer-reviewed original research, meta-analyses, and clinical trial results; (2) Studies focusing on the pathophysiology, epidemiology, or management of coexisting diabetes, hypertension, and CKD; and (3) Articles published in English. Data regarding prevalence, pathophysiological mechanisms, and therapeutic outcomes were extracted and synthesized to provide a narrative overview of the current landscape [18, 19, 20].

Epidemiology and Global Burden of Coexisting Conditions

Global Trends in Prevalence and Mortality

The coexistence of diabetes, hypertension, and chronic kidney disease (CKD) represents a major global health crisis, reflecting a profound shift toward non-communicable diseases. Over the past four decades, the prevalence of diabetes has quadrupled—from 108 million in 1980 to 422 million in 2014 [21]—while hypertension now affects over 1.13 billion adults worldwide [22]. In parallel, CKD affects approximately 9.1% of the global population, ranking among the top ten causes of mortality [23, 24].

This rising prevalence has translated directly into a growing burden of disability and death. Between 1990 and 2017, CKD-related disability-adjusted life years (DALYs) increased by more than 60%, a statistic that underscores the compounding lethality of diabetes and hypertension. These coexisting conditions substantially elevate cardiovascular mortality and impose heavy economic and social burdens, particularly in regions where diagnostic capacity is outpaced by disease progression.[25, 26]

Interrelationship between Diabetes, Hypertension, and CKD

Diabetes and hypertension are the predominant causes of CKD, together accounting for more than 70% of end-stage renal disease (ESRD) cases globally [26]. Type 2 diabetes, which constitutes nearly 90% of all diabetes cases, induces microvascular and metabolic alterations leading to glomerular injury and nephron loss [27]. Hypertension further accelerates renal decline through hemodynamic stress and endothelial dysfunction. The coexistence of these disorders creates a synergistic effect, amplifying renal and cardiovascular risk. Epidemiological data show that individuals with both diabetes and hypertension experience a faster decline in glomerular filtration rate (GFR) and higher rates of cardiovascular morbidity compared to those with either condition alone [26, 27].

Regional and Socioeconomic Disparities

The global burden of these interlinked diseases is unevenly distributed. Nearly two-thirds of all diabetes and CKD cases occur in low- and middle-income regions, where access to early diagnosis and treatment is limited. The Global Burden of Disease (GBD) 2017 analysis reported an 87% increase in CKD prevalence and a 98% rise in CKD-related mortality between 1990 and 2016 [28]. Sub-Saharan Africa, South Asia, and Latin America have shown the steepest growth in disease burden, largely due to inadequate healthcare infrastructure and competing priorities with infectious diseases. In contrast, high-income nations demonstrate stabilized or declining trends due to improved screening and treatment protocols [29].

Table 1: Global Burden and Trends of the Diabetes-Hypertension-CKD Triad

Condition/Metric	Global Prevalence / Trend	Key Observations & Disparities
Diabetes	Quadrupled since 1980 (108 million to 422 million) [23]	~90% of cases are Type 2; major driver of glomerular injury and nephron loss.
Hypertension	Affects >1.13 billion adults worldwide [24]	Accelerates renal decline via hemodynamic stress; creates synergistic risk when combined with diabetes.
Chronic Kidney Disease (CKD)	Affects ~9.1% of the global population [25]	Prevalence increased by 87% (1990–2016); rapid rise in Low- and Middle-Income Countries (LMICs).
Mortality & Disability	CKD-related DALYs increased by >60% (1990–2017) [25]	CKD-related mortality rose by 98% (1990–2016); disproportionate burden in Sub-Saharan Africa and South Asia.

Pathophysiological Interplay:

Linking Hyperglycemia to Metabolic Toxicity

Chronic hyperglycemia acts as the primary metabolic driver of diabetic kidney disease (DKD), initiating injury through distinct biochemical pathways. Elevated glucose levels trigger the polyol pathway and protein kinase C (PKC) activation, while simultaneously fueling the formation of advanced glycation end-products (AGEs). These metabolic disturbances act as potent stimuli for oxidative stress, generating reactive oxygen species (ROS) that overwhelm renal antioxidant defenses [28, 29]. The accumulation of AGEs within the renal matrix cross-links proteins, altering tissue structure and upregulating pro-inflammatory cytokines like NF-κB. This metabolic toxicity creates a "pro-fibrotic" environment, where inflammation and oxidative damage converge to thicken the glomerular basement membrane and expand the mesangium, setting the stage for structural renal failure [30].

Hypertension and Hemodynamic Stress

While hyperglycaemia drives metabolic injury, hypertension inflicts mechanical damage through hemodynamic stress. Chronic elevation in systemic blood pressure exerts shear stress on the renal vasculature, inducing smooth muscle hypertrophy and vascular remodelling. A critical mediator in this process is Endothelin-1 (ET-1), a potent vasoconstrictor that is overexpressed in hypertensive states. ET-1 activation exacerbates the inflammatory cascade initiated by hyperglycaemia, stimulating further fibrosis and oxidative stress within the vascular wall [31, 32, 33]. This hemodynamic strain compromises endothelial integrity, reducing nitric oxide bioavailability and impairing the kidney's ability to autoregulate blood flow, thereby exposing the delicate glomerular capillaries to damaging systemic pressures [33, 34, 35].

Hypertension

Vascular Remodelling and Pressure Overload: Chronic hypertension exerts constant mechanical stress on the vascular wall, leading to smooth muscle hypertrophy and collagen deposition. These structural changes increase arterial stiffness and reduce elasticity, impairing the ability of vessels to adapt to fluctuating blood pressure. As a result, blood flow to critical organs, including the kidneys, becomes compromised. Over time, this persistent overload contributes to left ventricular hypertrophy and progressive nephrosclerosis, forming a vicious cycle of cardiac and renal injury.

Endothelial Dysfunction: The endothelium plays a vital role in maintaining vascular tone. In hypertension, oxidative stress and inflammation diminish nitric oxide (NO) bioavailability, disrupting the balance between vasodilation and vasoconstriction. This dysfunction promotes platelet aggregation, leukocyte adhesion, and vascular inflammation, which further damage the renal microcirculation and promote glomerulosclerosis.

Role of Endothelin-1 (ET-1): Endothelin-1 is a potent vasoconstrictor peptide overexpressed in hypertensive states. It binds to ETA receptors, stimulating fibrosis, oxidative stress, and inflammation in vascular and renal tissues. Elevated ET-1 activity narrows arterioles, increases systemic resistance, and directly injures glomerular capillaries, thereby accelerating renal impairment [36, 37, 38].

Genetic Influence: Genetic variations, particularly the rs9349379 G-allele in the *EDN1* gene, enhance ET-1 expression and increase susceptibility to microvascular dysfunction. These polymorphisms may explain why certain individuals develop hypertension-related kidney or heart disease earlier and more severely.

Therapeutic Advances: New targeted therapies such as selective ETA receptor antagonists (e.g., zibotentan) are being investigated to counteract the harmful vascular effects of ET-1. By improving endothelial function and reducing oxidative stress, these agents hold promise for personalized treatment of hypertension-related microvascular and renal damage [39, 40].

Renal Injury

The convergence of metabolic toxicity (from hyperglycemia) and hemodynamic stress (from hypertension) triggers a specific cascade of structural renal injury. These systemic insults do not act in isolation; rather, they synergize to progressively dismantle the kidney's filtration unit, moving from functional adaptation to irreversible fibrosis.

Early Functional Alterations – Glomerular Hyper filtration: One of the earliest renal abnormalities in diabetes and hypertension is glomerular hyper filtration. Increased intraglomerular pressure results from afferent arteriole dilation and efferent arteriole constriction, leading to excessive filtration of plasma through the glomeruli (Tonneijck et al., 2017). Though initially adaptive, chronic hyper filtration causes capillary wall stress and progressive podocyte injury, setting the stage for diabetic nephropathy.

The earliest renal response to this dual assault is glomerular hyperfiltration. Driven by the imbalance between afferent arteriolar dilation (from hyperglycemia) and efferent constriction (from Angiotensin II and pressure overload), intraglomerular pressure rises significantly. While initially adaptive to maintain filtration, this chronic mechanical strain causes capillary wall stress, creating a physical pathway for progressive nephron injury [41, 42, 43].

Podocyte Damage and Proteinuria: Podocytes maintain the glomerular filtration barrier. Persistent mechanical and metabolic stress damages these cells, causing detachment and loss of slit-diaphragm integrity. This disruption allows albumin and larger proteins to leak into urine, producing proteinuria—a key diagnostic marker of renal injury and disease progression.

As intraglomerular pressure rises, the podocytes—specialized cells maintaining the filtration barrier—are subjected to immense mechanical stretch and oxidative toxicity. This leads to podocyte detachment and the loss of slit-diaphragm integrity. The functional consequence is the leakage of albumin into the urine (proteinuria), a hallmark of the transition from early injury to overt kidney disease [44, 45, 46, 47].

Inflammation and Fibrosis: Prolonged hyperglycemia and hypertension activate pro-inflammatory cytokines such as TNF-α, IL-6, and TGF-β, which promote extracellular-matrix accumulation and interstitial fibrosis (Alicic et al., 2017). This fibrotic remodeling reduces renal oxygen diffusion, exacerbating hypoxia and tubular apoptosis.

The damage extends beyond the glomerulus into the tubulointerstitial compartment. Proteinuria itself is toxic to tubular cells, triggering a secondary wave of inflammation involving TNF-α and TGF-β. This promotes the transformation of differentiation of tubular cells into myofibroblasts, leading to widespread extracellular matrix deposition. The resulting interstitial fibrosis constricts the renal microvasculature, exacerbating hypoxia and driving irreversible nephron loss [48, 49, 50].

Oxidative Stress and Mitochondrial Dysfunction: Mitochondrial overload due to high glucose and lipid exposure generates reactive oxygen species (ROS). These free radicals impair ATP production and damage DNA and lipids, accelerating nephron loss and glomerulosclerosis [51, 52].

Understanding this cascade has shifted treatment paradigms from simple symptom management to targeted disease modification. Modern therapies, including SGLT2 inhibitors and non-steroidal mineralocorticoid receptor antagonists (MRAs), are now designed to intervene at specific points in this pathway—reducing intraglomerular pressure, dampening inflammation, and blocking fibrosis—offering new hope for halting the progression of cardiorenal failure [53, 54, 55].

Tubulointerstitial Injury: Beyond glomerular damage, renal tubular cells also suffer from metabolic overload and ischemia. The tubulointerstitial compartment becomes fibrotic, leading to irreversible nephron dropout and declining renal function.

Emerging Therapeutic Perspectives: Modern therapies such as SGLT2 inhibitors and endothelin-receptor antagonists show promise in reducing intra glomerular pressure, oxidative stress, and inflammation, thereby slowing renal decline. These agents represent a shift toward pathophysiology-based management of diabetic and hypertensive kidney injury [56, 57].

Role of the Renin–Angiotensin–Aldosterone System (RAAS) in Disease Progression:

Overview of RAAS biology relevant to diabetes, hypertension and CKD:

The RAAS plays a pivotal role in both systemic and intrarenal hemodynamic regulation, as well as in driving direct profibrotic and proinflammatory signaling within the kidneys. In diabetes, hyperglycemia and local mediators stimulate the upregulation of intrarenal RAAS components, including renin, angiotensin II, aldosterone, and local receptor expression. This activation contributes to glomerular hypertension, increased glomerular permeability (albuminuria), oxidative stress, inflammation, and progressive tubulointerstitial fibrosis – all critical pathways implicated in the development and progression of diabetic kidney disease (DKD) [58, 59, 60, 61].

The RAAS operates as a pivotal regulator of both systemic hemodynamics and local tissue injury. While systemic activation defends blood pressure, the intrarenal RAAS often functions autonomously and is disproportionately upregulated in diabetes. Hyperglycemia and local metabolic mediators stimulate the intrinsic production of renin and angiotensinogen within the kidney, leading to local

concentrations of Angiotensin II (Ang II) that far exceed systemic levels. This "local" activation is a key driver of glomerular hypertension, podocyte injury, and tubulointerstitial fibrosis, acting independently of systemic blood pressure [62, 63, 64, 65].

Mechanisms by which RAAS activation drives disease progression:

Angiotensin II impacts hemodynamics by causing the constriction of efferent arterioles, raising intraglomerular pressure. This increase accelerates glomerular damage and triggers the progression of proteinuria. In terms of cell signaling and fibrosis, angiotensin II and aldosterone activate pathways such as TGF-β, NF-κB, and oxidative stress within podocytes, mesangial cells, and tubular cells. This activation drives extracellular matrix deposition and promotes the emergence of fibrosis. Aldosterone, through mineralocorticoid receptor stimulation, exacerbates inflammation and tubular injury by increasing pro-inflammatory cytokine release and encouraging macrophage infiltration. Furthermore, MR activation contributes to sodium retention, which plays a role in cardiac and vascular remodeling as well as renal fibrosis [66, 67, 68, 69].

Angiotensin II exerts a dual pathology:

Hemodynamic Effect: It potently constricts the efferent arteriole, increasing intraglomerular pressure to maintain filtration fraction. While initially compensatory, this sustains the "hyperfiltration" state discussed in Section 3.3, mechanically shearing podocytes [70].

Tissue Injury: Beyond hemodynamics, Ang II and aldosterone act as direct pro-fibrotic cytokines. They activate the TGF-β and NF-κB signaling pathways, promoting macrophage infiltration and the transformation of fibroblasts into myofibroblasts. This results in the excessive deposition of the extracellular matrix, scarring the kidney and solidifying the decline in renal function [71].

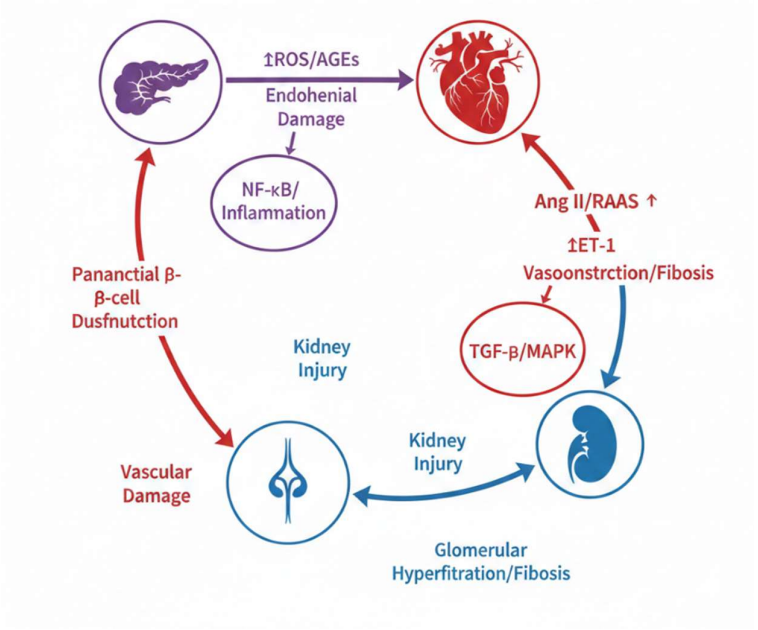

Fig 01:

Pathophysiological cycle linking diabetes, cardiorenal disease, and key mediators (RAAS, ET-1, TGF-β).

Legend: The diagram illustrates the "vicious cycle" of cardiorenal organ damage. (Top) Chronic hyperglycemia induces oxidative stress (ROS) and advanced glycation end-products (AGEs), triggering endothelial dysfunction and inflammation (NF-κB). (Right) This systemic toxicity activates the Renin-Angiotensin-Aldosterone System (RAAS) and upregulates Endothelin-1 (ET-1), leading to potent vasoconstriction and fibrosis via the TGF-β pathway. (Bottom/Left) These mediators synergize to cause glomerular hyperfiltration, vascular remodeling, and progressive kidney injury, which in turn exacerbates hypertension and cardiac strain, perpetuating the cycle of multi-organ dysfunction.

This image depicts the interconnected cycle of damage in diabetes and cardiorenal disease, where oxidative stress and advanced glycation end products cause endothelial damage and inflammation, leading to both pancreatic beta-cell dysfunction and vascular injury. These processes trigger kidney injury, glomerular hyperfiltration, and fibrosis, which then activate pathways like RAAS, endothelin-1, TGF-beta, and MAP kinase, further contributing to vasoconstriction, fibrosis, and additional injury to the heart, kidneys, and pancreas, thus perpetuating a cycle of organ dysfunction and disease progression.

Clinical evidence for RAAS blockade in patients with diabetes and CKD:

ACE inhibitors and angiotensin receptor blockers are vital in managing diabetic kidney disease, as they help reduce albuminuria, slow the decline of estimated glomerular filtration rate in early-to-moderate stages, and lower cardiovascular risks in diabetic patients. These benefits establish renin-angiotensin-aldosterone system blockade as

a foundation of care for this population, with leading clinical guidelines recommending these agents as the first-choice renoprotective antihypertensive therapy for diabetic kidney disease. However, while RAAS blockade is effective in many cases for reducing albuminuria and slowing progression, its impact on delaying major outcomes like kidney failure can vary significantly depending on factors such as chronic kidney disease stage, baseline renal function, and accompanying health conditions. Research indicates that the efficacy of RAAS inhibitors diminishes in advanced stages of CKD. Managing care requires a thoughtful approach that prioritizes reductions in proteinuria and optimal blood pressure control while carefully mitigating risks like hyperkalemia and acute kidney injury [72, 73, 74, 75].

Given these mechanisms, RAAS blockade remains the cornerstone of renoprotection. Major clinical guidelines, including KDIGO 2024 and the ADA, unanimously recommend ACE inhibitors (ACEi) or Angiotensin Receptor Blockers (ARBs) as first-line therapy for patients with albuminuria and hypertension. These agents are proven to reduce proteinuria and delay the progression to end-stage kidney disease (ESKD) [76]. *(Note: A detailed discussion of specific ACEi/ARB regimens and their comparative efficacy is provided in Section 5).*

Risks of excessive RAAS inhibition and dual blockade:

Dual inhibition of the renin-angiotensin-aldosterone system (RAAS), through the combination of ACE inhibitors with ARBs or the inclusion of renin inhibitors, has demonstrated greater reductions in proteinuria based on findings from meta-analyses and randomized controlled trials (RCTs). Despite these effects, this strategy is linked with heightened risks of hyperkalemia, hypotension, and acute kidney injury (AKI), without definitive evidence of improved mortality rates or significant advantages for preventing kidney failure. Consequently, the routine application of dual RAAS blockade is not recommended. Mineralocorticoid receptor antagonists (MRAs), such as the steroidal agents spironolactone and eplerenone, are effective in decreasing albuminuria but also elevate the risk of hyperkalemia when used alongside ACE inhibitors or ARBs. In contrast, the newer non-steroidal MRAs like finer none have shown encouraging cardio renal benefits in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), offering a favorable safety and efficacy profile in clinical studies. Nevertheless, the potential for hyperkalemia remains a concern, emphasizing the importance of cautious and individualized use [77, 78, 79, 80].

While blocking the RAAS is beneficial, "more" is not necessarily better. The hypothesis that combining an ACEi with an ARB (dual blockade) would offer superior protection was tested in major trials (e.g., ONTARGET, VA NEPHRON-D) and yielded a cautionary result. While dual blockade significantly reduced albuminuria, it disproportionately increased the risk of adverse safety events, specifically hyperkalemia and acute kidney injury (AKI), without improving survival or preventing ESKD. Consequently, current standards strictly advise against the routine combination of ACE inhibitors and ARBs [81, 82].

Translational and therapeutic implications:

Aldosterone breakthrough—where aldosterone levels rise despite ACEi/ARB therapy—remains a significant residual risk.

Steroidal MRAs (e.g., Spironolactone): While effective at reducing fibrosis, their widespread use in CKD has been limited by a high risk of hyperkalemia and hormonal side effects (gynecomastia).

Non-Steroidal MRAs (e.g., Finerenone): The development of selective, non-steroidal MRAs represents a therapeutic breakthrough. Unlike their steroidal predecessors, agents like finerenone potently block the mineralocorticoid receptor with a more favorable safety profile. Large-scale trials (FIDELIO-DKD, FIGARO-DKD) have demonstrated that finerenone significantly reduces the risk of CKD progression and cardiovascular events in patients with type 2 diabetes, even when added to maximal ACEi/ARB therapy [83, 84, 85].

Current Therapeutic Arsenal: From Cornerstones to Novel Paradigms

Lifestyle & BP Control Foundation

Management begins with foundational lifestyle modifications, including dietary sodium restriction (<2g/day) and weight management, which potentiate the antiproteinuric effects of pharmacological therapy. Blood pressure control remains pivotal; recent guidelines recommend a target of <130/80 mmHg to minimize hemodynamic strain on the glomerular capillary bed [86, 87].

RAAS Inhibition (ACEi, ARBs):

The Established Backbone ACE inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) remain the first-line pharmacotherapy for patients with albuminuria. By inducing efferent arteriolar vasodilation, they significantly lower intraglomerular pressure—a mechanism distinct from their systemic antihypertensive effect.

ACE Inhibitors: Block the conversion of Angiotensin I to II and inhibit the breakdown of bradykinin, which promotes vasodilation but may cause a dry cough.

ARBs: Selectively block the AT1 receptor, offering a similar renoprotective profile with better tolerability. Clinical consensus dictates utilizing the maximum tolerated dose of *either* agent to achieve regression of albuminuria, rather than combining them [88, 89, 90].

Novel Agents with Cardiorenal Benefits: SGLT2 Inhibitors & GLP-1 Receptor Agonists

The treatment landscape has shifted from "glucocentric" to "cardiorenal risk reduction."

SGLT2 Inhibitors (e.g., Dapagliflozin, Empagliflozin): Originally glucose-lowering agents, these drugs have revolutionized nephrology. By blocking glucose and sodium reabsorption in the proximal tubule, they restore tubuloglomerular feedback (TGF), causing afferent arteriolar constriction. This reduces intraglomerular pressure (mitigating hyperfiltration) independently of insulin [91, 92].

GLP-1 Receptor Agonists (e.g., Semaglutide, Liraglutide): These agents reduce albuminuria and cardiovascular risk

through anti-inflammatory and anti-oxidative mechanisms, alongside significant weight loss. They are particularly indicated for patients with atherosclerotic cardiovascular disease (ASCVD) or those unable to tolerate SGLT2 inhibitors [93, 94].

Emerging Role of Non-Steroidal MRAs (Finerenone)

Aldosterone breakthrough remains a residual risk in patients already on ACEi/ARB therapy. Finerenone, a novel non-steroidal mineralocorticoid receptor antagonist (MRA), selectively blocks the pro-fibrotic and pro-inflammatory effects of aldosterone with a lower risk of hyperkalemia compared to spironolactone. The FIDELIO-DKD and FIGARO-DKD trials demonstrated that finerenone significantly reduces the risk of CKD progression and cardiovascular events in patients with T2D and CKD, establishing it as a new pillar of therapy [95, 96, 97].

Practical Considerations & Combination Strategies

The modern "pillars of therapy" for Diabetic Kidney Disease now include: (1) RAAS Blockade, (2) SGLT2 Inhibitors, and (3) Non-steroidal MRAs (Finerenone), with GLP-1 RAs added for cardiovascular risk. Clinicians must navigate the initiation of these agents carefully, monitoring serum creatinine (expecting a reversible initial dip in eGFR with SGLT2i/RAASi) and potassium levels to avoid hyperkalemia [98, 99].

Novel Antidiabetic Agents with Cardiorenal Benefits

Novel antidiabetic agents such as SGLT2 inhibitors and GLP-1 receptor agonists have shown compelling cardiorenal benefits beyond glycemic control, with recent high-impact clinical trials and reviews providing detailed insights on this evolving standard of care for type 2 diabetes and cardiorenal risk management [100, 101].

Sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are the most promising drug classes for cardiorenal protection in diabetic and non-diabetic patients. SGLT2 inhibitors act by promoting urinary glucose excretion, leading to reduced blood sugar, as well as osmotic diuresis, blood pressure reduction, and beneficial effects on heart and kidney hemodynamics. GLP-1 receptor agonists, which potentiate glucose-dependent insulin secretion, also directly influence cardiac and renal tissue by reducing inflammation, oxidative stress, and fibrosis, along with weight reduction and improved endothelial function [102, 103, 104].

Cardiorenal Outcomes from Recent Trials

SGLT2 inhibitors significantly reduce hospitalizations for heart failure (by 25-35%), slow progression of chronic kidney disease (by 30–45%), and lower the risks of dialysis or kidney transplantation events [105, 106].

GLP-1 receptor agonists, as proven by recent large-scale studies like the FLOW trial, reduce the composite outcome of kidney failure, major cardiovascular events, and cardiovascular mortality by up to 24% in type 2 diabetes [107, 108].

Both drug classes are associated with reduced major adverse cardiovascular events (MACEs), lower all-cause and cardiovascular mortality, and fewer adverse kidney outcomes compared to other antidiabetic drugs [109, 110].

Safety and Clinical Implications

SGLT2 inhibitors generally show low risk for acute kidney injury, although patients with advanced cardiovascular disease might see less pronounced benefits.

GLP-1 receptor agonists offer broad benefits across subgroups (hypertensive, advanced CKD, insulin users) and demonstrate early, sometimes acute, risk reductions for cardiovascular and kidney events.

DPP-4 inhibitors are also under investigation, though their cardiorenal superiority is not as clearly established; current evidence supports their non-inferiority [111, 112, 113].

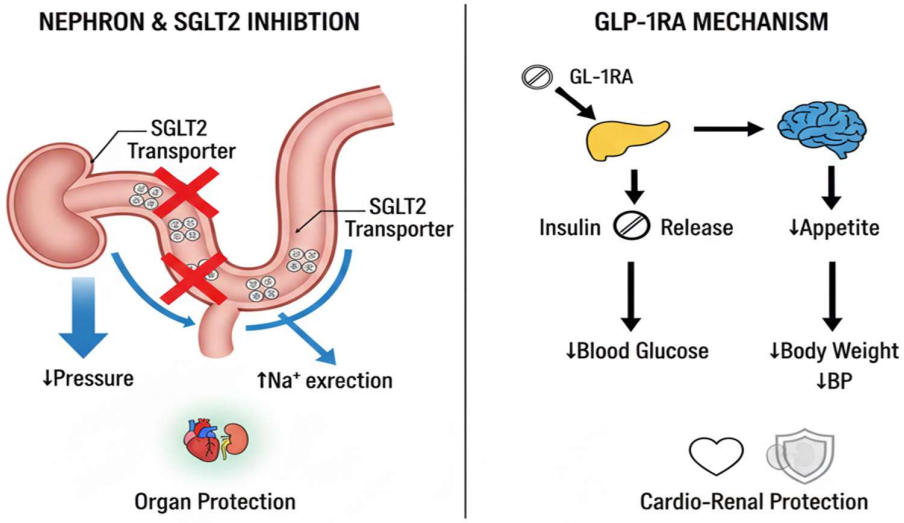

Fig 02: Proposed mechanisms of cardiorenal protection for SGLT2 inhibitors and GLP-1 receptor agonists.

On the left side, the diagram shows the action of SGLT2 inhibitors within the kidney. These drugs block the SGLT2 transporters located in the proximal tubule, which leads to increased excretion of sodium ions and a reduction in

intrarenal pressure. By reducing pressure and increasing sodium excretion, SGLT2 inhibitors help protect organs, especially the heart and kidneys. The right side depicts the mechanism of GLP-1 receptor agonists. These agents act on the pancreas to reduce insulin release and also affect the brain to suppress appetite. The downstream effects include lower blood glucose, decreased body weight, and reduced blood pressure. Collectively, these changes lead to protection of both cardiovascular and renal systems. Both SGLT2 inhibitors and GLP-1 receptor agonists offer significant clinical benefits in managing metabolic, cardiovascular, and renal complications. Their combined use may provide additive protective effects for patients with cardio-renal risk.

Future Directions and Expanding Indications

Ongoing research includes the effect of dual or triple agent therapies and exploring use beyond diabetes, for obese or overweight patients with underlying cardiorenal disease. New mechanistic pathways—including epigenetic modulation, mitochondrial metabolism, and immune system effects—are being investigated for even broader cardiorenal protection. [114, 115]

Table 2: Cardiorenal Benefits of Novel Antidiabetic Agents

Drug Class	Cardio Benefit	Renal Benefit
SGLT2 Inhibitors	↓ HF hospitalization, ↓ MI risk	↓ CKD progression, ↓ dialysis
GLP-1 R Agonists	↓ MACE, ↓ all-cause mortality	↓ kidney failure, ↓ eGFR decline
DPP-4 Inhibitors	Non-inferior in CV safety	Data emerging

All recent reviews emphasize an integrated approach, using these agents for multi-system protection rather than only glucose control.

These developments represent a paradigm shift, reshaping the management of diabetes with high cardiovascular and renal risk, and promising improved patient outcomes through novel and synergistic drug therapies [116, 117].

Future Directions and Opportunities

Summary of the Paradigm Shift

The management of cardiorenal disease is undergoing a fundamental transformation. The historical "glucocentric" approach—focusing primarily on HbA1c normalization—has been superseded by a comprehensive "cardio-kidney-metabolic" (CKM) model. This new paradigm prioritizes organ protection over simple biomarker correction, treating diabetes, hypertension, and CKD not as isolated comorbidities but as an interconnected syndrome requiring holistic, multimodal intervention [118, 119, 120].

Precision Medicine: From "One-Size-Fits-All" to Phenotyping A critical opportunity lies in moving beyond generic treatment algorithms toward precision nephrology.

Biomarkers: Current reliance on creatinine and albuminuria detects injury too late. Emerging research focuses on "liquid biopsy" biomarkers such as Kidney Injury Molecule-1 (KIM-1), Uromodulin, and TNF receptors, which can predict tubulointerstitial damage before GFR declines [121, 122, 123].

Genetic Stratification: The integration of Polygenic Risk Scores (PRS) and single-cell transcriptomics (scRNA-seq) is beginning to identify patient subgroups who are genetically predisposed to rapid progression. This allows clinicians to deploy aggressive therapies earlier in those with the highest "molecular risk," rather than waiting for clinical failure [124, 125, 126].

Beyond Diabetes: The CKM Syndrome The success of SGLT2 inhibitors and GLP-1 RAs has blurred the lines between specialties. Future guidelines are expected to codify the treatment of Cardiovascular-Kidney-Metabolic (CKM) Syndrome, extending the use of these agents to:

Non-Diabetic CKD: Trials like EMPA-KIDNEY have already proven efficacy in non-diabetic cohorts, suggesting these mechanisms treat the *kidney*, not just the sugar [127, 128].

Heart Failure & Obesity: With the recognition of "Nephrogenic" heart failure (HFpEF) and "Adiposopathy" (sick fat), future strategies will likely position weight management (via high-dose GLP-1s) as a primary renoprotective maneuver rather than a secondary cosmetic goal [129, 130, 131].

Novel Therapeutic Targets

As we maximize RAAS and SGLT2 inhibition, research is pivoting to upstream molecular targets:

Inflammation & Autophagy: Targeting the NLRP3 inflammasome and enhancing autophagy (cellular recycling) offers a way to halt the "sterile inflammation" that drives fibrosis [132, 133].

Epigenetics: Hyperglycemia leaves a "metabolic memory" on DNA through methylation. Epigenetic modulators are being investigated to "erase" this memory, potentially reversing susceptibility to vascular damage even after glycemic control is re-established [134, 135].

Digital Health & Implementation Science

The gap between scientific discovery and patient care remains the largest hurdle.

AI & Predictive Modeling: Artificial Intelligence models are being developed to scour Electronic Health Records (EHRs) and flag "silent" CKD patients who meet criteria for SGLT2i/GLP-1 initiation but remain untreated [136, 137].

Overcoming Disparities: Digital health platforms and wearables offer a bridge to underserved populations, but implementation science must ensure these tools do not widen the "digital divide" for patients in low-resource settings [138, 139].

The Future of Clinical Trials

The next generation of clinical trials must evolve from placebo-controlled studies to head-to-head comparisons and combination designs. Crucially, we need data on "Triple Therapy" (SGLT2i + GLP-1 RA + Finerenone) to determine if hitting three distinct pathways simultaneously can induce actual regression of kidney disease rather than just slowing its decline [140, 141, 142].

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